ISSN 0971-5851
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

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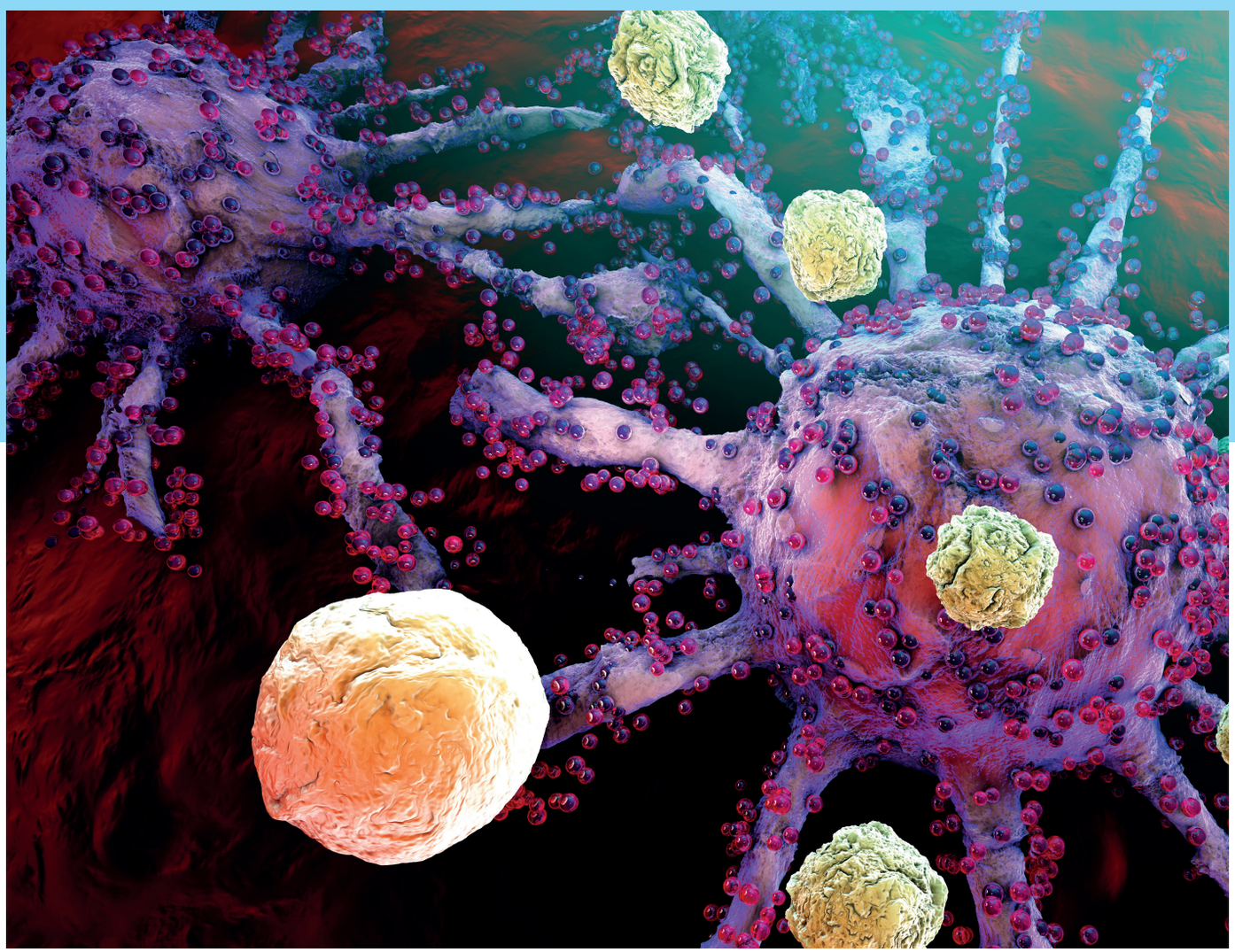
Number 3 • Volume 43 • Pages 223–322 • June 2022



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Indian Journal of Medical and Paediatric Oncology is published 6 times a year in February, April, June, August, October, and December by Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India. Tel: +91-120-4556600, Fax: +91-120-455-6649.

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Indian Journal of Medical and Paediatric Oncology is indexed in *Emerging Sources Citation Index* and SCOPUS. Thieme Medical Publishers is a member of the CrossRef initiative.

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Typesetting: Thomson Digital, Noida, India
Printing and Binding: Replika Press Pvt. Ltd.
Printed in India

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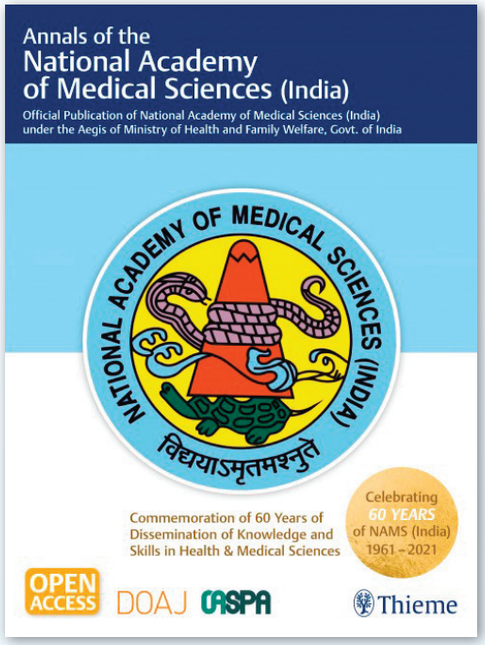

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GLOCAL Oncology: Global Oncology That Is Relevant to Local Needs

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Ind J Med Paediatr Oncol 2022;43:223–224.

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"Vasudhaiva Kutumbakam" in the Sanskrit language means the "World is One Family." This philosophy was embraced in our scholarly texts thousands of years ago. It truly encompasses what global health, including global oncology, should stand for.

As globalization increases, the disparities increase among countries and even within regions and people. The disparities are magnified in the field of oncology.[1–3] A significant amount of money is invested by companies to make the next blockbuster anticancer drug.[4] However, most patients with cancer across the world, especially those in low-income and low- and middle-income countries (LLMICs), cannot access these life-prolonging or life-saving drugs due to the high costs.[5–7]

The global oncology agenda is heavily influenced by the Global North and the developed economies.[8–10] Individuals and organizations from emerging economies find it difficult to make their voices heard globally. The *Indian Journal of Medical and Pediatric Oncology* (IJMPO) wants to break this barrier and provide a platform for researchers worldwide, especially LLMICs, to share their experiences.

I would propose the word GLOCAL (Global + Local) Oncology as not all global initiatives can be implemented locally due to cultural, demographic, financial, or administrative issues. Modifying global solutions to local needs (GLOCAL) can ensure that cancer patients worldwide benefit. Examples of GLOCAL initiatives that have helped reduce cancer treatment costs and increase accessibility include low-dose immunotherapy, drug repurposing for chemotherapy-induced nausea and vomiting, weekly versus 3-weekly cisplatin in head and neck squamous cell carcinomas, and weight-based dosing for immune checkpoint inhibitors.[11,12]

The special global oncology issue of IJMPO is truly a global village with articles and authors from the Dominican Republic, Sri Lanka, Pakistan, the United States of America, Turkey, and India. The articles focus on a wide range of issues that impact the global community, including palliative care, the nursing workforce, the coronavirus disease 2019 pandemic, education and training, quality of life, access to drugs, research, and alternative treatments.

The global oncology space does not belong to oncologists alone. We need to bring all stakeholders like nurses, social workers, paramedical staff, basic scientists, patients, and caregivers to the global table.[13] Without the involvement of these stakeholders, the dream of global oncology transcending borders to impact lives positively cannot be achieved.

How can emerging economies change the global oncology narrative? The first step toward this would be to support research that answers questions relevant to the local needs. This is best achieved through the formation of collaborative groups.[14,15] The next step is to translate the local research to global needs.[15] This is a bigger task that requires the pharma industry, governments, academic centers, and collaborative groups to come together. Countries like India and China are the manufacturing hubs for the pharmaceutical industry. They have trained staff to do research and clinical trials. We should use the strength of patient numbers and the pharmaceutical industry to conduct relevant studies that will change practice worldwide.

DOI https://doi.org/10.1055/s-0042-1750737.
ISSN 0971-5851.

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The time has also come to have experts from LLMICs be a part of consensus guidelines in oncology.[16] These guidelines are heavily influenced by key opinion leaders from the Global North. Sometimes, there are no experts, or they are in the minority from LLMICs for guidelines made for LLMICs.

To conclude much more needs to be done to make global oncology inclusive. One step toward this is for journals from LLMICs to start participating in the global health agenda, and IJMPO is moving in that direction.

Funding
None.

Conflict of Interest
None declared.

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Pharmacoeconomics

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Ind J Med Paediatr Oncol 2022;43:225.

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With the rising cost of cancer care, there is a necessity felt to address this unique demanding situation. Unique in sense, desperation and hope are playing the main role for economic expenditure by the patients in diseases where outcomes are largely limited. However, in certain diseases, immunotherapy and small molecules (tyrosine kinase inhibitors) have improved outcome that is never witnessed in the past. For example, chemotherapy combined with programmed death (PD) 1 or PD Ligand 1 inhibitors in lung cancer. This creates a situation of "between the devil and the deep blue sea" for patients when cost is beyond the reach.

Patients have been supported financially by various central and state governments, nongovernmental organizations, close relatives, and friends. In spite of this, high cost of treatment is a new cause of poverty in our country. To protect our patients and their families from financial toxicity, it is the collective social responsibility of all stake holders in cancer care including the treating doctors to protect patients from financial hardship. Academia has immense potential and has to come forward in bringing the solutions for this perpetual problem in cancer care. One of the solutions or answers is "Pharmacoeconomics."

In this special issue of *Indian Journal of Medical and Pediatric Oncology*, we have worked with eminent medical oncologists from India and overseas and tried to provide few simple and easier ways of reducing the cost of cancer treatment. I hope the readers of this journal will enjoy reading this special issue and learn new approaches of cost saving.

DOI https://doi.org/10.1055/s-0042-1750739.
ISSN 0971-5851.

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Breaking the Bad News in Cancer: An In-Depth Analysis of Varying Shades of Ethical Issues

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Ind J Med Paediatr Oncol 2022;43:226–232.

Abstract

Oncology has a range of ethical issues that are difficult to address and breaking the bad news is probably the most important and common across the world. Conventionally, breaking the bad news has been exclusively used in the situation where definitive diagnosis of cancer is to be conveyed to the patient. On a practical note, for the treating doctor, breaking the bad news is not restricted only to the confirmation of cancer and its prognosis at the initial diagnosis but also includes conveying futility of curative treatment, changing from curative to palliative treatment, recurrence/metastasis posttreatment, end of life care, and finally informing death of the patient to the family members. In addition to this, informing pregnant women that she has been diagnosed with cancer, about surgery-induced body disfigurement, loss of fertility due to chemotherapy/ radiotherapy, and of treatment-induced irreversible health complications are also challenging for the treating oncologist. On the basis of an in-depth analysis, the current review presents the various situations, complexities, and the related ethical issues in breaking the bad news in various situations from the perspective of an oncologist in detail in Indian context.

Keywords
- ethical issues
- breaking the bad news
- end-of-life issues
- oncofertility

DOI https://doi.org/10.1055/s-0042-1750738.
ISSN 0971-5851.

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Introduction

Ethics is an integral part of medicine and healthcare professionals are obligated to make sound clinical decisions, reduce harm, by considering the patient's religious beliefs, cultural values and societal norms.[1–4] In this regard, the four main principles of bioethics "autonomy, beneficence, nonmaleficence, and justice" form the base for all ethical dealings and behavior in healthcare sciences.[2] Importantly, all healthcare workers have to remember this and take the most suitable decision and choose standard medical interventions by keeping the best interest of the patient and their family members as priority.[2] On the part of the treating doctor, honoring these principles during medical practice and in personal life is considered ethical to ensure that he is doing full justice to his patient and their family members.[1–4] Treating doctor has to also ensure that the patient's rights are protected in accordance with the recommended guidelines on moral principles and will also have to help the patients and their family members navigate through the trajectory of the treatment, recovery, and rehabilitation.[2]

In addition to this, the healthcare professionals will also have to follow the principle of sincerity and accountability for the decisions they take while attending to the patients and their family members while making complex choices [5] considering the moral norms of the right conduct that transcends the barriers of cultures, geographical regions, and religions.[1,6] Principally, moral norms which by definition means "*rules of morality that people ought to follow*" are classified in to two groups as common morality and particular morality.[1,7] Terminologically, common morality indicates aspects like not causing any harm or suffering to others but instead relieving them of it, while particular morality refers to norms that tether people to their culture, religious beliefs, and professional standards.[7] It is also important that the healthcare workers and the treating doctor endure value in cancer care by focusing on patient's physical and psychological welfare with empathy and professionalism.[2–4] In spite of all these guidelines, healthcare workers face a multitude of ethical dilemmas at regular intervals, and at most times they are distressing and difficult to handle.[8,9]

When compared with other specialties in medical sciences, the ethical issues in cancer care are divergent and complicated. Some of the most important ethical issues reported are in the areas of cancer screening, genetics, diagnosis, breaking the bad news, the extent of patient information to be provided, and topics in planning the optimal treatment, follow-up, cost–benefit aspects, psychological and physical rehabilitation, sexuality and reproductive aspects, supporting the caregivers, transitioning from curative to palliative treatment, care of vulnerable groups, and the various end-of-life issues.[10–13] On a practical note, arriving at an ethical decision for some of the above said aspects is straightforward and with a solution, while few end as unresolved and inflict conflicting moral injury, feelings of frustration, and powerlessness in the oncology staff.[8,9] On a comparative note, when compared with the developed countries, the situation of helplessness and moral injury in healthcare workers working in cancer care in resource limited developing countries may be more, but is under reported.

Previous studies aimed at understanding the most difficult situation for medical doctors in treatment and care of cancer patients in Indian context had indicated that breaking the bad news was the most difficult.[8,9] Although myriad factors are documented to be associated with the complexity and difficulty in breaking the bad news, in the Indian context one of the important factor that contributes to the difficulty is the role of the family member in the process and requesting to withhold information from patients.[14,15] The principal reason for this is that the family members feel that revealing the bad news can cause fear and depression in the patient and can lead to self-harm and suicide.[14,15] For a treating doctor, the conflicting requests of the patient versus that placed by their family members present a dilemma because withholding information from patients is against the tenets of medical ethics.[1]

On the contrary, most patients are desirous to know the prognostic details, treatment choice and the sequence, side effects, chances of recurrences, complications of treatment, quality of life, and the life expectancy posttreatment.[16] Nonmaleficence is the principle of refraining from causing unnecessary harm and not informing the patient about their diagnosis and prognosis can cause anxiety and affects adversely.[1,17] The principle of justice mandates that the patient is informed of the diagnosis and made fully aware of the nature of his disease to allow them to be prepared for the disease trajectory and course of the disease treatment, and to face the adversities effectively.[1,17] The act of withholding information is maleficent and affects the patient autonomy and beneficence.[17,18] On the contrary, it is accepted to be beneficent to discuss the treatment options and allow the patient to choose.[19]

In principle, a doctor should ideally follow the principle of autonomy in accordance with good clinical practice with the recommended evidence-based treatment.[1,17] Some doctors often adopt a paternalistic attitude toward the diagnosis and treatment of patients and feel that the person who is ill does not have much role in treatment decision.[20] It was only in the recent past that physicians have begun to accept the importance of patient's autonomy.[20–22] Even today, physicians from the India are hesitant to break the bad news [23] and have reluctance to allow individual autonomy. This is common in several Asian societies that believe autonomy is more collective rather than being individualistic.[24–26]

Technically, accepting autonomy would mean that the physician and the patient would become partners in arriving at choices and decisions in the planned treatment and the schedule.[21] In this, the physician dons the role of teaching their layman patient to make logical decisions and must encourage and motivate them to make the right choices.[27] The "Autonomy" provides patient with their individual prerogative to the knowledge of their disease, its prognosis, the treatment choices, their benefit, ill effects, and costs.[22] This is especially important when a critical decision needs to be arrived at with regard to choosing complex treatment.[28,29]

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At times, when the doctor upholds patient's right to autonomy, he may also have to face the distressing challenge of watching the patient make erroneous decisions like choosing anecdotal alternative treatment or refusing treatment.[30] The important aspect here with is that the treating doctor will have to devote sufficient time to help and guide the patient and their family member with provision of care that is standard, cost-effective, and individual specific.[31,32]

Clinically, the right of the patient to make decisional control preferences is a major predictor of patient satisfaction and the doctor must actively assess a patient's decisional control preferences to ensure optimal communication and patient satisfaction.[16,17] For the treating doctor, this is an important aspect as this paves the way for a fruitful conversation and for arriving treatment decisions through discussion.[16,17] Reports also suggest that the educated patients desire more information than patients with less formal education [15,33] and that they value doctor's ability to provide sufficient details with emotional, structural, and informational support.[34] Also, patients who prefer to be active in decision-making during illness want more information about their illness and sequelae during and after the treatment.[19,27] On the contrary, studies by Ghoshal et al[16] have also shown that patients affected with advanced cancer prefer passive decisional control, where the family members make decisions on their behalf.[16] In the subsequent sections, the ethical dilemmas faced by oncologists in breaking the various bad news in oncology are addressed:

Initial Diagnosis

The disease cancer is associated with severe apprehensions, and reports suggest 50 to 90% of the patients expect a full disclosure,[35] and under these circumstances, the way the bad news is broken assumes importance. Historically, breaking the bad news was seldom done and the accepted practice was to withhold information from the patient as it was believed to be in their best interests.[36,37] However, in the recent past, most doctors and professionals share information with the patient along with their family caregivers. In most instances, the physicians break the bad news either directly to the patient or to the family member or the patient's caregiver with utmost sincerity and empathy.[38] Precisely at this stage, the doctor becomes a witness to shock, denial, rage, dismay, fright, acceptance, and sadness, intertwined with confusion and distress that culminate in heartbreaking emotions of the patient and their family members.[39] The situation is more complicated when breaking the bad news is about a child or when the individual is the sole bread earner with children and family to support.[8]

In India, at most times some family members exercise their right to autonomy and request the doctors to keep the diagnosis a secret from the patient citing psychological breakdown of the patient or fear of inflicting self-harm and suicide.[15,16] At this stage, most doctors and healthcare professionals find themselves at crossroads unable to decide whether they should follow and honor the patient's right to confidentiality, or if they should not disclose the information to the patient in accordance with the family's wish.[8] Under these situations, the treating doctor will have to assess the mental condition of the patient, ascertain the situation, and carefully divulge the details and the extent of information on cancer to the patient without breaking hope in an empathetic manner. Also, at times in certain cases, the doctor may have to answer questions like "*Why me*" or "*Why did this happen to my family*" presenting a difficult situation.[8]

The Transition from Curative to Palliative Treatment

In cancer, the therapeutic objective is principally to eradicate the ailment. However, at times, during the ongoing treatment, the clinical signs and diagnostic results can indicate that the patient has an aggressive refractory cancer and the planned treatment is not as effective as previously observed in other patients and expected to be. At this point, and more so when there are no alternative effective modality/regimen available, the treatment objective shifts from curative to palliative care. For the treating physician and the associated healthcare staff taking care of the patient, this is an extremely difficult situation and emotionally demanding.[40] This is principally because, during the course of the treatment, a bond would have developed between the patient, their family, and the healthcare workers, and the realization that the patient's health condition is plummeting is difficult to express for the treating doctor.[8]

When Cancer Has Recurred or Metastasized after Curative Treatment

The third and one of the most difficult situations for any doctor is to tell a cancer survivor treated long back that cancer has recurred or has spread to distant organs.[8] From the patient's and their family's perspective, the curative treatments are associated with severe immediate and long-term side effects and the patient endures it with the hope of living for self and their loved ones. With time, the intrinsic resilience and coping skills help the individual recuperate. Also, a strong support system and love from the family and the community help in reducing the ill thoughts and reintegrate the survivor back into society. Breaking the bad news that cancer has resurfaced triggers flashback memories of painful events endured by the patient and their family members during the initial curative treatment and informing the bad prognosis to the patients and their family members is distressing.[8]

End of Life Situation

The end-of-life situation, which by definition *"is the last few days or hours in a patient's life,"* is very tumultuous and draining to the family.[41–44] In most cases, the common symptoms seen include fatigue, pain, dyspnea, lack of hunger and thirst, delirium, drowsiness, short attention span, respiratory secretions, confusion and delirium, sudden movement or jerking of the body, labored rapid or hard noisy breathing,

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sounds of groaning or moaning indicating progressive decline in patient's health.[41,44,45] A patient whose death is imminent will require medication to mitigate the ill effects and provide comfort and have a less suffering death.[42,43] Morally, at this point of time the healthcare workers will have to also focus on supporting the family members, help them understand the progressive trajectory of the disease, and to expect death of their loved one anytime soon.[42–45] The healthcare team has to also support and honor the patient's treatment preference and worse at times make decisions on withholding or withdrawing life-sustaining treatments.[41,45] For the healthcare workers, these are very distressing and breaking the bad news of imminent death is a difficult task.

Breaking News of Death to Bereaved Relatives

Death, although an indispensable fact of life, is very difficult for the loved ones of the deceased to accept.[46] For the treating doctors, it is very difficult to convey to the family members that their loved one has succumbed to the ailment.[46] The problem is severe especially when the death is sudden than when expected. On a relative grade, in oncology breaking the news of death is not that stressful as relatives are aware of the serious nature of the illness and death is anticipated in advance.[47] However, there are instances in oncological setups where breaking news of death can be extremely difficult especially when the patient is a child, or when the family bonding is strong with the deceased individual. In these situations, the relatives of the deceased patient are sensitive and the atmosphere is emotionally charged and use of any unsympathetic callous words and neglect on the part of the treating doctor or by the healthcare staff can cause severe grief response.[46,48] Worse such instances can trigger angry action, maladjustment, violence, and vandalism against the staff and the hospital.[46,48] From a treating doctor's perspective such situations are extremely difficult. In these situations, the professionalism, empathetic communication, and the rapport the treating doctor has developed with the patient's family play a vital role.[49] In addition to this, facilitating the bereaved family to carry out the cultural and religious procedures always has a beneficial and long-lasting opinion of gratitude and appreciation toward the treating doctor and the hospital.[50,51]

Cancer during Pregnancy

Pregnancy brings joy, happiness, and satisfaction not only to the couple but also to the extended family. Reports suggest that malignancies during pregnancy are extremely rare and accounts to 0.07 to 0.1% of all cancer.[52] Of all cancers, the most common malignancies reported in pregnant women are cancers of breast, cervix, ovary, melanoma, lymphomas, and leukemia.[52–54] The ethical issues that arise in the process of care of the pregnant woman with cancer are extremely challenging because both chemotherapy and radiation, the two important modalities, are cytotoxic and can irreversibly affect the fetus.[55,56] Clinically, emphasis is to provide the best possible cancer treatment by minimizing harm to the fetus and planning safe maternal and neonatal outcomes. In this regard, factors like the gestational age of pregnancy, site and stage of the cancer, the planned treatment and its impact on the pregnancy need to be critically analyzed before initiation of the treatment.[57] The oncologists will have to coordinate with obstetrician and pediatrician, and have detailed discussion on proposed treatment considering the mothers and child's well-being.[57,58]

Clinically, if the fetus is above 36 weeks in age, delivery of the child is facilitated through normal process or through cesarean section, while if it is below 24 weeks, abortion may be required. These decisions that are based on tumor board discussion will be decided on the basis of the site and tumor prognosis and on the necessity for treatment intervention. Attempts are will always be toward saving mother and the child, while when faced with the inevitable choice of only one, the woman's life is the priority. Chemotherapeutic agents are mutagenic and teratogenic and can affect the fetus. Hence, there is a conflict of interest for use of chemotherapy in a pregnant patient. Although very rare, for the oncologists, breaking the bad news to a couple expecting their baby and in worse case scenarios that the baby may need to be aborted is an extremely difficult choice to make.

Body Disfigurement

Cancer surgery causes body disfigurement and this is observed in people affected with head and neck, breast, cervix, and penile cancer.[59] Performing partial or extensive excision of the organs to eliminate the cancer causes limited or severe functional and cosmetic changes and adversely affects the quality of life.[59] On a comparative note of all organs, the disfigurement of the head and neck has been extensively investigated and severely affects the functional efficacy of the oral cavity and also alters the facial appearance.[59] To support this, studies have shown that body image concerns should be ascertained before surgical intervention in oral cancer patients as disfigurement induces psychological stress and depression, and the patient and their family members should be aware of it in the initial stages and take part in discussion process [60]

With regard to breast, cervix, and penis, the surgical excision can help achieve complete cure when the cancer is localized and in early stage.[61–64] When compared with oral/head and neck cancer, the disfigurement is not visible. However, disfigurement in these organs can affect sexuality and this can severely hamper the psychological well-being, the sexual, and marital life, especially in the young cancer patients in the reproductive age group. This is ethically a very sensitive issue for the treating surgeon and factors like the age of the patient and socioeconomic factors during the breaking of the bad news can further complicate/aggravate the dilemma.

Fertility and Sexuality Issues

Cancer modalities like chemotherapy and radiation affect the rapidly proliferating normal tissues like the germinal

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epithelium and cause premature ovarian failure and azoospermia in females and males respectively.[65,66] In the past, main focus had always been on saving the life of the patient, and issues like loss of fertility were never considered.[67] The recent advances in oncological diagnosis and effective treatment have increased the disease-free condition for many cancers especially when detected early and the tumor is localized and in early stage.[67] Also, in recent years due to increased awareness and screening, the incidence of cancer being detected in people in the reproductive age group is high.[68] The early diagnosis and effective treatments have increased the patient survival and procreation and children of their own are desired by many cancer survivors with disease-free and good health condition and in the reproductive age group.[67–69]

In the recent past in the developed countries, "Oncofertility" has been gaining importance and fertility preservation like oocyte vitrification and sperm banking for female and male cancer patients is undertaken before start of cancer treatment.[69–72] However, the concept of fertility preservation is yet to gain acceptability and implemented throughout India. Worse there is no insurance coverage for oocyte or sperm preservation and this affects the patients and their family members. Under these situations, chemotherapy is initiated without preserving the gametes. For the treating doctor, it is very demanding situation to express the oncofertility issues to the parents of children and to young adults of reproductive age planning family.

Cancer Treatment-Induced Health Complications

In the recent past, cancer treatment-induced long-term side effects are being documented principally because the advancement of oncological treatment has increased the disease-free condition and survival in many patients.[73] Most of the side effects observed are understood to be specific to the treatment modality and the drug used for the curative regimen.[73] In cancer survivors, these side effects appear months or years after the completion of the treatment and present an additional health risk to the survivor. Some of the important long-term side effects include chemotherapy (-Herceptin/doxorubicin/ daunorubicin/ epirubicin/ cyclophosphamide), radiotherapy-induced heart problems, drug (bevacizumab/sorafenib/sunitinib)-induced hypertension, chemotherapy (bleomycin/carmustine/methotrexate)/radiotherapy-induced lung damage, drug (cisplatin)-induced kidney damage, and drug (chemotherapy, steroid medications, hormonal therapy)-induced osteoporosis.[73]

In addition to this, cancer treatment can induce metabolic syndromes like central obesity, dyslipidemia, hypertension, and insulin resistance in higher incidence in childhood cancer survivors and people with improved survival and disease-free conditions.[74] Also when compared with the general population, cancer survivors are at higher risks of cardiovascular events.[74,75] In cancer survivors who are disease-free, the development of these health issues adversely affects their quality of life and also causes severe financial toxicity. For oncologists, breaking the bad news of the development of long-term cancer treatment-induced side effects and addressing cancer survivor's apprehensions is difficult. This is principal because the oncologist is aware of the ordeal the patient has gone through and the statement "*why me*" and "*why this now*" has a colossal impact during breaking the bad news.

Conclusions

The current review attempted at presenting the difficulty healthcare workers and oncologists working in cancer care face in India especially with breaking the bad news. The review is based on an in-depth study performed with various groups of healthcare workers in both oncological and non-oncological settings for the past 5 years. The most important problem was with regard to handling emotions of not only the patient but also of the doctors and other healthcare workers. Gauging the reaction of the patient amid response would compromise the veracity principle, by taking the easy way out. Handling familial pressures and vagaries of treatment can lead to complications further, inciting problems. Such important issues were left to the hidden curriculum, forcing the medical fraternity to grapple with their imitable manners, which have antecedent risks. We emphasize that a structured training program that focuses on breaking the bad news through dyadic and triadic communication skills is necessary. Also, it is recommended that efforts should be directed toward improving the communication skills of healthcare workers and residents. Also, it is strongly recommended that structured training programs should be included mandated in the healthcare curriculum as this training will help in the effective handling of ethical issues.

Conflict of Interest
None declared.

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Palliative Care: From Global to Local Needs

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Ind J Med Paediatr Oncol 2022;43:233–235.

Abstract

Palliative care (PC) is a comprehensive approach that focuses on improving the quality of life of patients and families that face fatal diseases by optimal minimization of suffering. Seventy-eight percent of patients who benefit from palliative support live in low-and-middle-income countries, where the access to these services is limited. Six percent of the patients are below the age of 15. The aim of this study is to review briefly the history of PC and its global challenges and indicate its impact and barriers in the Dominican Republic. A literature review in PubMed and analysis of the history of impact globally of PC and a remark of Dominican Republic local program. Some of the identifiable barriers are the limited support from authorities and health systems, the discomfort of healthcare staff in providing PC, the lack of knowledge, as well as experience, and team support. Not only do low-and-middle-income countries face these challenges, but also globally there is an urgency of the integration of PC services to the different healthcare systems to improve quality of life. This was experienced in the Dominican Republic when the first PC program started in 2012. Currently, local efforts are being made to increase the impact of the program and to make it accessible to more patients and families.

Keywords
- palliative care
- global
- children

Introduction

In general, when the term "Palliative Care" is heard, the thought is usually focused on cancer patients, patients with a noncurable disease, or those on their deathbed. When this term is used for a child, the impact is more dramatic.

Globally, there is an enormous need to help, prevent, and relieve unnecessary suffering worldwide by reducing the disparity in access to pediatric palliative care (PC) and pain control. Around 78% of people in need of PC live in developing countries. Here, continued access to essential supportive medicines for pain control is not available. PC is globally recognized as a legitimate component of healthcare. It effectively improves the quality of life (QoL) of adults and children and should be a central feature of all good clinical practices.[1]

Remarkably, 6% of the requirements of PC are for children under 15 years old. This is a global concern as 27% of the world population is under the age of 15. In most parts of the world, it has been estimated that ~7 million children around

DOI https://doi.org/10.1055/s-0042-1748800.
ISSN 0971-5851.

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the world will need children palliative care (CPC) each year. CPC has a poor profile and often it is inaccessible to those who need it.[2–4]

Discussion

Historically, when we analyze the evolution of the concept of PC, until 1980, the World Health Organization (WHO) did not officially incorporate the concept of PC as a part of the "Cancer Control" program. Fifteen years later, in 1995, the Pan American Health Organization also officially incorporated it into its assistance programs.

It is essential to observe that these approaches focused solely and exclusively on patients with malignancies. In 2002, the WHO published a proper definition of this concept: active and comprehensive care of patients whose disease does not respond to curative therapies. Without a doubt, an advancement and increase in accessibility of the approach were observed; but in reality, institutions and clinical teams still continue to limit palliative care to noncurable and terminal patients.[5]

Over time, acceptance to consider dialogue between the different stakeholders like clinical caregivers (palliativists, algologists, psychologists, nursing team members), social workers, health administrators, health authorities; interdisciplinary analysis of applicability of PC in different regional settings; and the scope of PC were expanded. Currently, the WHO understands PC as the comprehensive approach that improves the QoL of patients and families that face diseases associated with life-threatening conditions through the prevention and relief of suffering, the early identification of stressful symptoms, the impeccable evaluation as well as treatment of pain with other physical, spiritual, and psychological problems.[6]

In 2014, the first global resolution on PC was issued, urging WHO and all member states to improve access to PC as a central component of health systems emphasizing on primary health care. The WHO recommended strengthening PC programs by:

- Integration into all relevant global disease control plans and health systems.
- Develop guidelines and tools to be integrated into all disease groups and levels of care for addressing ethical issues related to comprehensive PC.
- Improving access to pain and symptom management medications.
- Promote greater access for children (in collaboration with UNICEF).
- Direct financial resources to develop programs and research on the topic, especially in countries with limited resources.

However, healthcare professionals, including pediatricians around the world, despite its importance and benefits, find several significant barriers for the early integration of PC in the disease trajectory. Healthcare providers often find it challenging to provide proper support due to barriers such as prognostic uncertainty; time constraints; discomfort of healthcare staff in providing PC; lack of knowledge, experience, and team support.[7–9]

Palliative support begins when a life-threatening illness is reported and continues throughout the disease regardless of whether the treatment goal is curative or noncurative. It is essential for the management of chronic and severe conditions. It is imperative to emphasize that PC is no longer only advised for terminally ill patients; it can also be offered as support and as a complement to all patients with the intent of curative treatment.

Global Challenges in Numbers

It's important to highlight that most children (78%) in need of PC live in low- and middle-income countries.[10] In addition, Latin America has one of the highest percentages of children in need of oncologic, pediatric, and PC.[11,12]

Forty million people need PC yearly. Out of these, 20 million need PC at the end of their lives; 18 million die in pain due to lack of access to required pain medications; 78% of those who need it live in low-and- middle-income countries; 69% of patients who need it are people over 60 years old; 6% of the requirements are for minors aged under 15 years old. Fifty-five billion people do not have adequate access to pain medication. Only in 8.5% (20 countries) PC is integrated into health systems; more than a third of the world (42%) does not have access to PC. Only in 14% countries, terminally-ill patients had their PC needs met.[13]

Local Pediatric Palliative Care Experience in Dominican Republic

There are four leading entities for which a child can and should receive pediatric palliative care: Cancer, cystic fibrosis, progressive metabolic, and neurological disorders. In January 2012, in the Dominican Republic, the first palliative program with an oncopediatric approach in the country was created in the Onco-Hematology Unit of the Dr. Robert Reid Cabral Children's Hospital, the largest tertiary childcare center in the country. So far, specialized care has been provided with exclusive attention to terminal patients, palliative interventions for clinical and psychosocio-emotional stressing situations, as well as palliative-oncological follow-ups with outpatient consults. These consults focused on topics such as refractory disease to the first- or second-line treatment, metastatic disease with added psychosocial danger factors, or recurrent disease with a nonviable curative therapeutic option, among others.[14,15]

In the Dominican Republic, various barriers have been identified in the implementation of PC such as over demand for services, lack of health insurance coverage mainly among the most vulnerable sectors of society, even more so with catastrophic illnesses, the increase in migration over the past years, the absence of hospice care, and limited access to high-cost medications such as opioids. In educational terms, it is important to highlight the absence of formal local education

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and the low interest of clinical teams in the applicability of palliative support due to taboo concepts, misinformation, and fear of the use of opioid drugs.

The Oncology Unit of the Dr. Robert Reid Cabral Children's Hospital has been characterized as offering holistic support and a palliative approach to all children diagnosed with cancer. These children benefit from comprehensive care and symptom management, which has a "zero tolerance to pain" policy through interventions guided by "WHO international therapeutic guidelines" and protocols adapted to local needs of available drugs including the rational and responsible use of opioids. This vision and project have also been started at National Cancer Institute Rosa Emilia Sánchez Pérez de Tavares since 2016.[15]

Conclusion

Undoubtedly, PC for children is growing around the world; all regions have been developing and advocating for CPC services, recognizing them as a fundamental human right. A lack of CPC availability for children is not acceptable.

Countries should continue learning from each other for improvement, such as the timely referral, appropriate pain management, and end-of-life interventions for a child, creating a pediatric hospice, and improving the follow-up sessions for the bereaved family. There is a need to continue to strive for access to quality PC for children worldwide as well as support and empower those working to provide quality CPC services.

Neither children nor their parents should face the disjunctive of choosing a curative or palliative perspective; they should obtain both approaches concomitantly. Ministries of health, hospitals, healthcare institutions, principally from low- and middle-income countries, should integrate PC into the regular health approach of pediatric patients in sustainable ways, by strengthening healthcare systems, providing financial protection, and contributing to universal health coverage. All these steps are necessary to ensure that all children have access to these services when they need it; through advocacy this can become real. It is time to offer children access to a better quality of life globally.

Conflict of Interest
None declared.

Acknowledgment
None.

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A Cross-Sectional Study of Unlocking Childhood Cancer Services during COVID-19 Pandemic: A Pediatric Oncology Tertiary Care Center's Experience from a Developing Country

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Ind J Med Paediatr Oncol 2022;43:236–240.

Abstract

Introduction The global coronavirus disease 2019 (COVID-19) pandemic has made the provision of cancer care services a challenging task all over the world, even in developed countries. Multiple studies have already reported increased rate of diagnostic delays, interruptions in radiotherapy and chemotherapy administration, and shortage of health care personnel to deliver these services.

Objective The aim of this study was to analyze the impact of strategies used to deliver uninterrupted childhood cancer services at our center during the COVID-19 pandemic.

Materials and Methods This is a cross-sectional study of the children less than 18 years of age admitted at our center between March 2020 and September 2021 to assess the effect of strategies adopted to provide uninterrupted cancer services during the COVID-19 pandemic. All the children with cancer who were managed during the study period were included in the study. The children who had treatment interruptions/lost to follow-up prior to onset of COVID-19 were excluded from the study. The primary outcome was to measure the effect of COVID-19 on delivery of cancer care services. The secondary outcome was to assess whether the strategies followed at our center helped to reduce diagnostic delays or loss to follow-up during the COVID-19 pandemic.

Results Out of total 1,490 admissions, 199 children were managed during the study period. Among the 199 children managed, 124 of them were newly diagnosed, 75 had ongoing treatment, 16 children relapsed, 13 children received palliative care, and 6 families were lost to follow-up. Out of 1,471 tests done, only 16 children and 6 caregivers tested COVID-19 positive during routine screening. Thirty-five underwent surgery and 23 received radiotherapy during this period. Among 199 children, 143

Keywords
- lockdown
- interrupted childhood cancer care services
- multilevel supportive care model

DOI https://doi.org/
DOIPM: Please provide article history dates..
ISSN 0971-5851.

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(71.8%) received financial support for hospital expenses, 23 (11.5%) received travel support, 20 (10%) were provided free accommodation, and 15 (7.5%) received home delivery of oral chemotherapy and pain medications. A total of $86,989.05 was supported for diagnostic investigations, COVID-19 testing, chemotherapy, and supportive care; $1,144.90 for travel support; and $17,010.94 was waived off by hospital administration to support the poor families.

Conclusion The shared care model, support from nongovernmental organizations and hospital administration, and utilization of local resources productively and effectively helped to avoid diagnostic delays and treatment interruptions, and provide uninterrupted pediatric cancer care services at our center.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has disrupted the provision of health services and created unprecedented challenges for children with cancer in getting safe and effective cancer-directed therapy all over the world, even in developed countries. With initial reports suggesting that people with comorbidities had poor outcomes, we expected that children with cancer would develop severe disease and have adverse outcomes.[1] This complexity was potentiated by major void in the access to and availability of treatment facilities, and financial constraints due to lockdown.

Childhood cancer is highly curable when promptly diagnosed and appropriately treated. Interruptions in treatment delivery or compromise of intensive therapies are expected to result in treatment failure and increased rate of relapses. But it is also known that viral infections are associated with increased morbidity and mortality in these immunocompromised children. So, at the onset of pandemic, while the treating physicians were outweighing the risk versus benefits of continuing cancer treatment in such an unpredictable scenario, equally worrying were the concerns about dropouts due to travel restrictions, loss of employment, and increased cost of cancer treatments. Hence, we developed strategies anticipating these issues to continue our pediatric cancer care services uninterrupted, and to restrict the diagnostic delays and treatment interruptions to the minimal. We studied the effect of these strategies on newly diagnosed as well as children with ongoing treatment during COVID-19 pandemic.

Materials and Methods

This is a cross-sectional study of the effect of COVID-19 pandemic on delivery of pediatric cancer care services at our center. All children aged less than 18 years with cancer who were admitted at our center between March 2020 and September 2021 were included in the study. Details of age, gender, primary diagnosis, disease status at the time of admission, native place, distance traveled for treatment, travel expenses, and place of accommodation during treatment were collected. Additional details about COVID-19 positivity rate, dropouts, duration of treatment interrupted due to multiple factors, and failure of initiation of treatment after diagnosis were collected. All the children with cancer who were managed during the study period were included in the study. The children who had treatment interruptions/lost to follow-up prior to onset of COVID-19 were excluded from the study. The primary outcome was to measure the effect of COVID-19 on delivery of cancer care services. The secondary outcome was to assess whether the strategies followed at our center helped to reduce diagnostic delays or loss to follow-up during the COVID-19 pandemic.

Statistical Analysis

All analyses were performed using *Statistical Package for the Social Sciences* software version 20.0. The missing data were addressed by complete case-wise analysis or list-wise deletion.

Results

Out of total 1,490 admissions, 199 patients were managed during the study period from March 2020 to September 2021. The demographic details of the children are provided in ►**Table 1**. Among the 199 cases, 124 (62.3%) were newly diagnosed and 75 (37.7%) had ongoing treatment. Thirty-five children (17.5%) underwent surgery and 23 (11.5%) received radiotherapy during this period. Sixteen children relapsed (8%). Thirteen children received palliative intent treatment with supportive care without cancer-directed therapy during this period. Eleven children (5.5%) died either due to progressive or refractory or relapsed disease condition during study period. Among 199 patients managed, only 6 (3%) were lost to follow-up. Among the 124 newly diagnosed, only 4 (3.2%) of them did not initiate treatment. Among 1,471 tested, only 16 children (1%) and 6 (0.4%) of the caregivers were found to be positive for infection. All of them were asymptomatic and recovered uneventfully. Among the 16 COVID-19 positive cases, 3 were newly diagnosed acute lymphoblastic leukemias and they were initiated on induction phase after 1 week. The remaining 13 children had a treatment interruption of 10 days. Among the health care providers who were exclusively posted in pediatric oncology unit, only two nursing staff and one doctor became COVID-19 positive and all of them recovered uneventfully. Among 1,490 admissions, 97 were for febrile illness and all of them were found to be negative for COVID-19 infection.

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Table 1 Details of admissions during the study period

Variables	$n = 199$	%
Gender		
Male	108	54.3
Female	91	45.7
Age group (years)		
<1	30	15.1
1–5	69	34.6
5–12	63	31.7
>12	37	18.6
Distance traveled (km)		
<25	61	30.6
<100	39	19.6
100–500	38	19.1
500–1,000	37	18.6
>1,000	24	12.1
Total admissions	1,490	
Leukemia	770	52.0
Solid tumor	720	48.0
Newly diagnosed	124	
Acute leukemia	39	31.5
Solid tumor	85	68.5
Ongoing treatment	75	
Acute leukemia	48	69.6
Solid tumor	27	30.4
Relapsed	16	
Acute leukemia	8	50.0
Solid tumor	8	50.0
Death	11	
Acute leukemia	6	44.4
Solid tumor	5	55.6
Lost to follow-up	6	
Acute leukemia	2	33.3
Solid tumor	4	66.7

Twenty-four families had traveled more than 1,000 km and 37 families had traveled more than 500 km for the sake of their child's treatment. A total of $4,464.96 was raised by individual contributions toward treatment of these children. Among 199 children, 143 (71.8%) received support for hospital expenses, 23 (11.5%) received travel support, 20 (10%) were provided free accommodation, and 15 (7.5%) received home delivery of oral chemotherapy and pain medications. The details of financial assistance are provided in ►**Table 2**.

Discussion

The COVID-19 pandemic, the resultant nationwide lockdown, travel restrictions, and financial constraints, all have led to disruption of cancer care services all over the world. The very high infectivity rate and mortality rate during first wave and uncertainty regarding duration of pandemic have further complicated the family's social and psychological fears and added to their hesitancy in accessing appropriate care. Thus, the indirect effects of COVID-19 pandemic strained the health care systems and created barriers for the care continuum of the children with cancer.

But the consoling facts were that asymptomatic COVID-19 infection among pediatric patients was as low as 2.5% and most children did not need admission for infection.[2]

Though it was presumed initially that children with cancer would be at an increased risk of acquiring COVID-19 infection and develop severe form of the disease like any other viral infections in immunocompromised conditions, but within few months of onset, worldwide data have confirmed that children are less affected and COVID-19 infections in children with cancer are usually mild or asymptomatic and they recover without much interventions.[3]

At the same time, key stakeholders in treatment of pediatric cancer released consensus statements recommending continuation of standard care in the diagnosis, treatment, and supportive care whenever possible and discouraging elective modifications in cancer-directed treatments.[4]

Ours is a tertiary care center catering to around 100 to 125 new patients per year and we provide chemotherapy to families coming from various economic strata.

During this COVID-19 pandemic, although routine elective inpatient and outpatient services were closed at our center, oncology, perinatal, radiation oncology, emergency, intensive care, and dialysis services were continued. So, when we had decided to continue pediatric cancer care services, the next herculean task was to support families, anticipating their difficulties in accommodation, travel, and financial resourcefulness during the treatment, and also to reduce the risk of COVID-19 infections both for patients and the health care team. Hence, we formulated a multilevel supportive care approach to help the families manage the

Table 2 Details of financial support

Variables	Amount supported (US $)
COVID-19 testing, diagnostic tests, metastatic evaluation, chemotherapy, and supportive care (blood products, antibiotics, antifungals, and antivirals)	86,989.05
Travel support	1,144.90
Waiving off hospital fees	17,010.94

Abbreviation: COVID-19, coronavirus disease 2019.

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financial toxicity and help them in all possible ways so that they could continue their child's treatment with minimal risk to families as well as the health care community.

• **Tiara Haemophilia and Cancer Foundation**: The primary nongovernmental organization (NGO) that supports the cancer treatment of poor children at our center agreed to sponsor for the COVID-19 testing and supportive care in addition to supporting the diagnostic tests, metastatic evaluation, and chemotherapy drugs. They have supported a total amount of $67,808.66.

• **Golden Butterflies Children's Palliative Care Foundation**: An NGO that provides palliative care, counseling, medical aid, and financial assistance to families with children suffering from chronic and incurable diseases, supported the transportation expenses for those families who had to travel from other states/districts for their child's treatment and arranged for home delivery of pain medications.

• **St Jude India Child Care Centre**: An NGO that provides safe and hygienic housing facilities and free transport to and from treatment centers, provided free accommodation in their "Home away from home" center for 18 families and arranged for free transportation from the centers to the treating hospitals.

• **CanKids**: A national NGO that provides holistic support to child with cancer and family from the point of diagnosis, through treatment, and after, arranged for home delivery of oral chemotherapy drugs and provided free accommodation for three families.

Thus, all aspects of probable dropouts—medical, accommodation, and travel expenses—were taken care of, to limit treatment abandonment. In view of additional expenditure to support these children, additional funds to the tune of $4,464.96 were generated by means of contributions from staff and students from the institution and good-hearted people all over the world.

Though COVID-19 infection in children with cancer has been mostly mild or asymptomatic, the collateral effects have dramatically disrupted the diagnosis, treatment, and follow-up of these patients, which may in turn affect their overall survival and outcomes. Italy has reported a 50% decrease in new pediatric cancer cases when compared with previous years.[5]

With hospitals catering only to COVID-19 patients, combined with lockdowns, restricted transportation, and families' reluctance to seek care, diagnostic delays and fragmented care in children with cancer have been reported in high-, middle-, and low-income countries.[6]

Graetz et al in his cross-sectional survey across 79 countries have reported that 7% of centers had a complete closure for a median period of 10 days, 2% had stopped evaluating new cases, 34% centers had treatment abandonment, and 28% had interruptions in radiotherapy.[7] Pediatric Oncology East and Mediterranean group has reported that 24% of centers restricted admissions of new cases, and delays in treatment—chemotherapy, surgery, as well as radiotherapy—were reported in 29 to 44% of centers.[8]

In contrast, Germany has reported a higher incidence of new cases across all diagnostic groups and that diagnostic processes, timeliness of diagnosis, and delivery of treatment were hardly affected during the pandemic.[9] Mukkada et al in the cohort study from 131 institutions across 45 countries have reported that 55.8% had an interruption in the cancer-directed therapy.[10] A report from Saudi Arabia has quoted 60.5% delay in the treatment received for children with cancer.[11]

To reduce the risk of infection, we strategized effective and sustainable preventive measures to prevent infections among health care workers. All children and attenders were screened for COVID-19 infection prior to admissions. Dedicated group of doctors and nursing staff were posted in oncology units and they were exempted from regular COVID-19 ward duties. The working group was divided into two groups that worked on alternate basis to minimize the risk of exposure. To prevent unnecessary exposure to asymptomatic carriers, attenders accompanying patients were restricted and only one attender was allowed to stay with the child throughout the admission period. The numbers attending out patient were streamlined and given slots to avoid overcrowding. Number of admissions per day was restricted to maintain social distancing in the wards. Doctors and nurses were strictly adhering to compliance of personal protective equipment and other World Health Organization recommended safety measures. Families were emphasized to practice standard precautions for basic and respiratory hygiene and avoid sick contacts. Children presenting with fever or COVID-19-like symptoms had separate pathways for management until they were proven to be COVID-19 negative. Survivor clinics were canceled and online consultations were arranged for children who had completed therapy and for those who had minor complaints while on active treatment. A total of 401 online consults were made. Only two of our nursing staff and one doctor acquired COVID-19 infection and all of them recovered with a mild illness.

For those children who needed less intensive chemotherapy, we developed a strategy of shared care, in coordination with the oncologists or pediatricians nearby their residence. A total of 37 admissions were arranged near their native places. Permission letters to families were issued to facilitate the travel between states.

No diagnostic delays or interruptions in radiotherapy were noted for the children managed during this period. There were no shortage of blood products or chemotherapy drugs and routine supportive care was not compromised for any child.

Families with newly diagnosed children and who were coming from long distances faced difficulties in getting accommodation nearby the treating center. So, we sought the help of NGOs who provided them free accommodation facilities and transport services. Around 24 families had traveled more than 1,000 km and 37 families had traveled more than 500 km during the lockdown period for the sake of their child's treatment. Due to the complete lockdown and nonavailability of trains and buses, families had to spend an

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exorbitant amount for transport, but the NGOs offered to support the travel expenses.

The major socioeconomic impact of the pandemic was reduction/loss of income, thereby making cancer treatment unaffordable for most of the families. With the inputs from NGOs and individual sponsors, a total of $86,989.05 was supported for chemotherapy, diagnostic/metastatic investigations, and supportive care during febrile neutropenic periods and COVID-19 testing. An amount of $1,144.90 was supported for travel expenses and $17,010.94 was supported by the hospital administration by waiving off the bed charges.

Mahajan et al have reported that shared care through an NGO CanKids, which sponsored for diagnostic, chemotherapy, radiotherapy, surgery, and supportive care, has helped 55 children with cancer from 5 different hospitals to continue their care uninterrupted from April to November 2020.[12] Seth et al have reported that strict preventive measures followed inside hospital, usage of teleconsults, treatment modifications according to the risk status of the patients, proper utilization of human resources, and involvement of NGOs for transport, accommodation, and delivery of drugs have helped them to deliver pediatric oncology services during the pandemic.[13] In a study from a tertiary care center in North India, whose patients travel around 500 km, chemotherapy was administered at home or in the neighboring hospitals by the pediatricians, thereby avoiding interruptions and long travels.[14] Balduzzi et al highlighted the importance of having clean and COVID-19 pathways for children to prevent cross-infection in the hospital.[15]

As a result of this multilayered supportive care model, we were able to cater to the needs of 124 newly diagnosed children and 75 children with ongoing treatment. The extensive financial support in the form of providing free accommodation, and sponsoring for travel expenses and chemotherapy, had helped us to maintain a lowest rate of dropouts (3%) during the study period. There were no diagnostic delays for newly diagnosed cases and no interruptions in radiotherapy were noted during the study period.

Limitations

It is a single institutional study with a small sample size.

Conclusion

To conclude, with the support from hospital administration, shared care with pediatricians, and involvement of NGOs and support groups, we can deliver uninterrupted cancer care services even during periods of crisis like COVID-19 pandemic.

Ethics

The Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research (IEC-NI/21/FEB/77/15(COVID-19)) approved this study. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1965, as revised in 2013. Informed patient consent was obtained prior to enrolment.

Funding

None.

Conflict of Interest

None declared.

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Virtual Teaching and Training Models in Pediatric Oncology: A Retrospective Study from an LMIC

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Ind J Med Paediatr Oncol 2022;43:241–249.

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Abstract

Introduction A multidisciplinary approach is essential for success in pediatric oncology treatment. Updated protocols, quality nursing care, psychosocial support, safe and standardized preparation of chemotherapy, infection control, and effective data management are key shareholders for the effective management of childhood cancer. The Department of Pediatric Oncology at Indus Hospital and Health Network (IHHN) initiated consistent teaching and trainings with the help of the My Child Matters Grant from Sanofi Espoir Foundation. These courses were conducted in person starting in 2019 and had to be postponed and restructured due to coronavirus (COVID-19) pandemic in early 2020.

Objectives The aim of this study was to determine the impact of virtual teaching models for healthcare workers employed in pediatric hematology/oncology departments in low-resource settings.

Materials and Methods After in-person courses in 2019, courses for all six disciplines (physicians, nursing, infection control, pharmacy, psychosocial care, and cancer registry) were conducted virtually starting December 2020, open to all and free of cost. A total of 878 registrations were obtained and 267 certifications given. Lectures with Q&A sessions were conducted via zoom and recordings shared through email. Each course was conducted by the relevant department at IHHN with pre- and postassessment conducted through Google Forms. Session feedback was taken through zoom polls and a comprehensive course feedback conducted after completion; e-certificates were awarded to successful participants according to a predetermined criterion.

Results A total of 434 physicians' registrations were done from around Pakistan and countries like Saudi Arabia, Malaysia, Jordan, and Canada for the online physicians' course, of which 110 received certifications after completing post-test and attendance criteria of 55%. Pharmacy, infection control, psychosocial care, and cancer registry courses saw participation and certification of 51, 41, 24, and 14 participants, respectively. Online sessions received positive feedback in terms of instructors, course content, convenience, and access from over 90% participants.

Keywords
- education
- pediatrics
- capacity building
- mentorship

DOI https://doi.org/10.1055/s-0042-1750206.
ISSN 0971-5851.

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Conclusion Due to the ease in coordinating hectic schedules and cost-effectiveness of online lectures, this virtual teaching model will persist despite the trajectory of the COVID-19 pandemic. Similar ventures aimed at pediatric oncology teaching and training are needed in a widespread manner to improve outcomes of childhood cancer.

Introduction

One of the greatest challenges that low-to-middle income countries (LMIC) face in the realm of childhood cancer is the lack of specialist pediatric oncologists, nurses, and other personnel. Over 8,000 patients are diagnosed with cancer each year in Pakistan, an underestimated figure due to lack of access to facilities and diagnosis.[1] A meager number of seven physician fellowship programs in pediatric hematology/oncology are registered with College of Physicians and Surgeons Pakistan, requiring a minimum 2-year commitment after first fellowship in pediatrics.[2] Similarly, specialized oncology training in nursing is mostly done informally instead of mandatory focused educational programs. In 2009, the first Pediatric Oncology Nurse Technician 1-year diploma was initiated by the Sindh Board,[3] but due to limited access, most nurses practicing in childhood cancer wards are unequipped in specialized skills. The difficulty of attaining a position in the limited training programs coupled with the commitment of traveling long distances to cities has led to a dire shortage of specialists in smaller urban and rural centers across the country. Despite there being roughly 13 pediatric oncology units (POUs) currently functioning in Pakistan,[1] most of these units are consequently lacking formally trained pediatric oncology healthcare teams, leading to stunted progress in capacity and quality of available care.

In line with the World Cancer Declaration drafted in 2013, nations need to focus on increasing number of training opportunities available for health professionals in different aspects of cancer control.[4] The Indus Hospital and Health Network (IHHN) was awarded the My Child Matters (MCM) grant by the Sanofi Espoir Foundation for teaching and capacity building in POUs across Pakistan in 2009. Along with oncologists, pediatricians, and nurses, theoretical and hands-on courses for clinical pharmacists, psychosocial staff, infection control specialists, and cancer registry operators have also been developed and implemented.

The coronavirus (COVID-19) pandemic provided the world of medicine with a unique opportunity to revolutionize healthcare via the incorporation of technology for education of healthcare workers and delivery of patient care. Telehealth has given medical professionals the ability to learn from experts around the world and several medical societies have made webinars and online lessons easily accessible and free of cost.[5] There are several benefits of telehealth and education in pediatric oncology care, improving patient care through advancements in clinical aptitude an virtual case discussions as shown in Brazil.[6] The objective of our initiative was to use similar virtual techniques for education and trainings and ultimately improve survival rates of children with cancer, especially in third-world countries and underprivileged areas within developed countries.

Materials and Methods

This is a commentary article on the period from January to December 2020, during which courses were conducted through purely virtual modes of teaching due to the COVID-19 pandemic. The focus of these training programs was primarily on the 10 IHHN-partnered POUs; however, registrations were open to the general public, completely free of cost. This was a major shift from the previously followed format of in-person courses requiring physical presence of individuals from each unit at IHHN Korangi Campus. After onset of COVID-19, MCM funds were redirected to improving infrastructure of POUs. Teleconferencing equipment sets (LED screens, webcam, keyboard, CPU) along with reliable and prepaid internet connections were sent to nine partnered centers, ensuring consistent participation by a larger number of staff than was possible previously.

The physicians' course was divided into leukemia, lymphoma, solid tumors, and supportive care and therapy modules with weekly sessions for 13 weeks. Nursing course sessions were biweekly for 1 month. Psychosocial, infection control, pharmacy, and cancer registry courses were held daily for 1 week each. Course objectives and content were designed by specialists from each discipline, adapted from standardized lecture series, as shown in ►**Table 1**. The target audiences for each course are also included in ►**Table 1**, with flyers and course registration forms circulated on public forums 2 weeks before starting date, as well as through unit heads and personal contacts. External, in-house, and international faculty from different institutions were engaged as specialist instructors. The MCM-partnered centers did not have specialized nurses, physicians, and other healthcare workers; therefore, all necessary basics of pediatric oncology knowledge were included as assessed by field experts at IHHN. These gaps in training were evaluated during the course of partnership under the grant.

Presentations, reading material, and recordings were emailed to all registered participants following each session along with reminders for the upcoming session. A test comprising multiple choice questions was shared with participants after completion of course as an online form. Test questions and answer keys were contributed by respective department heads after internal reviews. Test result was autocalculated and sent to participant on submission of test form. Attendance, participation, and feedback from

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Table 1 Course curriculum for all disciplines

N.	Courses conducted	Duration (h)
1.	**Physicians' course:**	
	Target: Pediatricians, junior fellows, and medical officers working in POUs	
i	Childhood cancer status in Pakistan and when to suspect Malignancy	1 hour
	Leukemia module	
ii	Approach to a child with suspected leukemia	1.5 hours
iii	Pediatric oncological emergencies; hyper leucocytosis and TLS	1 hour
iv	Blood transfusion guidelines and transfusion reactions	1 hour
v	AML, CML, and JMML management guidelines	1 hour
	Lymphoma module	
vi	Hodgkin lymphoma in children; classification, workup, and management	1 hour
vii	Non-Hodgkin lymphoma in children; workup and management	1 hour
	Solid tumor module	
viii	Approach to abdominal masses in children	1 hour
ix	Approach to brain tumor	1.5 hours
x	Approach to retinoblastoma	1.5 hours
	Supportive care and therapy module	
xi	Pain management and psychosocial support	1 hour
xii	Management of infections in immunocompromised patients	1 hour
xiii	Breaking bad news	1 hour
2.	**Nursing course**	
	Target: Nurses and students with an interest or posting in POUs	
i	Pediatric cancers, treatment, and oncological emergencies	1 hour
ii	Chemotherapy and toxicity	1 hour
iii	Safe handling and immediate complications	1 hour
iv	Procedure and CVAD	1 hour
v	Blood transfusion and reactions, nutrition	1 hour
vi	Supportive care and caring for caregivers	1 hour
vii	Survivorship and grieving and counselling	1 hour
viii	Pediatric cancers	1 hour
3.	**Pharmacy course**	
	Target: Clinical pharmacists, nurses, technicians, and other HCWs involved in chemotherapy preparation	
i	Introduction to oncology pharmacy and standards of practice	1 hour
ii	Classification of anticancer agents and potential interactions	1 hour
iii	Chemotherapy toxicity and symptoms management	1 hour
iv	Supportive care medications	1 hour
v	Use of antimicrobials in cancer patients	1 hour
4.	**Psychosocial course**	
	Target: Psychologists, social workers, and physicians involved in counselling of childhood cancer patients	
i	Basics of psychosocial care for pediatric patients	1 hour
ii	Communicating with pediatric patients and their families	1 hour
iii	Breaking bad news	1 hour
iv	Grief and trauma	1 hour
v	Self-care for professionals	1 hour

(*Continued*)

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Table 1 (*Continued*)

N.	Courses conducted	Duration (h)
5.	**Infection control course**	
	Target: Infection control practitioners and nurses	
i	Introduction to IPC program and facility assessment	1 hour
ii	Transmission-based precautions aseptic technique: concepts and principles	1 hour
iii	COVID-19 prevention and control	1 hour
iv	Environmental cleaning and disinfection: best practices in resource-limiting settings	1 hour
v	Construction and renovation in oncology unit	1 hour
vi	Safe handle of linen in immunocompromised population waste management	1 hour
6.	**Cancer registry course:**	
	Target: Childhood cancer registry data entry operators and supervising physicians	
i	Introduction to cancer registry	1 hour
ii	Introduction to ICD-O3	1.5 hours
iii	Chemotherapy toxicity and symptoms management	1 hour
iv	Supportive care medications	1 hour
7.	**Disease-specific protocol discussion sessions for physicians—Level 2**	
	Target: Oncopediatricians and fellows at partnered POUs	
i	ALL	1.5 hours
ii	APML	1.5 hours
iii	Hepatoblastoma	1.5 hours
iv	Germ cell tumors	1.5 hours
v	Wilms tumor	1.5 hours
vi	Neuroblastoma	1 hour
vii	Retinoblastoma	1.5 hours
viii	Medulloblastoma and other CNS tumors	1.5 hours
ix	Bone tumors	1.5 hours
x	LCH and sarcomas	1.5 hours

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; CVAD, central venous access device; HCWs, healthcare workers; IPC, infection prevention control; JMML, juvenile myelomonocytic leukemia; LCH, Langerhans cell histiocytosis; POUs, pediatric oncology units.

participants was used to measure outcomes. Session feedback was collected via a poll after each session and detailed feedback forms sent to students at the end of each course. Criteria for course certification were completion of the test and attendance of at least two sessions.

Following completion of the online physicians' course, disease-specific protocol discussion sessions were also conducted to create uniformity in patient approach and management among the 10 MCM-partnered institutes across Pakistan. This particular module was not open to public and focused on interactive disease-wise discussions by field experts based in IHHN to address queries from the previous course. Tests and feedback were not collected in these sessions

Limited 1-week hands-on training opportunities were also offered to individuals selected as focal persons by unit heads at IHHN Korangi Campus. Data operators, infection control practitioners, and psychologists visited IHHN in July 2021. Physicians and nursing hands-on trainings could not be scheduled due to frequent COVID-19 spikes and strenuous working schedules. This hands-on training week was used to reinforce concepts taught in theory with practical observations and practice.

Statistical Analysis

Data was collected from course participants through online forms for registration and feedback. Data was stored in an encrypted server and all identifying information of participants was kept private. Descriptive statistics of demographics was calculated on Microsoft Excel (v16.38) and plotted on graphs.

Ethics

The authors declare that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendment as of 2013 or comparable ethical standards. Ethics

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Table 2 Course-wise registrations, certifications, and test averages

	Physicians	Nurses	Pharmacists	Psychosocial	Infection control	Cancer registry
Total registrations	434	68	135	67	147	27
Total certifications	109 (25%)	28 (41%)	51 (38%)	24 (36%)	41 (28%)	14 (52%)
Partnered units	64/109 (58.7%)	22/28 (78.6%)	35/51 (68.6%)	11/24 (45.8%)	15/41 (36.6%)	13/14 (92.9%)
	Physicians	Nurses	Pharmacists	Psychosocial	Infection control	Cancer registry
Avg. pretest	23/40 (56.2%)	13/19 (68.4%)	12/15 (80%)	11/19 (57.9%)	17/30 (56.7%)	22/29 (75.9%)
Avg. post-test	29/40 (71.9%)	15/19 (78.9%)	13/15 (86.7%)	11/19 (57.9%)	20/30 (66.7%)	23/29 (79.3%)
p-Value (two-tailed)	0.001789	0.043325	0.004534	0.012372	0.000265	0.0976

exemption letter (IHHN_IRB_2022_02_009) was issued by the Institutional Review Board for this article.

Results

Primary Outcomes

The total number of participants and completion certifications awarded for the first six courses are outlined in ►**Table 2** along with test averages. Significant difference (p-value <0.05) in pre- and post-test results were seen in all courses except cancer registry on independent t-tests. The seventh course for informal protocol discussions was open to all physicians at partnered units and were not followed by formal certifications, the impact of which will be assessed through patient outcome data, such as number of annual registrations, treatment complications and reduction in mortality among others. The physicians' course had the greatest number of participants (given location-wise in ►**Fig. 1**) with multiple international registrations from countries such as Malaysia, Jordan, Ethiopia, Saudi Arabia, Canada, and Kuwait. The cancer registry course had the highest percentage of course completion with over half the participants having received certifications. ►**Table 2** highlights the number of participants who attempted the test after completion of each course and their performance. Overall, irregular attendance was observed by working professionals in most courses, possibly due to differing schedules as live sessions took place at fixed timings in the afternoon.

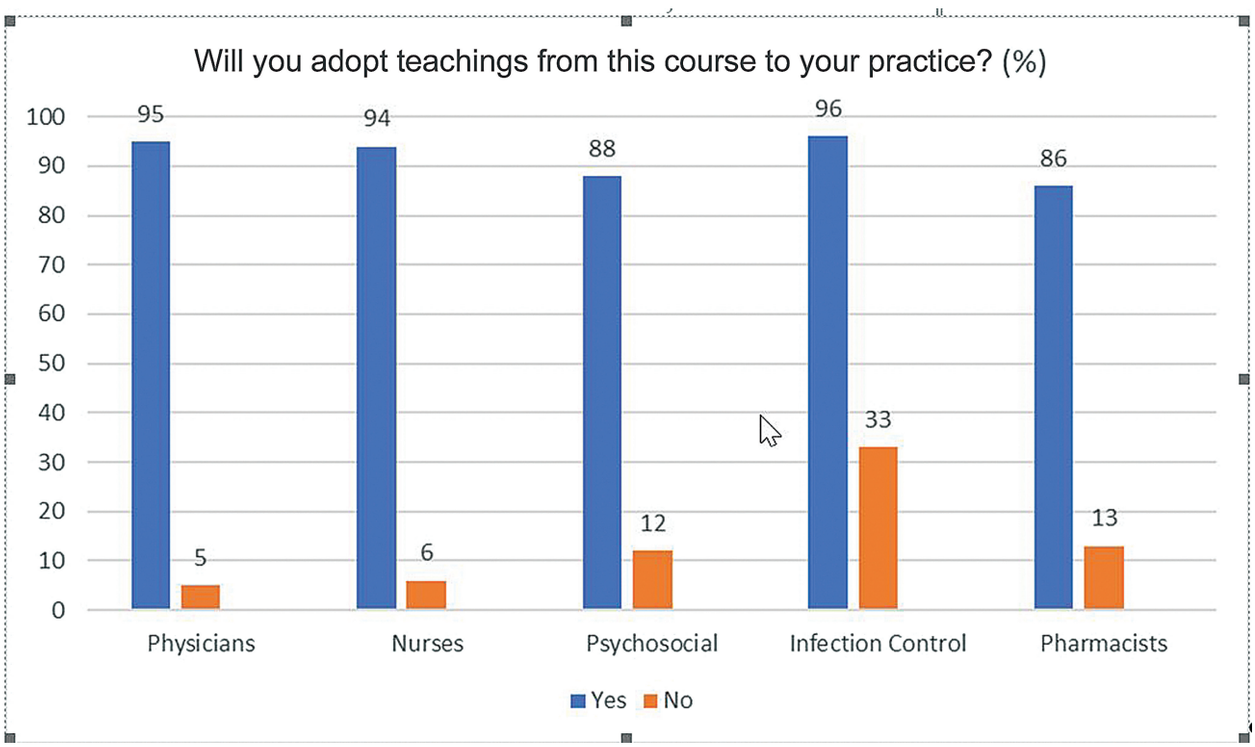

Fig. 1 Feedback responses (course teachings).

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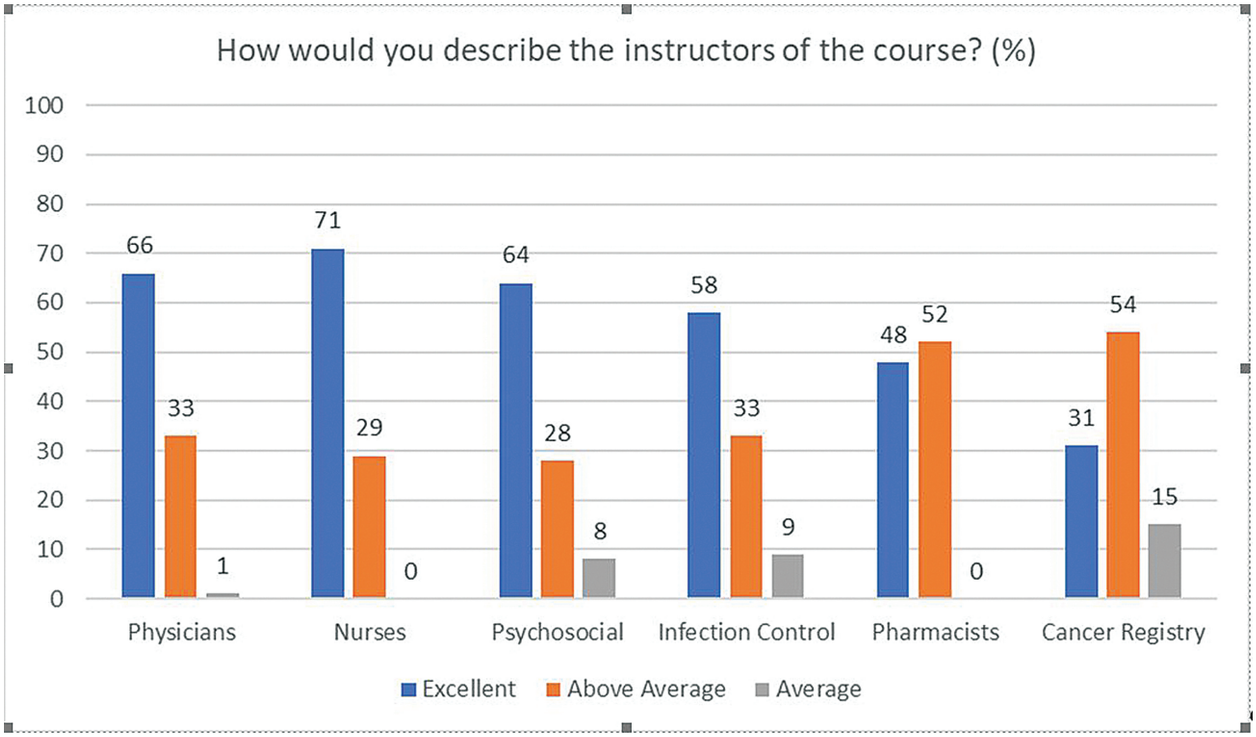

Fig. 2 Feedback responses (instructors).

A total of 267 participants were certified across all courses in 2021, out of which 253 participants filled the feedback form, containing structured questions and open-ended comments. As shown in ►**Fig. 2**, most participants reported a willingness to change their practices after attending their respective courses, emphasizing the effectiveness of online teaching. ►**Figs. 3** depicts a high satisfaction of participants with the lecturers of all courses, with all

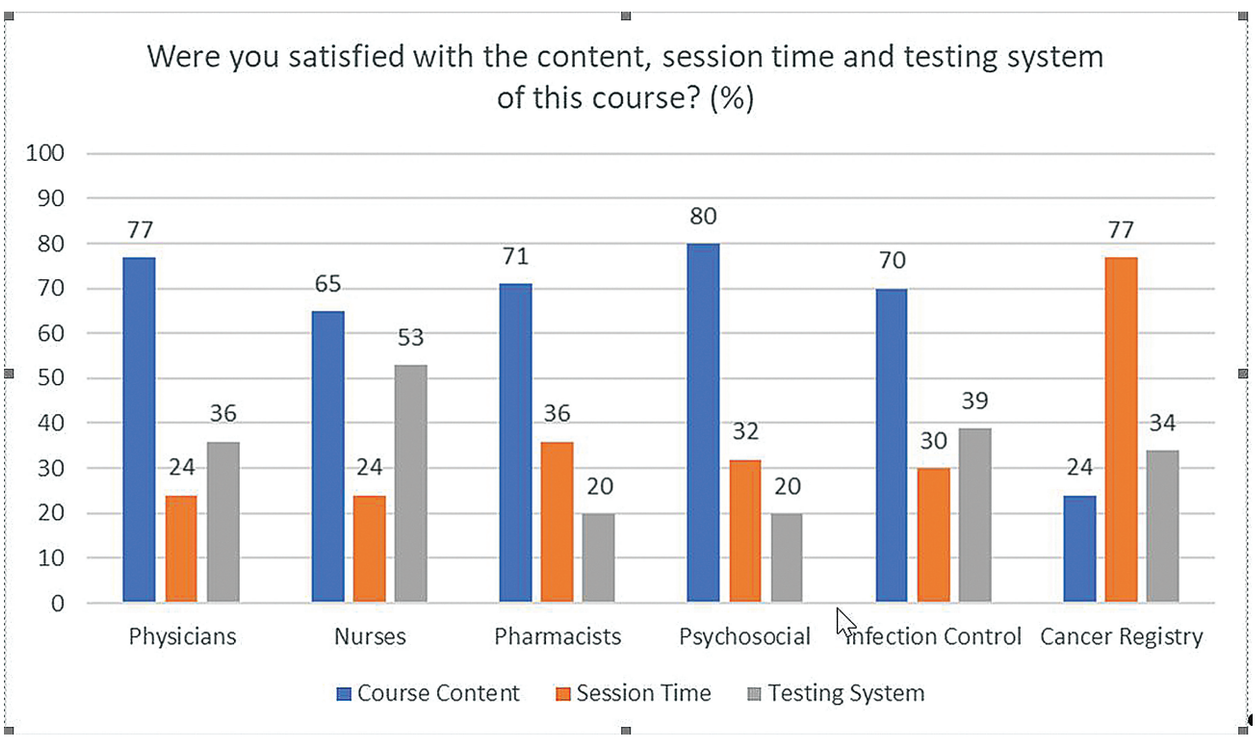

Fig. 3 Feedback responses (course satisfaction).

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participants describing their instructors as average or above.

Secondary Outcomes

A total of 10 healthcare workers (6 data operators, 1 infection control practitioner and 3 psychologists) visited IHHN after attending the online course for hands-on training. A total of 1 week of practical observations and practice was conducted for each of these participants in a multidisciplinary environment. Each of these 10 participants has stayed connected to IHHN after training for mentorship and continued guidance in their practice.

Discussion

For years, tele-education has played a vital role in providing learning opportunities for rural and remote healthcare workers.[7] However, with the COVID-19 pandemic came a global prospect to innovate and implement quality online teaching methods with willing widespread acceptance.[7] Virtual education can be described as synchronous, that is, happening in real-time through chat rooms, or asynchronous that occurs without real-time interaction through prerecorded online channels.[8] Advantages of virtual education include flexibility of schedules, efficient use of time, accessibility from any location, exposure to national, and international faculties and worldwide distribution of knowledge and resources.[8–11] For our pediatric oncology courses, a synchronous real-time teaching model was used to allow live interaction with participants. A large variety of individuals involved in pediatric oncologic care were able to connect and attend sessions from different cities and countries, saving expenditure on travel and accommodation.

The online form-based testing system was not as preferred by participants as reflected in the feedback form with only 36% (physicians), 53% (nurses), 20% (pharmacists), 20% (psychosocial), 39% (infection control), and 34% (cancer registry) satisfied with this testing method. When asked for open ended comments, most of these participants cited delays in connectivity and lack of technological expertise as reasons for this feedback. This resistance to adopt virtual teaching among participants reflects the environment prevailing in public institutes lacking resources. Most participants belonged to government hospitals and had to resort to using personal smartphones and mobile data to login to sessions.

Due to difficulty in synchronizing schedules, the convenience of the instructors was prioritized and a time slot was fixed in the afternoon. Most sessions were scheduled for 1 hour to avoid fatigue and redundancy and WhatsApp chat groups were created after each course for continued communication, mentorship, and learning. However, other than cancer registry participants, each course saw decreased satisfaction regarding session time in physicians (24%), nurses (24%), pharmacists (32%), psychosocial, and infection control (30%) courses. It was noted that the entire 1 hour was not used for teaching as coordination, mic, and slide sharing issues recurred in every session, reducing the content discussion time. Since physicians of every level were free to participate in the course, the level of questions and understanding varied, potentially contributing to the dissatisfaction with session time.

Recordings of lectures were shared with all participants immediately after the session along with the slides presented by the instructor. As techniques such as avoidance of cognitive overload and monitoring task completion times are effective in improving engagement in an online setting,[12] assessments and question and answer sessions were conducted after each module to increase participation and motivate individuals to engage in fruitful discussions. Unfortunately, increased engagement was not seen among participants as test completion rate was limited to 25% (physicians), 41% (nurses), 38% (pharmacists), 36% (psychosocial workers), 28% (infection control), and 52% (cancer registry). A possible reason for this was the lack of course fee; without monetary commitment participants did not hesitate to drop out and did not seem to prioritize the course as the organizers hoped.

Drawbacks of virtual education can be largely categorized into three groups: (1) technology and infrastructure barriers, (2) educators' barriers, and (3) learners' barriers.[11] With a drastic shift to online education, there has been an urgent need for instructors and learners to be well-versed in the use of technology. Investment in appropriate technological services is essential for teaching faculties to be well-equipped for efficient virtual learning and training and for continued education when face-to-face interactions are not feasible.[13,14] Moreover, many professionals rely on free and reliable Wi-Fi services, access to which greatly varies according to economic class, especially in LMICs like Pakistan.[7,15] A statistically significant difference has been observed between students of developed and developing countries, the former being better equipped and trained in virtual mediums of education.[16] To cater to the dearth of technological resources and infrastructure at the under-resourced public institutes partnered with IHHN, the MCM grant was used to provide teleconferencing equipment sets to remove barriers to national and international sessions for the local staff. However, despite consistent effort and assistance, many centers fall in areas where networks and connectivity remain a persistent issue causing disturbances while they attend sessions and attempt tests.

Connection with large audiences was a significant challenge for IHHN instructors. The attention and participation of individuals were difficult to gauge due to mics and cameras staying switched off, with exception of the cancer registry course that had the smallest number of participants. Many individuals claimed to have watched session recordings due to unavailability during working hours; however, there was no way to verify this. Therefore, it was decided to limit the number of participants per session for future virtual training courses.

For uniformity and improvement in targeted care, MCM centers and other institutions that look toward IHHN for mentorship in pediatric oncology services were engaged in online training sessions for specific tumor protocols. Case-

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based scenarios along with diagnosis, risk stratification, options in low-resource setting, treatments, and their complications were discussed in great detail while addressing queries from attendees. Assessment of the long-term impact of these focused sessions according to patient outcomes is currently under progress. In the face of digitalization, those who teach and have been taught using conventional, in-person methods are less familiar with virtual teaching methods and thus, more likely to face difficulties adapting.[17] In particular, laboratory-based courses, student placements, and field work have been adversely impacted and methods of assessments have required restructuring, requiring constantly learning and adjustments on the part of teachers and students alike.[18]

Online learning is particularly challenging for acquiring technical skills; for example, clinical training in medical professionals is better conducted hands-on.[16] Keeping this in mind, the focal person of each MCM-partnered unit was requested to identify key personnel in each discipline from their institutes. Select employees were offered travel and accommodation funds and invited for brief 1-week hands-on training opportunities in the infection control, data registry, and psychosocial departments at IHHN. These visits allowed better communication, practical observations, and improved execution of theoretical knowledge, while strict COVID-19 measures were observed. The aim of this process was to retain trained personnel long-term so that they can serve as trainers to other individuals once they return to their home institutes.

Since distance and in-person education both have distinct advantages and disadvantages, a middle-ground approach in the form of blended learning must be adopted.[19] Among medical and nursing students in Uganda, a 75% preference for blended learning was observed.[20] Similarly, a combination of online modules and subsequent practical assignments was proven to be successful in training medical personnel in an intensive care unit and emergency room in Germany.[21] A unique problem being faced in pediatric oncology in Pakistan is the lack of specialized training among physicians and nurses. Ranging from freshly graduated house officers and medical officers, pediatricians, medicine residents, and nurses with various certifications, most institutes have staff of diverse backgrounds responsible for childhood cancer patients. This is an additional challenge while designing teaching and training activities, further compounded by the fact that trained individuals often rotate indefinitely out of the service soon after attending the course. Since the courses for cancer registry, psycho-oncology, infection control, and pharmacy were spread over less than 12 hours, they would be considered workshops or web series rather than courses. The described courses were not certified from an educational institute, a limitation that IHHN is actively pursuing for the improvement in future courses. Despite the significant change in pre- and post-test averages seen in five courses, translation of this knowledge to patient care is a major challenge. Further studies are recommended for blended models along with innovative ways to engage and motivate healthcare workers of childhood cancer in low-resource settings.

Conclusion

Virtual teaching models will persist despite the trajectory of the COVID-19 pandemic due to their ease and accessibility. Enhancement of knowledge of healthcare workers engaged in paediatric oncology may be possible through virtual models and requires further study in low resource settings. Further studies regarding the impact of blended and virtual learning models and their effectiveness in pediatric oncology teaching and training are needed in a widespread manner to improve outcomes of childhood cancer.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
We would like to acknowledge the contribution of the Departments of Nursing Education, Pharmacy, Infection Control, Electronic Medical Records (EMR), Psycho-Oncology and Drs. Sadia Muhammad and Ghulam Qadir Pathan for their hard work to execute these courses.

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Challenges in the Management of Retinoblastoma during Nationwide Lockdown: An Observational Study from a Retinoblastoma Center in South India

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Ind J Med Paediatr Oncol 2022;43:250–254.

Abstract

Introduction The nationwide lockdown due to coronavirus disease 2019 led to travel restrictions resulting in a delay in diagnosis, treatment, and follow-up of children with retinoblastoma (RB).

Objectives We audited the impact and challenges of lockdown among RB children over 1-year period (May 2020–2021).

Materials and Methods It is a cross-sectional study of 104 children with RB, who presented within the 1-year study period. The demographic details, clinical presentations, and outcome of treatment due to lockdown were studied.

Results Of the 152 eyes of 104 children, unilateral RB was observed in 52% and bilateral in 48%, in which four children had metastatic disease and one child had trilateral RB. International classification groups D ($n = 64$ eyes, 42%) and E ($n = 38$ eyes, 25%) were in majority. Almost, half of the children ($n = 53$, 51%) underwent enucleation. Overall, the vision was preserved in 32% of the children and globe preservation in 49% of children. Eleven children (10.5%) succumbed due to disease progression. But, only five children were affected with severe acute respiratory syndrome coronavirus 2 infection. The majority of children ($n = 72$, 69%) had to travel more than or equal to 1,000 km for treatment. About 57% ($n = 60$) patients were newly diagnosed during the lockdown period and due to the travel restrictions, they had a mean delay of 2.2 months (range: 0–15 months) in starting treatment and 27% ($n = 29$) of children on treatment had an interruption of treatment.

Conclusion Multidisciplinary team management with strategies to support the RB families during locked down crisis is essential to continue care without interruptions.

Keywords
- COVID-19
- children
- retinoblastoma
- lockdown
- travel restrictions

DOI https://doi.org/10.1055/s-0042-1750204.
ISSN 0971-5851.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has created a significant void in the availability and accessibility of treatment modalities and timely intervention for children with cancer. The lockdown with travel restrictions and financial constraints has been a major cause. Furthermore, in retinoblastoma (RB) already a strong disparity exists between the delay in diagnosis, stage of presentation, abandonment, and survival in the developing and developed countries prior to the COVID-19 pandemic.[1] Despite the development of healthcare in diagnosis and treatment, 50% of children with RB in developing countries present at a more advanced stage and succumb to the disease, whereas in developed countries, it is less than 5%.[2,3] The COVID-19 pandemic has caused an additional strain on the diagnosis and treatment process of RB children. There are multifactorial reasons for treatment delay including hospital resource constraints, affordability of transport, financial constraints along with the fear among parents regarding the implications of COVID-19 rather than RB.[4,5] The major reason is the inability to reach their respective health centers leading to interruption of treatment.[6,7] Our study is to assess the challenges of the COVID-19-related nationwide lockdown on disruption of access to healthcare and its impact on the management of children with RB and the strategies we developed to overcome these challenges.

Materials and Methods

This is a cross-sectional study of 104 children with RB, who presented within the 1-year study period (May 2020–April 2021) to Sankara Nethralaya (SN) tertiary referral eye hospital in Tamil Nadu. These children were collectively managed by both the pediatric oncology unit in Sri Ramachandra Institute of Higher Education and Research (SRIHER), and SN. The demographic details, clinical presentations, initiation delay and interruptions of treatment, and the outcome of treatment during this lockdown period were collected. Initiation delay was defined as time from onset of symptoms to initiation of treatment of more than 4 weeks. Interruptions are defined as a delay of more than 2 weeks during therapy. The examination included comprehensive eye evaluation under anesthesia (EUA), ultrasonography of the eye to measure the tumor dimensions, RetCam imaging, magnetic resonance imaging of the brain and orbit to assess the optic nerve status, and presence of the primary neuroendocrine tumor. Children diagnosed with RB but continued treatment in their native place were excluded from study.

The staging was based on International Intraocular Retinoblastoma Classification (IIRC) in SN; patients were referred to the pediatric hemato oncology unit in SRIHER for staging evaluations, intravenous chemotherapy, and radiotherapy.[8] Metastatic work if needed included bone marrow aspiration and lumbar puncture for cerebrospinal fluid analysis. The treatment modalities consisted of focal therapy, intravenous, intra-arterial, intravitreal chemotherapy, radiotherapy, and enucleation as per staging after the discussion in the combined institutional tumor board. The outcome was measured based on vision salvage, globe salvage, and life salvage.

Chemotherapy regimens commonly used are of two types: standard dose VEC (vincristine, etoposide, carboplatin) for intraocular RB and high-dose VEC for extraocular RB. For metastatic and trilateral RB, four drug regimen was used: vincristine (1.5 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by cisplatin (80 mg/m^2) and etoposide (200 mg/m^2). Enucleation was performed when required. The enucleated eyes were analyzed for high-risk features, which were involvement of optic nerve, choroid invasion, anterior segment, scleral, and extrascleral involvement.

The impact of lockdown on delay in diagnosis, interruption of treatment, and outcome was studied. The reasons for treatment interruption like transport restrictions, financial constraints, and accommodation difficulty were analyzed. The residence of the RB children, the distance needed to travel to reach the treating hospital during the lockdown times, financial constraints, difficulty in accommodation during the lockdown, and the challenges faced were obtained. History pertaining to COVID-19 infection in any of the family members was obtained. The treatment outcome was measured in terms of vision salvage, globe salvage, and life salvage.

Statistical Analysis

The data collected was entered in MS Excel and the mean, percentage, and statistical analysis were performed by SPSS version 20.1

Ethics

Ethics clearance was obtained from both the institutional ethics committee (SN and SRIHER- CSP-MED/21/JUN/69/97) in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from either of the parents prior to enrolment.

Results

A total of 104 children were treated during this period from May 2020 to April 2021. This included both newly diagnosed cases and follow-up children already on treatment. The total number of children who underwent EUA was 122 in the previous year (pre-COVID-19 lockdown) and the newly diagnosed was 67 as compared with 60 during the lockdown period (May 2020–April 2021).

Of the 152 eyes of 104 children, 52% were unilateral RB and 48%were bilateral RB in which four children had metastatic disease and one child had trilateral RB. The mean age at diagnosis was 34 months (range: 1–132 months), with 52% males and 48% females. Leukocoria was the most common presenting feature (94%). Family history of RB was positive in only 7.5% ($n = 8$) (►**Table 1**). The cases were classified based on IIRC, and majority were in groups D (42%; $n = 64$ eyes) and E (25%; $n = 38$ eyes). Almost, half of the children 51% ($n = 53$) underwent enucleation. Overall, the vision was preserved in 32% of the children. The globe salvage was achieved in 49% of children, of which 29 children had unilateral and 22 had

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Table 1 Demographic and clinical details

Demographics		$n = 104$ children (%)	95% CI
Age at diagnosis		34 months (range: 1–132 months)	
Gender	Male	54 (52)	(42.3, 61.5)
	Female	50 (48)	(38.4, 57.6)
Distance needed to travel	<500 km	26 (25)	(16.7, 33.3)
	500–1,000 km	6 (7)	(1.2, 10.3)
	>1,000 km	72 (68)	(60.3, 78.1)
Family history of RB	Yes	8 (7.5)	(2.57, 12.8)
	No	96 (92.5)	(87.2, 97.4)
Laterality	Unilateral	54 (52)	(42.3, 61.5)
	Bilateral	50 (48)	(38.5, 57.7)
Vision salvage		43 (32)	(31.9, 50.8)
Globe salvage		51 (49)	(39.4, 58.7)
Life salvage		94 (90)	(84.7, 96.1)
Death		10 (10)	(3.9, 15.3)

Abbreviations: CI, confidence interval; RB, retinoblastoma.

bilateral RB. In comparison, globe salvage was achieved in 54% of children in the previous year. Eleven children (10.5%) succumbed to the disease due to disease progression.

We developed a protocol to contact the patients telephonically periodically to prevent abandonment. We also made efforts to arrange transport for families to reach the hospital with special permissions and coordinated accommodation with the help of the home-away-home program and coordinated nongovernment organizations (NGO) support for funding for invisible expenses also like food. Financial assistance for EUA, local therapy, chemotherapy, and radiotherapy treatment was completely supported by both hospitals together with NGOs. Whenever required transport and rent allowance for the extended stay during locked down were also supported by NGOs.

Majority of children, 69% ($n = 72$) had to travel more than or equal to 1,000 km for the treatment (►**Table 2**). About 57% ($n = 60$) of children were newly diagnosed during the lockdown period and due to the travel restrictions, they had a mean delay of 2.2 months (range: 0–15 months) in starting treatment and 27% ($n = 29$) of children on treatment had an interruption of treatment. Only three of our children had tested positive for COVID-19 during routine screening. When the children were positive, we withheld treatment for 2 weeks. They were asymptomatic and continued treatment after the resolution of COVID-19 infection.

Table 2 Impact of lockdown on RB follow-up

	(*n*, %)
Loss to follow-up	29, 27
Travel restrictions	18, 62
Financial constraints	8, 28
COVID-19 positivity in family	3, 10

Abbreviations: COVID-19, coronavirus disease 2019; RB, retinoblastoma.

Discussion

COVID-19 was declared a pandemic by the World Health Organization) on March 11, 2020. Following this, many countries went into complete lockdown. India declared lockdown on March 24, 2020, leading to transport restrictions and the inability to reach the healthcare facilities. Children with life-threatening diseases in need of continued hospital care like our oncology patients were affected the most.[9] Children with pediatric solid tumors, transplant recipients, and ocular cancers such as RB faced a major difficulty in continuing their treatment, majorly due to the inability to reach their healthcare providers.[10,11]

Pediatric cancers have also been observed to affect the low (41%) and middle socioeconomic (43%) class more than the upper class (16%), and 90% of the global cancer deaths are from low- and middle-income countries.[12,13] Similarly, RB accounts for 2.5 to 4% of all childhood cancers in most developed countries, and a two- to threefold increase has been reported in India.[14] India accounts for nearly one-third of RB cases in the Asia-Pacific region. The survival of RB is between 95 and 100% in developed countries; however, in parts of Asia and Africa, it is between 30 and 60%.[15] With the already existing social issues prepandemic, the lockdown has caused more strain on the developing counties. Multifactorial reasons have been identified for treatment delay—financial constraints, transport restriction, accommodation issues, and no caregiver to accompany.

Fabien et al in their global RB study from 94 countries have reported approximately 42.3% of families had delays in treatment due to travel restrictions during the current

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pandemic as compared with only 10% before the pandemic. They also mentioned that the availability of life-saving treatment modalities such as EUA, enucleation, intravenous chemotherapy, and intraarterial chemotherapy have significantly dropped from 95.9 to 55.2%, 100 to 89.6%, 96.9 to 93.8%, and 49.7 to 37.8%, respectively, before and after the pandemic.[16] Similarly, Gupta et al had reported an average duration of delay in follow-up was 14 days (7–20 days) during pre-COVID-19, as compared with 336 days (56–560 days) during the lockdown period.[17]

This COVID-19 lockdown situation has led many ophthalmic and pediatric oncology centers to revise the policy of examining, treating, and admitting their patients. One such study by Hadjistilianou et al, from Italy, has studied the policies adopted during the COVID-19 pandemic and RB patients. They have observed a wide disparity between various ophthalmology tertiary care centers as to when and who should be tested for COVID-19. Although swab testing was mandatory to ensure the safety of both patients and healthcare workers, only 2 out of 16 institutions they reviewed had ensured mandatory testing in all centers.[18] In our center, mandatory testing was done for both patients and the accompanying attenders and 3 were found to be COVID-19 positive.

During the era of global lockdown and travel restrictions, to help flatten the COVID-19 curve, telemedicine has been fundamental in connecting patients to their healthcare providers. This helped in triaging the patients, hence identifying those requiring immediate medical assistance and others to continue the medical care through teleconsultations.[19]

The COVID-19 pandemic and the nationwide lockdown have created a negative impact on overall healthcare in particular on chronic diseases needing long-term management. Hence, it is imperative to establish a network with necessary support across the hospitals, with the help of government, nongovernment social organizations, shared care with primary practitioners and telemedicine, keeping in mind the psychological impact of the pandemic on the families.

Future Research Directions

A multicentric study, comparing the RB children during the COVID-19 lockdown period with the non-COVID-19 period in various countries, would help us understand the support system across the centers that can help in preparedness future pandemics.

Limitations of the Study

It is a single-center experience with a limited study population.

Conclusion

Our study has shown that providing collaborative care has enabled 73% of patients to receive emergent care and continue their treatment. Through our study, we advocate that with the involvement of NGOs and meticulous planning of funding support we can provide a structured management strategy during global pandemics. In conclusion, there is a delicate balance of risk assessment and management of RB patients during the pandemic. The decision-makers should make bold new policies weighing the risks and benefits of the situation.

Funding
None.

Conflict of Interest
None declared.

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Quality of Life of Parents of Children with Cancer —Single-Center, Prospective Cross-Sectional Study from South India

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Ind J Med Paediatr Oncol 2022;43:255–261.

Abstract

Introduction Holistic care for children with chronic diseases including cancer should include psychological support for children and their families. The impact of pediatric malignancies in regard to quality of life (QOL) of parents is poorly described.

Objectives We aim to study the QOL of parents of children diagnosed with cancer in physical, psychosocial, environmental, and social domains.

Materials and Methods A prospective, cross-sectional study was conducted with 162 parents of children diagnosed with malignancy for 3 months or more. Assessment was done by World Health Organization quality of life (WHOQOL-BREF) questionnaire that includes four domains with a total of 26 questions. Data analysis was done by using Statistical Package for Social Sciences (SPSS) version 20.0; *p*-value less than 0.05 was considered significant. Results on continuous measurements were presented as "Mean $\pm$ SD" and categorical measurements were presented as percentages (%). Differences in the quantitative variables between groups were assessed by unpaired-t-test; comparison between groups by nonparametric Mann–Whitney U test and chi-squared test was used to analyze categorical variables with *p*-value of < 0.05 using a two-tailed taken as statistically significant.

Results Mean raw scores of QOL in physical health, psychological, social, and environmental domains were 20.10, 15.28, 8.10, and 25.24, respectively, with social relationships being the lowest; inadequate or low QOL was noted in 50% study population and it was maximally affected by increased duration of treatment, multimodality treatment, socioeconomic status, rural population, education and occupation status of the parents, and increased cost of care. Type of family or place of

Keywords
- quality of life
- WHOQOL-BREF scores
- socioeconomic status
- psychosocial support
- childhood cancer

DOI https://doi.org/10.1055/s-0042-1749402.
ISSN 0971-5851.

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residence, family history of psychiatric illness, or malignancy did not influence the QOL of parents of children with cancer.

Conclusion Psychological support from the beginning of the treatment along with financial, social support should be offered through a comprehensive care program to improve the QOL.

Introduction

Each year, ~400,000 children and adolescents from 0 to 19 years old are diagnosed with cancer across the globe.[1] The diagnosis of cancer in children is often very devastating to the family and has a negative impact on caregivers especially parents in terms of stress (physical, emotional, and financial). It affects their quality of life (QOL) as compared with parents of healthy children and the general healthy population. Impact on QOL may be in terms of physical or personal distress, marital disharmony, economic constraints, or difficulties in adapting to a major change in routine life.[2,3]

Holistic care for children with cancer should include psychological support and assistance in financial needs to parents apart from medical management of these conditions.[4] In resource-limited settings, lesser accessibility to health care, delayed presentation with advanced stage, and financial restraints are very rampant. Hence, priorities to improve the healthcare and financial aspects should be focused upon to improve accessibility. Structured and proper programs to help parents cope up with their stresses (similar to counseling sessions) by dedicated psycho-oncologists and nurses in developed countries are lacking in developing countries.

There is a lack of substantial research in the subject of QOL of parents of children with cancer, especially from developing countries. This study is intended to measure QOL in parents of children with cancer and to assess relationships of parental QOL with personal, child, disease, and treatment characteristics.

Materials and Methods

This is a cross-sectional study conducted in our tertiary care pediatric hemato-oncology unit in South India between March 2019 and August 2020. One sixty-two participants (either of the parents of children who were diagnosed, admitted in ward for chemotherapy or supportive care, and getting treated for malignancy) were selected as the study group. Parents of children who received chemotherapy or multimodality therapy, on treatment for at least 3 months duration, were included. Those who were diagnosed within 3 months and those who had only surgery/radiation as treatment modality, with relapsed malignancies, or were unwilling to consent were excluded. Children with cancers who were admitted in intensive care units with a complication/morbidity were also excluded.

The World Health Organization quality of life-100 (WHOQOL-100) assessment tool was developed by the WHOQOL group with 15 international field centers simultaneously, in an attempt to develop a QOL assessment tool that does not have differences cross culturally.[5] The WHOQOL-BREF is a scaled down version of the original instrument that may be used more conveniently in large research studies or clinical trials. In World Health Organization Quality of life (WHOQOL-BREF), 26 items were completed by the participant in their language of preference (Tamil or English) themselves or were helped by the principal investigator (the postgraduate doing the study or one of the treating doctors of the team from pediatric hemato-oncology team), when the participant was illiterate. The WHOQOL-BREF questionnaire assesses mainly four domains such as physical (D1), psychological (D2), social (D3), and environmental (D4) with 7, 6, 3, and 8 questions, respectively.

The first two questions assess health and QOL in general. Hence, 26 items related to QOL were answered by the study participants.

Scores in each domain range from 4 to 20 (domain score), where 4 is the worst and 20 is the best score in the domain. They were converted to a score range of 0 to 100 (transformed score), a part of the questionnaire. The transformed scores were used to define the QOL as follows: score >60 as high, 45 to 60 as moderate, <45 as low.

Socioeconomic status was calculated using modified Kuppuswamy socioeconomic scale (updated for the year 2019).[6] It comprises of occupation of the head of the family, educational qualification of the head of the family, and total monthly income of the family. The scores range from 3 to 29. It is divided into five classes based on scores into lower <5, upper lower 5 to 10, lower middle 11 to 15, upper middle 16 to 25, and upper 26 to 29.

Demographic details of the children like name, age, sex, address, diagnosis, and treatment plan were noted down. Details of the parents like education status, income, job details, type of family, and recreational activities were also noted. We wanted to analyze the QOL scores in each domain as primary outcome measures and the factors associated with low QOL as secondary outcome measures.

Based on extensive literature search on QOL studies, with mean score of 47.36 and standard deviation 22.53, sample size was calculated as 127 with relative precision of 10% and desired confidence level of 95%.

Statistical Analysis

Data analysis was done using SPSS (statistical package for social sciences) version 20.0 (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp, Armonk, New York, United States).

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Table 1 Baseline characteristics of the families of children with cancer in our study

Parameter	Frequency (*n*)	Percentage (%)
Type of family		
Nuclear	103	63.6
Joint	59	36.4
Living status of parents		
Together	147	90.7
Single/separated	15	9.3
Positive family history of cancer	11	6.8
History of psychiatric illness in family	19	11.7
Socioeconomic status*		
Upper class	0	0
Upper middle class	8	4.9
Middle	66	40.7
Lower middle class	76	46.9
Lower class	12	7.4
Residence		
Rural	69	42.6
Urban	93	57.4

* Based on Modified kuppuswamy scale.

Difference in quantitative variables between groups was assessed by means of unpaired *t*-test. Nonparametric data was analyzed using Mann–Whitney U test. Categorical variables were analyzed using chi-squared test. Regression analysis was done to analyze dependent variables that were significantly associated with different levels of QOL. *p*-Value of < 0.05 was considered significant.

Ethics

Institutional Ethics Committee approval was obtained from our institutional research ethics committee board from Sri Ramachandra Institution of Higher Education and Research (SRIHER - Ref:CSP-MED/19/Mar/51/28) conducted on 02.07.2019. Informed consent was appropriately taken prior to enrolment. Privacy, integrity, and confidentiality of personal information of research subjects were confidentially maintained as per Helsinki declaration.

Results

Among total of 186 children, 20 had relapsed malignancies and 4 parents did not consent for the study. In our study population ($n = 162$), 61.1% (99) children were boys and 38.9% (63) were girls and 40.1% (65) were less than 5 years of age. Of the 162 children, 62.3% (101) were suffering from hematological malignancies like acute lymphoblastic leukemia (ALL), acute myeloid leukemia, and lymphomas. The rest children (37.7%, 61) had solid tumors including neuroblastoma, renal tumors, germ cell tumors, hepatoblastoma, Ewing's sarcoma, brain tumors, soft tissue sarcomas, and rare tumor types including pancreatoblastoma, adenoid cystic carcinoma, and nasopharyngeal carcinoma.

Among the 162 participants, 79% (128) were mothers while information was provided by fathers in 21% (34). Most of the productive life of parents has been lost in the ordeal against cancer in their children. The mean age of the father was 38.56 years while that of the mother was 34.36 years in our study population. Among 162 parents, most of the parents were educated with 50% up to high school; 55% (89) fathers were unskilled laborers by occupation and 72% (117) mothers were unemployed.

In our study, 63.6% families had a joint family pattern, 9% parents were single, 11.7% had family history of psychiatric illness, and 57% were from urban background. Majority of them belonged to middle or lower middle class (87%), as detailed in ►**Table 1**.

For the sake of treatment of their children, 57. 4% (93 families) had to relocate from native place and 68.5% (110 families) needed to lose some property to manage the visible and invisible expenses. Details of cancer treatment including cost and financial support for treatment are given in ►**Table 2**.

The mean scores of QOL in each domain across the study population are depicted in ►**Table 3**. QOL was lowest in the psychological domain followed by social domain with environmental domain having relatively better QOL (►**Fig. 1**). Overall, nearly half of the study population (48.1%; 78) had low/inadequate QOL followed by 36.4% (58) having moderate QOL and only 15.4% (24) were noted to have high QOL. QOL grades were low/inadequate when the age groups of the children were in the extremes, that is, < 5 years (50%) and > 10 years (54.5%); however, they were not statistically different between different age groups ($p = 0.585$) or sexes ($p = 0.631$). Majority of the parents of cancer affected children who were uneducated ($p = 0.004$) and who were unskilled laborers ($p = 0.007$) experienced low

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Table 2 Details of cancer management and financial support

	Frequency (*n*)	Percentage (%)
Ward of admission		
Private	69	42.6
General	93	57.4
Insurance to support treatment present	58	35.8
Funded	92	56.8
Risk stratification of cancer—high risk	86	53.1
Duration of treatment		
< 1 year	42	25.9
1–3 years	39	24.1
> 3 years	81	50
Type of treatment		
Chemotherapy	101	62.3
Chemotherapy with surgery	23	14.2
Chemotherapy with surgery and radiotherapy	38	23.5
Cost of treatment		
1–5 lakhs	24	14.8
5–10 lakhs	99	61.1
> 10 lakhs	39	24.1

Table 3 QOL domain scores in various domains in study population

Domains	Mean scores (SD)	Minimum score	Maximum score
Physical health (D1)	20.10 (±4.06)	10	35
Psychological (D2)	15.28 (±4.07)	6	29
Social relationships (D3)	8.10 (±2.33)	3	15
Environment (D4)	25.24 (±4.37)	14	36
Overall QOL score	45.89 (±14.16)	14	91

Abbreviations: QOL, quality of life; CI, confidence interval. SD, standard deviation.

QOL scores (both in mothers and fathers). The difference in QOL values was significant for lower socioeconomic class ($F = 20.44$, $p < 0.0001$), type of treatment employing multimodality therapy including chemotherapy with surgery and radiotherapy ($F = 5\,0.168$, $p = 0.007$), longer duration of treatment (1–3 years of treatment) ($F = 12.27$, $p < 0.001$), and high cost of treatment amounting to 5 to 10 lakhs ($F = 5\,0.182$, $p = 0.044$), as per the logistic regression analysis shown in ►**Table 4**.

The lower socioeconomic class of people experienced the lowest QOL scores among all domains. As shown in ►**Fig. 2**, the QOL scores increase as the socioeconomic status increases, highlighting the importance of poverty in determining the outcome of QOL.

Among the other factors, it was found in our study that QOL scores were high in urban population ($p = 0\ 0.039$); however, they were not different between nuclear or joint family type ($p = 0.871$), positive or negative history of psychiatric illness in the family ($p = 0.808$), positive or negative family history of cancer ($p = 0.214$), or risk stratification of any cancer type ($p = 0.148$).

Discussion

Parents of cancer children from developing countries still face fundamental problems like financial stress, social stigma, disrupted family structure, and lack of access to treatment in remote areas, leading to decline in their QOL, as seen in 50% of study population in our study.[7] Research shows that there is long-term physical and psychological impact by cancer on children and families especially during and after treatment when the child appears to be cured or to be a "survivor."[7]

There were no significant differences among QOL scores in various domains across the age groups in our study. The male to female distribution was 1.5:1. Acute lymphoblastic leukemia (ALL) was the most common childhood cancer constituting 43.8% cases followed by retinoblastoma and Hodgkin

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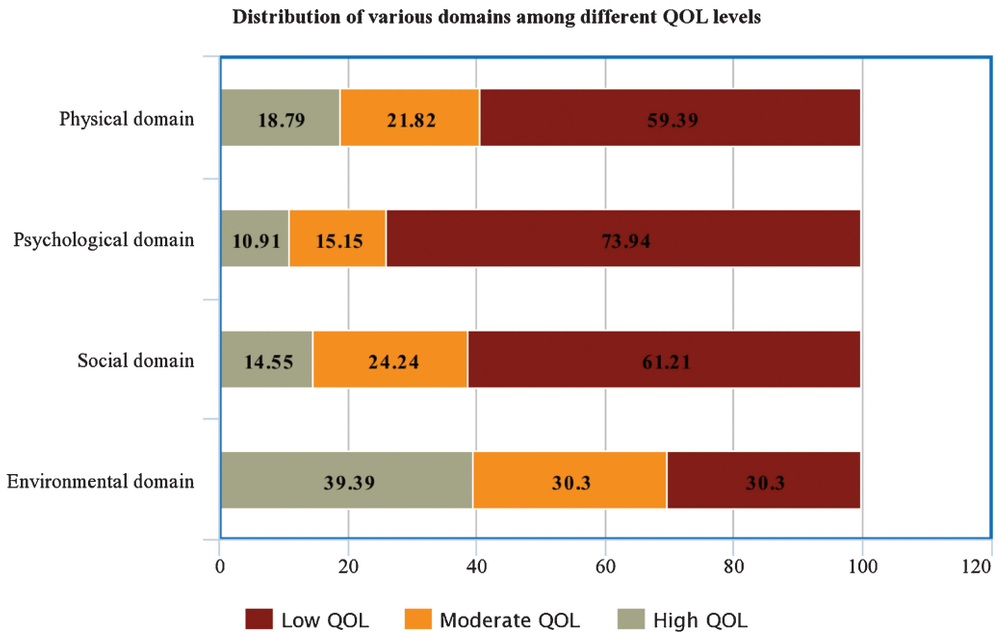

Fig. 1 Distribution of quality of life (QOL) in various domains in the study.

Table 4 Logistic regression analysis of various factors having significant differences in QOL scores

Parameter	F-Value	Odds ratio	95% CI	*p*-Value
Lower socioeconomic class	20.44	3.522	11.17–39.93	<0.001
Chemotherapy with radiotherapy and surgery	5.168	8.0	2.45–19.71	0.007
Treatment cost: 5–10 lakhs	5.182	2.174	0.00–0.64	0.044
Treatment duration: 1–3 years	12.27	10.82	0.33–0.96	<0.001

Abbreviations: CI, confidence interval; QOL, quality of life; SD, standard deviation.

lymphoma. Similar distribution of cancers was noted by epidemiological studies by Swaminathan et al with leukemias, lymphomas, retinoblastomas, and renal tumors being the most common cancer types.[8]

Study by McCubbin et al[9] shows that support from extended family especially from grandparents and in-laws provided assistance in several forms including parental respite, care of the sibling, transportation to the place of treatment, monetary and emotional support. In our study, there was no significant difference noted between QOL scores based on the type of family, probably due to the lack of transparency within families and prevailing stigma. In our study, the parents' WHOQOL-BREF scores were low especially in physical, psychological, and social domains with lowest being the psychological domain. Various other scales including PAT2.0 have been used by Mccarthy et al for the measurement of QOL in caregivers of children with cancer.[10] These findings were comparable to a study by Sajjadi et al[11] wherein the QOL of the caregivers in physical, psychological, and environmental domain was significantly lower than the QOL of the general population that shows the effect on caring for a child with a life-threatening disease. Similar findings have also been seen in studies on the QOL of caregivers of brain tumor patients by Chien et al.[12] Studies by Lin et al and Yuen Shan Leung on caregivers of children with disabilities also reflect similar findings and have attributed these decreases in QOL to a combination of stress and socioeconomic pressures.[13–15]

Parents from rural setting had lower QOL in our study that may be due to major disruption in family dynamics because of relocation for treatment needs. Educated parents had better QOL than uneducated, as they were able to be involved in decision making for the child and understand the process of treatment better. The parents who are professionals had better QOL in all domains as they were able to manage the financial burden in a better way, whereas unemployed mothers, on the other hand, had low QOL in all domains, probably due to better social and financial situation of the family.[16] Study by Kim and Spillers in 2010[17] have noted that caregivers with more than a high-school education had a positive influence on the QOL measured at a minimum period of 2 years after the child was diagnosed with cancer.

QOL was lowest in all the domains when the time of duration of treatment was more than a year that is proportionate to the financial burden and disruption of family routine for longer duration. Studies by Litzelman et al also support similar findings especially among caregivers of children affected with brain tumors. After 3 years, parents

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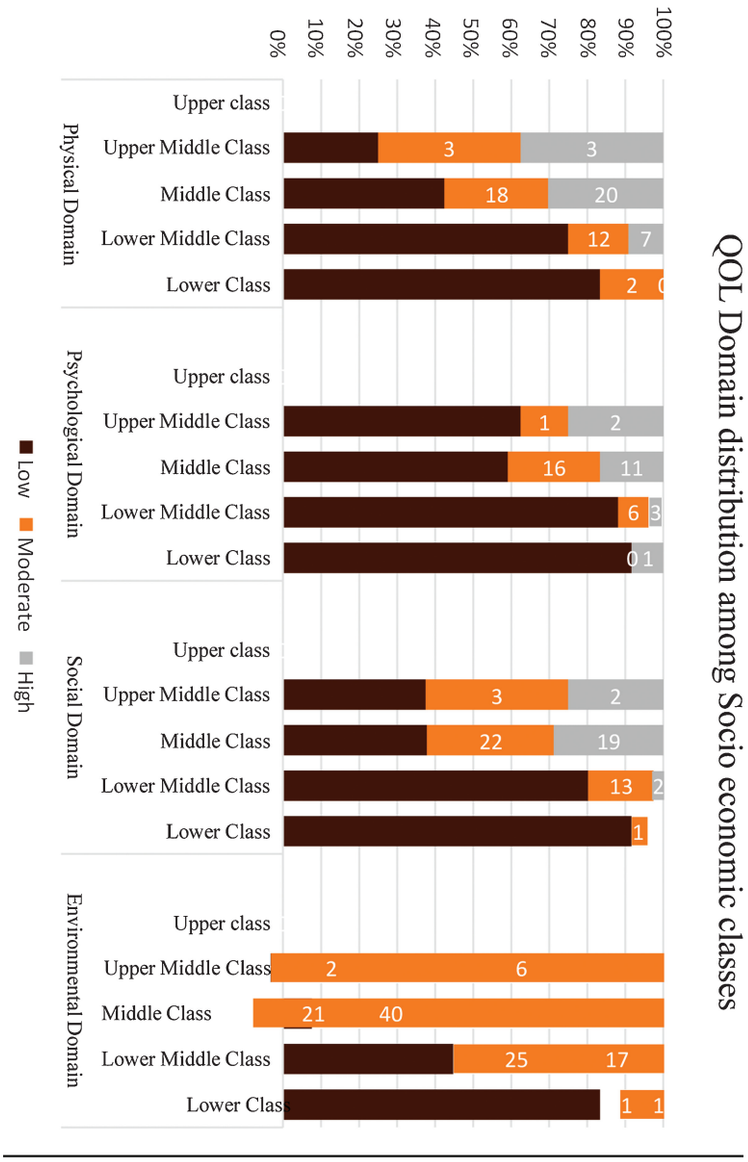

Fig. 2 Quality of life (QOL) scores in various domains among various socioeconomic classes.

learn to accept and cope up with the disease. Also, most probably, the treatment would come to an end at this point in most of the cases.[2]

The QOL was low in parents of children whose treatment cost was high. QOL of parents was low in all domains for children who need all three modalities of treatment with radiotherapy, surgery, and chemotherapy compared with those who received chemotherapy alone. This is due to the increased financial burden, side effects, and deformities associated with treatment.[18]

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This study adds significant information to a growing body of research on parents of children living with cancer beyond the initial phase of the illness trajectory. The need for professional support with the help of psychologist is emphasized through this study. A further study to assess the QOL of parents at different time points might give more strength to the study to arrive at better meaningful conclusions. A multi-institutional study to avoid bias arising due to cultural and social differences might be more appropriate. A larger study with more sample size and a control group is definitely warranted to generalize the conclusions.

Several standards and guidelines that highlight these parameters on the different domains of life are available from developed countries, as summarized by Lorie Weiner et al, where the scenario of social security schemes is different from that of a developing country like India.[19] While several coping measures are available in developed

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countries, such extensive programs that focus on the QOL among parents are lacking in developing countries.[20,21] Our study has been conducted as a cross-sectional study drawing results from one-time assessment. Study in a larger population and repeat assessments of the QOL scores in same cohort at periodic intervals might give more insight to make meaningful conclusions. This study would serve as a launch pad for similar research focusing on different domains of QOL among parents of children diagnosed with cancer.

Conclusion

Nearly 50% of the study population experienced low QOL in our study; it was significantly associated with illiterate parents, lower socioeconomic status, prolonged treatment duration, and increasing cost of treatment. Psychological support from the beginning of the treatment of a child with cancer, apart from the appropriate treatment and financial support through various resources, should be a part of the comprehensive care program to be led by the pediatric oncologists. Evaluation and intervention in a professional manner with routine and timely care would certainly help in reducing the psychological burden of the caregivers and would indirectly improve the quality of care the child and family.

Authors' Contributions

SGJ wrote the initial draft and it was revised for intellectual content by DJ, JXS, and GM. All the other authors were involved in the management of the child. All authors read and approved the final manuscript.

Funding

None.

Conflict of Interest

None declared.

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Child's Understanding of Cancer when Faced with Advancing Disease: A Retrospective Chart Review

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Ind J Med Paediatr Oncol 2022;43:262–269.

Abstract

Introduction It is difficult to comprehend a child's understanding of disease-related information as they might be unwilling to talk or feel inhibited about raising their concerns. Understanding children's perception is important to facilitate better communication in palliative care.

Objectives To study child's understanding of advancing disease when referred to the Pediatric Palliative Care Services.

Materials and Methods A retrospective chart review of 34 case record forms from March 2019 to March 2020 was conducted after obtaining a waiver of consent and Institutional Ethics Committee approval. The inclusion criteria were children having advanced cancer referred for palliative care, incomplete records were excluded. Data were analyzed using thematic analysis.

Results Twenty-three were male, and 11 were female children, the mean age was 12 years. Five major themes were identified—the child's understanding of disease diagnosis and prognosis, nature of communication between parents and the child, barriers to communication, child's means of support, and interventions used during counseling.

Conclusion Communication between children suffering from advanced cancer and their parents/caregivers is a sensitive issue, and noncommunication is often due to mutual effort to shield each other from the stress of difficult conversations. Lack of communication contributes to poor coping and forces children to seek comfort in other sources leaving parents distressed. Psychological interventions like resource building and psychoeducation are effective.

Keywords
- cancer
- palliative care
- pediatrics
- thematic analysis
- qualitative research
- chart review

DOI https://doi.org/10.1055/s-0042-1750208.
ISSN 0971-5851.

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Introduction

Most parents would like their child's prognosis to be explained to them, however difficult it could be for them to accept.[1] Sometimes it is the oncologist who is not ready for the discussion.[2] When the prognosis turns adverse due to relapse or resistant disease, a palliative care referral can help parents to cope.[3] Routinely in a pediatric palliative care clinic, communication channels are opened for discussion of prognosis. Keim et al have shown that open communication with parents (especially mothers) helped them to cope with advanced cancer at the end of 1 year.[4]

At the department of palliative medicine, pediatric palliative has been offered to children and their families since 2002. Routinely, the cases are discussed in a tumor board/multidisciplinary clinic, and children with resistant disease or relapse are referred for palliative care. At this clinic, the child is "counseled" separately. With the help of toys, stories, and other diversion methods, the counseling psychologist, along with a trained child life counselor comprehends the concept of what the child understands about the disease and how he/she is coping. These observations are conveyed to the psychologist and doctor who are counseling parents separately. If necessary, they are also communicated to the parents, to aid in communication between the child and parents. All of these are documented routinely in the case record form and this workflow has been described in an earlier paper.[5]

It has been observed that many children, aged 6 years and above, have some understanding of the disease and their condition based on their self-reporting about disease-related questions.[6] This may give rise to related queries and concerns, but in most cases, children do not feel comfortable speaking about this with physicians or parents. Sometimes it is the parents who can be a barrier to effective communication, as they might favor collusion to protect their child from bad news.[7] A major shift in children's understanding of key biological concepts about the structure and function of the human body and disease transmission takes place between the ages of 7 and 11 years.[8] Yet, parents may have their own set of reservations and beliefs against communicating with a child, regarding a child's disease and its progression. Parents' decisions not to talk to their children might also reflect their emotional distress and a desire to protect themselves from the "unbearable reality of the situation."[9]

Like adults, facing challenges against a serious illness like cancer can provoke thoughts of death and dying in children as well; but there can be unique ways in which children cope, and it is worthwhile to provide a supportive framework for such kids to express themselves. Studies have found out that a child might learn about their disease and how serious it is without being explicitly told.[10] Children might be unwilling to talk, or feel inhibited about raising their concerns, particularly if they are aware of their parents' anxiety and discomfort around the subject.[11] Also, a child's perception of the disease can give a deeper insight into their disease burden. According to Rutishauser, understanding this burden of illness can help in forming the basis for negotiating age-appropriate therapeutic goals and strategies.[12] Also, communication between the child, their parents or caregivers, and health care professionals helps to gain the trust of the child and is associated with enhanced adherence through improved understanding of illness and the importance of treatment.[13]

There is inadequate information in the literature on how the child perceives a referral to the palliative care services amid advancing disease. This retrospective chart review was planned to understand this lacuna and will help the pediatric palliative care team plan future strategies in bridging any communication gaps between the child with cancer and the parents.

This project aimed to record a child's understanding of cancer and its prognosis, and the psychosocial methods employed.

Objectives

The primary objective is to study the child's understanding of advancing disease when referred to the pediatric palliative care services. Second, to assess how much of a communication gap exists between the child and parents and also to understand psychosocial strategies used to overcome any such barrier.

Materials and Methods

Sample and Setting

At the Department of Palliative Medicine, Tata Memorial Centre, Mumbai, Maharashtra, India, pediatric palliative has been offered to children and their families since 2002. The cases are discussed before a multidisciplinary team meeting in pediatric oncology and children with a resistant disease or relapse are referred for palliative care. Every child who is referred to the pediatric palliative care service is seen separately by a counseling psychologist and/or a trained child life counselor. Their evaluation is recorded in the Case Record Form. The notes which are compiled for every interview were retrospectively analyzed to look for:

1. The child's understanding of his/her disease, prognosis, related concerns, and the psychosocial interventions offered in aiding these concerns.
2. Communication between parents and child regarding disease and prognosis and barriers to it.
3. Any other sources of help obtained.

Inclusion Criteria

Every chart where the child and parents were counseled separately at referral to the Department of Palliative Medicine, Pediatric Unit between March 2019 and March 2020.

Age range was between 6 and 18 years.

Exclusion Criteria

Any incomplete case records, that is, a medical record that fails to tell the patient's whole story, and lacks clarity, specificity, or completeness.

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Data Collection and Procedure

The primary outcome measure was to record the child's understanding of cancer and its prognosis, while the secondary outcome was to record the psychosocial methods employed. We recorded demographic and clinical data from the patient charts. The data were summarized by descriptive statistics. Counseling notes were analyzed for emerging themes. We could screen through 50 participants from case records. The final sample size was determined by thematic saturation, the point at which new data appears to no longer contribute to the findings due to the repetition of themes and comments by participants.[14] At this point, data generation was terminated.

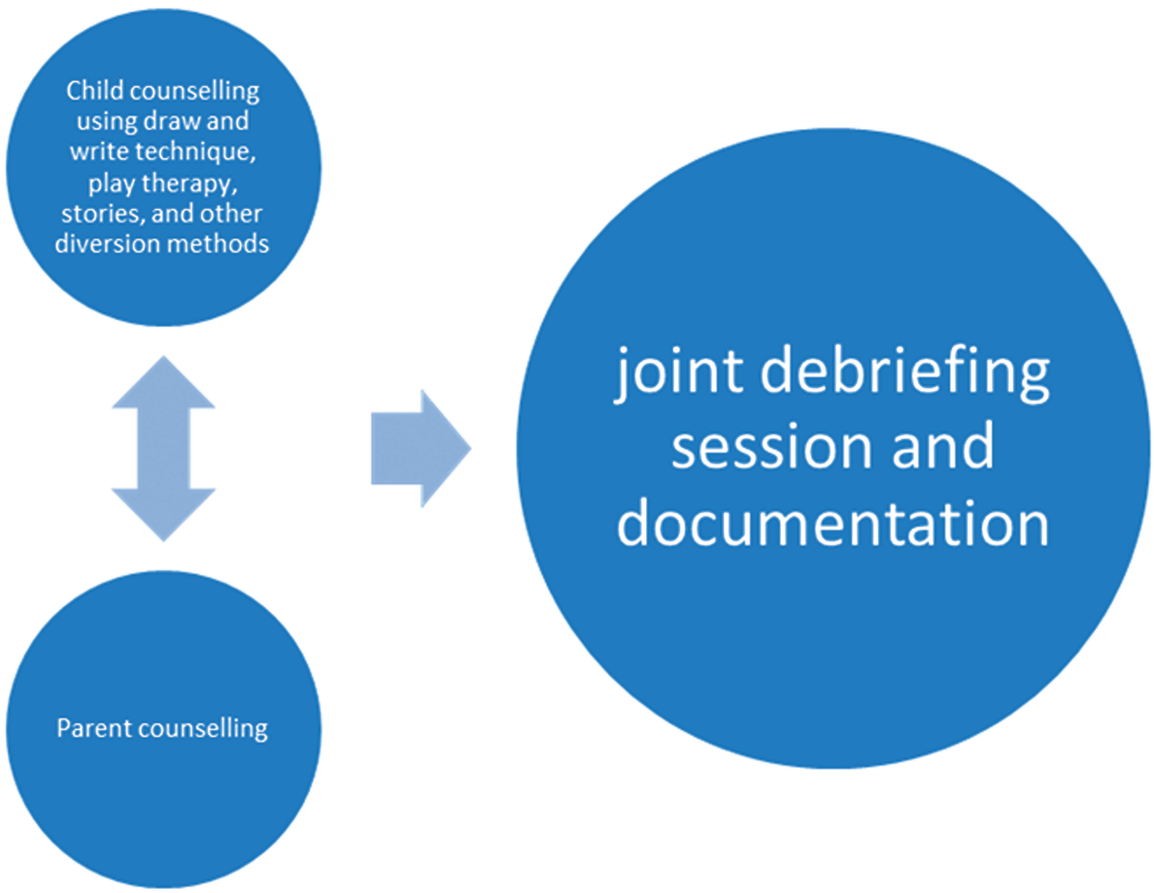
The information in the study records/audio records was kept confidential and the clinical charts are housed in the Tata Memorial Hospital Clinical Research Secretariat in safe custody, made available only to persons conducting the study and to the regulatory authorities. No reference has been made in oral or written reports which could link the participant to the study. No extra funding was needed for this chart review.

Workflow Process

In a palliative care clinic, the child is "counseled" separately from the parent with their permission. Child counseling often involves communicating with children using the draw and write technique, and play therapy with toys, stories, and other diversion methods; duly backed by evidence from the literature.[15–18] The draw and write technique[15] and play therapy[17] are jovial methods of engaging with children,[18] where they draw/write about their thoughts about cancer, and about things which help them to cope. In this activity, children are encouraged to work individually but have the option to clarify doubts with the child psychologist/researcher if they want to. Following this activity, the psychologist has a joint session with the children and their parents for any clarifications. These observations are conveyed to the psychologist and doctor who counsel parents separately. A final debriefing session involves all coming together at the end of the consultation. Everything is documented in the case record form in the English language. Parents are given contact details from the clinic for office/out-of-office hours communication and are scheduled for a follow-up visit.

Data Analysis

Techniques of thematic content analysis were followed by two different researchers to develop an initial list of codes.[19,20] First, an initial list of codes was generated from the transcripts, followed by discussions to have an agreement on the set of codes. The level of intercoder agreement



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from a random selection demonstrated a 98% level of agreement.[21] Remaining data was then systematically examined through these sets of codes to check for consistency and any emerging codes. Finally, themes were generated based on the agreed set of codes. Quantitative data analysis like calculation of median, percentage, and range was done for the demographic and clinical variables collected.

Ethical Approval and Informed Consent

All procedures performed in studies involving human participants were per the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethics approval was granted by the Institutional Ethics Committee (Project 900683/IEC III) at the Tata Memorial Centre, dated 18.11.2020. The committee waived the need for informed consent as the study utilized anonymized patient charts.

Results

Data from the chart review are presented below using tally counts to indicate the frequency of specific codes, subthemes, and themes. Most of the cases provided more than one, so the codes have been collapsed together to generate the final number of subthemes and themes. Of the 50 charts screened, 34 charts with complete data were identified and analyzed after reaching the point at which no new themes emerged.[14] Out of 34 participants, 23 were male and 11 were female. The demographic and clinical details of the patients are presented in ►**Table 1**. Average age of patients was 12 years (range 2–16 years).

Table 1 Demographic and clinical profile of participants

	Numbers (%)	
Gender distribution of primary decision maker in family		
Male	28 (82.35)	
Female	6 (17.65)	
Monthly family income (₹)		
5,000 or below	15 (44.12)	
5,001–10,000	9 (26.47)	
10,001–20,000	5 (14.71)	
20,001–30,000	5 (14.71)	
Children		
Gender distribution of child		
Male	23 (67.65)	
Female	11 (32.35)	
Age distribution (y)		
2–12	13 (38.24)	
13–16	21 (61.76)	
Cancer diagnosis		
Medulloblastoma	2 (5.88)	
Ewing's sarcoma	5 (14.71)	
Hematological malignancy	12 (35.29)	
Melanoma	2 (5.88)	
Neuroblastoma	1 (2.94)	
Osteosarcoma	9 (26.47)	
Retinoblastoma	1 (2.94)	
Rhabdoid cancer of kidney	1 (2.94)	
Pancreatoblastoma	1 (2.94)	
	Median	**Range**
Age at diagnosis (y)	12	3–17
Months since diagnosis	3	0–85

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Table 2 Themes and subthemes of the chart reviews from participants

Themes	Subthemes	Example quotes
Child's understanding of the disease diagnosis and prognosis	Ignorance/avoidance of communication about the disease	I do not want to talk about it (P7)
	Something is there which is bad	I am not sure, but I do not have a good feel about it (P13)
	Everything is fine	All is well (P22)
	God will help with illness	I leave it to God (P20)
	Knows it is cancer	I know it is a dreadful disease (P16)
	Knows the exact diagnosis	I know I have cancer (P17)
Nature of communication between the child and the parents	Child not communicating with the parents because they take stress	I cannot watch my parents sad (P33)
	Child suspects parents have given partial information	I am sure that my parents know everything, but they never tell me (P12)
	Caregivers choosing not to tell child	We cannot tell him this (P18)
	Child choosing not to speak to parents	I better not speak about it (P1)
	Open communication	I share everything with my parents (P2)
Recognized barriers to communication	Child worries for the caregiver	I feel sad for my parents (P30)
	Poor coping of the parents	We cannot see him like this (P5)
	Parent's wishes to protect the child	Nothing will happen to him (P31)
	Hope for cure	My child will get better (P34)
	Child's preference	I do not want to talk about it (P29)
	Conflicts and issues other than the disease	My parents have dispute with my uncle (P23)
Psychosocial interventions to improve communication	Encouraged parents to communicate about the disease with the child	You should talk to each other about this (P10)
	Supported child for better coping	You should share your thoughts with someone (P21)
	Counseled caregivers to cope and support child	You must be open and supportive about this (P11)

Thematic Findings (►Table 2)

Five major themes regarding the child's understanding of advanced illness were identified: (1) child's understanding of disease diagnosis and prognosis, (2) nature of communication between parents and the child, (3) barriers to communication, (4) child's means of support, and (5) interventions used. Fourteen of 34 (41%) children were inquisitive about the illness, 13/34 (38%) of children were inquisitive but were not communicated openly about their disease, only 3/34 (9%) of children did not want to talk about the disease despite acknowledging the parents' stress about it, and there was no data for the remaining 4 (12%).

Theme 1: Child's Understanding of the Disease Diagnosis and Prognosis

The child's understanding of disease-related information ranged from not knowing that something is wrong with them to know the exact diagnosis and prognosis. Four children reported not knowing anything—one child wanted to know more about the disease, while the rest expressed their wish to go back home based on what the authority figure (parent/doctor) had told them. This kind of avoidant coping was found in parents and children alike. Four children were aware of something bad happening as the symptoms worsened, two children understood that the lack of chemotherapy is not a good indication, four children knew that something bad is awaiting them as they could sense helplessness in their parents, and one child knew about a bad prognosis. The children who believed everything is fine were around the ages of 10 to 14 years. They were in denial and were accompanied by family collusion. Six children knew about the diagnosis of advanced cancer—two believed that their disease was curable, while four chose to not discuss anything with their primary caregiver to prevent further stress. Children who were aware of the exact diagnosis also tend to be better informed about the prognosis and were

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between 13 and 15 years of age. Five children belonging to a relatively higher socioeconomic group had better awareness about treatment options for cancer care which had a positive bearing on their illness experience, compared with the rest.

Theme 2: Nature of Communication between the Child and the Parents

Children who knew that something bad is happening preferred not to talk to their parents at all, however, often they expressed their hopelessness through their behavior (11 cases). Eight caregivers decided to avoid all sorts of disease-related communication with their children as they felt overwhelmed with the emotional burden. Family dynamics also resulted in lesser communication when the primary caregiver was someone other than the parents like a brother or cousin (in two cases). One child was unable to communicate with his parents due to parenteral conflict, and in another case, the mother was suffering from mental illness. Six children could open up to their parents. In one such case, the parent and the child both shared anger and resentment toward the doctors and the hospital for cancer to progress to advanced stages despite early initiation of therapy.

Theme 3: Identified Barriers to Communication

There were both parent-related and child-related factors. The most common reason was to protect each other from distress; however, one child did not want to talk because he did not like to talk to anyone about his feelings. Poor coping on the part of parents was a deterrent, however, some resorted to avoidance by trying to play down the seriousness of the situation (two cases). Three families were in denial and believed in the cure. These ideas were often backed up by alternate support systems like alternative forms of medicine or belief in a higher power like God, all hampering communication about poor prognosis. Six children, who preferred not to talk to parents, were utilizing peer networks to share their feelings.

Theme 4: Psychosocial Interventions to Improve Communication

After recognizing the communication barriers, interventions like psychoeducation, resource building, relaxation therapy, diversion, and cognitive behavior therapy were utilized and were found to be useful. The decision on the technique(s) used was made by the team. Parents were encouraged to communicate more with their children in friendly ways to reduce stress and mend communication gaps. This resulted in many families finding their communication portals and resulted in adaptive coping. The caregivers were supported to cope with anticipatory grief and were advised to seek support for themselves if overwhelmed. Family counseling sessions were organized to help in decision making, psychosocial support systems were strengthened for parents to take better care of children, work with collusion, and involve siblings in care. However, in four cases the families did not return for counseling as they shifted to their native place knowing that cancer has become incurable. The psychologist reached out to those families by telephone.

Theme 5: Sources of Support

The sources of support were varied—extended family (14 cases), siblings (13 cases), mother (8 cases), father (3 cases), and friends (3 cases). Only in one case, did the child use diversion as a method of support.

Discussion

These results demonstrate the variations in awareness levels of children, their belief systems, coping strategies, and the magnitude of possible improvement in communication between parents and their children using case-directed psychosocial interventions. The cues and methods we followed in the clinic were based on standard practice patterns.[22] Children demonstrated good awareness of advanced cancer, thoughts about potential outcomes, and unique coping skills; however, there were wide variations in children's views about their diagnosis and prognosis.

The nature of communication between the child and their parents were influenced by interpersonal relationships and family dynamics. The psychosocial interventions implied here to improve communication ranged from encouraging parents and children toward opening up with each other for support and supporting parents to cope better.[23] For engaging with children we followed the draw and write and play therapy approach, as backed up by literature evidence. However, it was more effective in older children compared with the rest. The older children also had more defined ideas about the issues related to the advanced nature of cancer which was not found in the younger children. Interestingly, we could also appreciate that affluent children were better aware of therapeutic options for relapsed/advanced cancers compared with children from socioeconomically weaker sections of the society, who found poverty, job loss, and debts cause hindrance to their treatment. It is well known, that in the developing world, socioeconomic conditions are an important determinant for outcomes in children's health, but not much is known about how these complex factors shape their perspectives about health or the health care system.[24] In this era of "choosing wisely" in cancer therapeutics, we think that this is an important area that can be further explored.[25]

When comparing the contents of drawings/writing in this study with the seminal paper by Oakley et al,[26] we found that our study participants score similarly in terms of cancer awareness, casualty, and its overall impact; but differ in the psychological coping strategies. This is expected, as advanced cancer, unlike other pediatric illnesses or cancers, possesses unique challenges like options of experimental therapy, a higher burden of suffering due to complex physical-psycho-social issues, and a lot of time being spent in the health care institutions rather than a home which makes the whole thing challenging for kids. In the absence

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of previous experience or learning, children's expression highlighted the influence that social media, television, print media, and peer network can have on them in illness understanding. This highlights the importance of formal channels of health/disease-related communication between school and community. Drawing parallels from this, we think that ethnographic research can be a better way to understand how information about advanced cancer needs to be delivered to kids in their social worlds as has been shown elsewhere.[27]

The draw and write technique proved to be useful in a busy clinic like ours, as it is open-ended; and some children enjoyed it so much that similar techniques were started in the inpatient settings. It is important to note here that literature suggests using a combination of writing and drawing as it can elicit more information than either technique used alone.[16] One challenge to using this technique within the typical clinic setting is to provide children with a quiet place free from interruption to work independently, and supervision to avoid copying from others. In our study, the psychologist tried her best to watch the children carefully so that they were able to work in peace, and discouraged copying as best as she could. Also, as we could see a similar pattern of the main responses at different periods, the findings as depicted here are likely independent of any instances of such copying if that ever happened. It is interesting to note that the median time since diagnosis of the cohort was 3 months, compared with 18 months in a recent review.[28] This observation is a reflection of our local practice for palliative care referral which is typically triggered earlier in the cancer journey for children with high symptom burden, but also is short as many patients attend the cancer clinic at a refractory or early relapse stage after being referred from elsewhere. Other limitations in this study relate to the retrospective nature of the data extraction, and information that may have been expressed by parents/caregivers in local languages was documented in the charts in the English language following the working policy of the institute, which might have had a bearing on the results and interpretation related to translations of quotes.

Conclusion

This study suggests that the knowledge of children on advanced cancer and cancer care is shaped not only by formal channels of health information communication but also by informal routes like peer groups, and the Internet. Illness-related communication between such children and their parents/caregivers is stressful and results in avoidance. There are wide variations, however, which need careful psychosocial assessments. Interventions like resource building and psychoeducation are effective but would need to take into consideration the socioeconomic and cultural contexts of children's lives which can influence their choices and behavior. A prospective study and/or large sample size will be needed for validating these results.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
To all the project staff from the Department of Palliative Medicine at the Tata Memorial Centre, the participants, and their families.

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Complementary and Alternative Treatment Use in Breast Cancer Patients in the Eastern Black Sea Region—A Cross-Sectional Study

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Ind J Med Paediatr Oncol 2022;43:270–277.

Abstract

Introduction Complementary and alternative therapies (CAMs) are being increasingly and frequently used in the treatment of cancer patients in the last two decades.

Objectives It was aimed to examine the frequency of the use of CAMs in patients with breast cancer who applied to the outpatient clinic.

Materials and Methods Patients who were admitted to our clinic between January 2020 and 2021 and diagnosed with breast cancer for at least 3 months were included in the study. A questionnaire consisting of 37 questions was asked to the patients by the interviewer. Sociodemographic characteristics and CAM methods of the patients were questioned in the questionnaire.

Results This is a cross-sectional study that includes 338 patients. After the questionnaire was completed, the answers were evaluated, and it was detected that 147 (43.4%) patients were using CAM. Herbal treatment methods were preferred most frequently. The most frequently used herbs were turmeric, nettle, ginger, and linden. The second method used was treatments based on religious belief. The use of CAM increased as the income level of the patients increased and the duration of diagnosis increased.

Conclusion It was determined that our patients frequently used CAM methods and mostly preferred herbal methods. Since the use of CAMs during or after treatment may create undesirable results in the treatment of patients, it is necessary to be careful about this issue and inform as well as question the patients about the same.

Keywords
- breast cancer
- complementary and alternative therapies
- herbal

Introduction

Breast cancer is the most frequently diagnosed cancer worldwide, after lung cancer, with more than 2 million cases diagnosed each year.[1] In women, it is the most common cancer that is diagnosed and the second most common cause of cancer-related deaths.[2] There are treatment methods in breast cancer such as surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy. Depending on the stage of the disease and the patient's clinic, one or more of these treatment methods can be used. Many side effects such as nausea, vomiting, weakness, suppression of immunity,

DOI https://doi.org/10.1055/s-0042-1749400.
ISSN 0971-5851.

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and impaired blood count may develop during treatment or depending on the disease itself. These side effects and factors such as the long duration of the treatments may lead patients to use complementary and alternative treatments (CAMs) to improve their quality of life.

Complementary therapies like vitamin supplements, massage, yoga, acupuncture, and herbal remedies are supportive treatments used to control symptoms, reduce drug side effects, contribute to the general care of the patient, and improve quality of life. Alternative treatments, on the other hand, are treatments that are used instead of the prescribed patient's medical treatment and whose effectiveness has not been proven yet.[3] CAMs are frequently used in cancer patients. Various studies are reporting that this rate is between 10 and 60% in cancer patients.[4] Across Europe, ~40% of all cancer patients refer to CAM during their oncological treatment.[5,6] There has been an increase in the rate of using these treatments in the last two decades.[7] A guideline on CAMs used in breast cancer patients reported that meditation, yoga, and relaxation are routinely recommended for the treatment of problems such as anxiety and mood disorders.[8] This study was aimed to reveal the rates of CAM use in patients with breast cancer after diagnosis, whether receiving chemotherapy or not, the factors affecting this situation, the side effects or benefits observed under these treatments, and the reasons that lead people to try these treatments.

Materials and Methods

This is a single-center, cross-sectional study conducted between January 2020 and January 2021. A total of 338 volunteers from patients over the age of 18, who applied to Karadeniz Technical University outpatient clinics and chemotherapy units, who were followed up with a breast cancer diagnosis, were included in the study. Patients with poor performance, communication problems, and those who did not want to participate in the survey were not included in the study.

After reviewing the literature, a total of 37 questions were asked by a single interviewer (medical oncologist) to explore the use of CAM.[9–11] The primary outcome of our study was to detect the frequency of the use of CAM in breast cancer patients. The secondary outcome was to detect the most common CAM that is used by the patients. In the survey, the sociodemographic status of the patients such as age, place of birth, education level, place of residence, occupation, number of children, income level, and medical characteristics such as diagnosis time, family history, disease stage, and other accompanying diseases were questioned. Questions based on whether they use CAM, if they do, what they use, how long they use it, why and with what expectation they use it, in which periods of the disease they use it, whether they experience any side effects while using it, what kind of side effects develop in those who do, whether they benefit or not were asked to the patients. Additionally, q u e s t i o n s like how the beneficiaries benefited, where they heard about these treatments, how much they paid monthly for these treatments, whether they informed their follow-up doctors, why those who did not inform, why the informants did, and whether they continued the CAMs were asked.

Statistical Analysis

Data analysis was done in IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, New York, United States) package program. Whether the distribution of discrete numerical variables was close to normal was examined using the Kolmogorov–Smirnov test. For discrete numerical variables, they were expressed as mean ± standard deviation or median (minimum- maximum), while categorical variables were expressed as several cases and in percent (%). The significance of the difference between the groups in terms of mean values was evaluated with the Student's *t*-test, and the significance of the difference in terms of discrete numerical variables with a far-normal distribution was evaluated with the Mann–Whitney U test. Pearson's $\chi 2$ test was used in the analysis of categorical data unless otherwise stated. On the other hand, if the expected frequency is below 5 in at least ¼ of the cells in the 2×2 cross tables, the categorical data in question were evaluated with Fisher's exact probability test, in cases where the expected frequency was between 5 and 25, evaluation was made with continuity corrected $\chi 2$ test. Multivariate logistic regression analysis was used to determine the most determinant factor in differentiating the group that did not use CAM before versus the group that used CAM. All variables found to be $p < 0.25$ as a result of univariate statistical analyzes were included in the regression model as candidate factors. In addition, odds ratio, 95% confidence interval (CI), and Wald statistics for each variable were calculated. For $p < 0.05$, the results were considered statistically significant.

Results

The mean age of the patients included was 52.8 ± 11.6 years. When the clinical and demographic characteristics of the patients using and not using CAM were compared, there was no statistically significant difference found between the groups in terms of mean age, marital status, number of children, education level, place of residence, occupation, active employment, family history, and disease stage ($p > 0.05$). On the other hand, the income level of the group using alternative treatment was statistically significantly higher ($p < 0.001$) and the duration of diagnosis was statistically significantly longer ($p = 0.030$) compared with the group that did not use alternative treatment (►**Table 1**). The percentage of coexisting disease was 42.9%. Hypertension is the most frequent coexisting disease and there was no statistically significant difference between the group not using CAM and the group using CAM in terms of comorbidities ($p > 0.05$).

Of the 39 patients who had never tried these alternative treatments, 43.6% considered trying them. ►**Table 2** shows 147 (43.4%) patients using CAM, the reasons for taking these treatments, their expectations while taking them, when and for how long they started using CAM, whether they

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Table 1 Demographic and clinical characteristics of the cases according to the groups using and not using CAM

	Total ($n = 338$)	Nonuser ($n = 191$)	User ($n = 147$)	*p*-Value
Age (years)	52.8 ± 11.6	53.7 ± 10.8	51.6 ± 12.5	0.096[a]
Marital status				0.977[b]
Never married	24 (7.1%)	13 (6.8%)	11 (7.5%)	
Married	283 (83.7%)	161 (84.3%)	122 (83.0%)	
Divorced	12 (3.6%)	7 (3.7%)	5 (3.4%)	
Widow	19 (5.6%)	10 (5.2%)	9 (6.1%)	
Number of children	2 (0–5)	2 (0–5)	3 (0–5)	0.357[c]
Education status				0.502[b]
Illiterate	51 (15.1%)	32 (16.8%)	19 (12.9%)	
Primary school	171 (50.6%)	94 (49.2%)	77 (52.4%)	
Middle school	21 (6.2%)	14 (7.3%)	7 (4.8%)	
High school	51 (15.1%)	30 (15.7%)	21 (14.3%)	
University	44 (13.0%)	21 (11.0%)	23 (15.6%)	
Abode				0.678[b]
Village, town	44 (13.0%)	27 (14.1%)	17 (11.6%)	
District	125 (37.0%)	72 (37.7%)	53 (36.0%)	
Province	169 (50.0%)	92 (48.2%)	77 (52.4%)	
Job				0.495[b]
Housewife	263 (77.8%)	152 (79.6%)	111 (75.5%)	
Health employee	10 (3.0%)	4 (2.1%)	6 (4.1%)	
Teacher	20 (5.9%)	9 (4.7%)	11 (7.5%)	
Other	45 (13.3%)	26 (13.6%)	19 (12.9%)	
Working status				0.709[d]
Working	31 (9.2%)	19 (9.9%)	12 (8.2%)	
Not working	307 (90.8%)	172 (90.1%)	135 (91.8%)	
Income level				**<0.001[b]**
≤1,000 TL	195 (57.7%)	128 (67.0%)	67 (45.6%)	
1,001–3,000 TL	84 (24.8%)	37 (19.4%)	47 (32.0%)	
>3,000 TL	59 (17.5%)	26 (13.6%)	33 (22.4%)	
Diagnosis time				**0.030[b]**
<1 year	184 (54.4%)	116 (60.7%)	68 (46.2%)	
1–5 years	84 (24.9%)	41 (21.5%)	43 (29.3%)	
>5 years	70 (20.7%)	34 (17.8%)	36 (24.5%)	
Family history	71 (21.0%)	42 (22.0%)	29 (19.7%)	0.613[b]
Stage				0.055[b]
Early	83 (24.6%)	44 (23.0%)	39 (26.5%)	
Locally advanced	144 (42.6%)	92 (48.2%)	52 (35.4%)	
Metastatic	111 (32.8%)	55 (28.8%)	56 (38.1%)	

Abbreviation: CAM, complementary and alternative therapy.
[a]Student's *t*-test.
[b]Pearson's χ^2 test.
[c]Mann–Whitney U test.
[d]Continuity correction χ^2 test.

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Table 2 Findings related to the experiences of cases who have tried alternative treatment before ($n = 147$)

	Number of cases	%
Reason for seeking alternative treatment		
Failure to respond to medical treatment	10	6.8
Disbelief in medical treatment	1	0.7
Environmental effects	60	40.8
Hopelessness, despair	21	14.3
Believing that alternative therapy can be helpful	95	64.6
Other	1	0.7
The expectation in the use of alternative therapy		
Supporting and assisting the treatment given by the doctor	74	50.3
Decreasing complaints	61	41.5
Recovering from illness	86	58.5
Other	4	2.7
At what stage of the disease did the patient start using it?		
From the moment of diagnosis	110	74.8
As the disease progresses	37	25.2
How long did the patient use it?		
<1 year	117	79.6
1–3 years	23	15.6
>3 years	7	4.8
Currently using an alternative therapy	82	55.8
Continuing medical treatment with alternative therapy	137	93.2
Side effects associated with alternative therapy	8	5.4
How did the patient find alternative therapy?		
Useful	55	37.4
Little useful	10	6.8
Indecisive	59	40.1
Useless	11	7.5
Harmful	3	2.0
Didn't use enough	20	13.6
How was the alternative treatment helpful? ($n = 68$)		
İncreased resistance	20	29.4
Felt better	18	26.5
Blood values are improved	9	13.2
Complaints are decreased	24	35.3
Not used enough	2	2.9

continued these treatments, whether they had side effects, and whether they benefit from these treatments. ►**Table 3** shows where the patients using CAM have heard about these treatments, the monthly cost of these treatments, whether they have informed their follow-up doctor about it, whether they found these treatments to be effective from their medical treatments, and whether there was anyone who had applied them before. The distribution of treatment types used by patients who have tried CAMs is shown in ►**Table 4**.

All variables found to be $p < 0.25$ as a result of univariate statistical analyses were included in the regression model as candidate factors. There is no candidate level effect statistically when the characteristics such as education level and place of residence were taken into the regression model as confounding factors. The factors that were the most deciding in differentiating the groups who tried an alternative treatment and those who did not, respectively, income level and duration of diagnosis. Regardless of other factors, those with

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Table 3 Findings related to the experiences of subjects who had previously tried CAM ($n = 147$)

	Number of cases	%
Where did the patient hear about alternative therapy?		
Television	28	19.0
Newspaper	2	1.4
Friend	66	44.9
Family members	52	35.4
Internet	22	15.0
Doctor	14	9.5
Own decision	23	15.6
The average cost of alternative therapy		
None	14	9.5
≤50 TL	44	29.9
51–100 TL	34	23.1
101–200 TL	8	5.4
201–500 TL	12	8.2
501–1000 TL	14	9.5
>1000 TL	21	14.3
Explaining to the doctor whether the patient is using CAM		
Yes	57	38.8
Reason for disclosure		
Interaction with chemotherapy	10	17.5
Side effect	23	40.4
Due to being asked	9	15.8
Whether it is harmful	5	8.8
Thinking that the doctor should know	14	24.6
Other	3	5.3
No	90	61.2
Reason for nondisclosure		
Short time use	15	16.7
Considering not necessary	47	52.2
Thinking that it will hurt	13	14.4
Other	15	16.7
Alternative therapy versus drug therapy		
Finding more effective	9	6.1
Finding less effective	65	44.2
Indecisive	73	49.7
If alternative treatment was administered by someone else		
The patient was informed in advance	91	63.2
The patient was not informed in advance	53	36.8

Abbreviation: CAM, complementary and alternative therapy.

an income between 1,000 and 3,000 TL were 2.85 (95% CI: 1.617–5.030) times more likely to seek alternative treatment than those with an income below 1,000 TL. This difference was 3.03 (95% CI: 1.431–6.421) times higher for those with an income of more than 3,000 TL ($p < 0.001$ and $p = 0.004$). When adjustments were made for other factors, the tendency to choose alternative treatment increased 1.860 times (95% CI: 1.045–3.308) statistically in patients who had been diagnosed for 1 to 5 years compared with those diagnosed less than 1 year ago ($p = 0.035$). In ►**Table 5**, the combined

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Table 4 Frequency distributions of alternative treatment types used/tried by subjects who have tried CAM

	Number of cases	%
Herbal mix	31	21.1
Turmeric	23	15.6
Religious faith-based treatment	22	15.0
Nettle	18	12.2
Ginger	16	10.9
Linden	13	8.8
Honey	11	7.5
Grape molasses	9	6.1
Black seeds	9	6.1
Cerago	9	6.1
Psychotherapy	8	5.4
Exercise	8	5.4
Garlic	6	4.1
Leech	6	4.1
Blueberries	5	3.4
Cinnamon	5	3.4
Carob	5	3.4
St. John's Wort (Tipton weed)	4	2.7
Vitamin	4	2.7
Kefir	3	2.0
Rosehip	3	2.0
Oregano	2	1.4
Celery	1	0.7
Other	58	39.5
Total	147	100.0

Abbreviation: CAM, complementary and alternative therapy.

effects of the factors that are thought to be determinative in differentiating these two groups were analyzed by multivariate logistic regression analysis.

Discussion

Classical treatment methods such as surgery, chemotherapy, radiotherapy, and endocrine therapy can cause many physical and psychological side effects such as fatigue, nausea, vomiting, anxiety, pain, and depression in breast cancer patients.[12,13] Patients seek to get rid of these side effects and improve their quality of life, so CAMs are among the methods frequently used in breast cancer patients.[14,15] In this study, which we conducted with 338 patients in our clinic, 147 (43.4%) of the patients were using CAMs. Various studies in the literature show that this rate varies between 20 and 80%.[15,16] This rate varies similarly in studies conducted in our country.[17,18]

In our study, no statistically significant difference was found between the use of CAM and the patients' mean age, marital status, number of children, educational status, place of residence, occupation, active employment or not, and family history. However, the income level of the group using CAM was found to be statistically significantly higher than the group that did not use it. Independent of other factors, it was determined that those with an income level of 1,000 to 3,000 TL were 2.8 times more likely to turn to alternative treatment, and those with an income of more than 3,000 TL were found to be 3.03 times more likely. Similar to our study, in the study conducted in China in 2004 on the use of CAM in patients followed up with breast cancer, an increase in the use of CAM was found with an increase in income level.[19] This is because patients cannot allocate additional budgets for these treatments.

There are studies in the literature showing that patients with a life expectancy of less than 1 year apply to these treatments more frequently.[20] In our study, no significant difference was found in terms of the stage of the disease and these treatments. When adjusted for other factors, orientation to alternative treatment was found to be statistically significant 1.8 times more in those who were diagnosed for 1 to 5 years compared with those who were diagnosed less than 1 year ago. It was thought that the reason for this was the prolongation of the treatment period, increase in

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Table 5 Examination of the effects of factors thought to be determinative in differentiating the groups using and not using CAM therapy together with multivariate logistic regression analysis—alternative table

	Odds ratio	% 95 confidence interval	Wald	*p*-Value
Age	0.983	0.963–1.003	2.686	0.101
Income level				
1,001–3,000 TL	2.688	1.546–4.676	12.263	<0.001
>3,000 TL	2.281	1.232–4.223	6.884	0.009
Diagnosis time				
1–5 years	1.849	1.043–3.279	4.430	0.035
>5 years	1.773	0.933–3.372	3.053	0.081
Stage				
Locally advanced	0.759	0.426–1.355	0.869	0.351
Metastatic	1.163	0.611–2.215	0.211	0.646

Abbreviation: CAM, complementary and alternative therapy.

exposure to drug side effects, and accordingly, personal research and referral from the patient's relatives.

There are many herbs and herbal products that cancer patients frequently use, but the interaction between drugs used in cancer treatment and herbal products can be high.[21,22] In our study, the majority of our patients who applied to CAM were using herbal treatments. Herbal treatments were most often used in admixture. The single most commonly used methods were turmeric, nettle, ginger, and linden. Similar to our study, there are studies in which herbal treatment options are frequently used.[23] It was thought that the reason for frequent referral to herbal treatments was because patients thought that herbal treatments were safer, cheaper, and easily accessible. Since herbal CAMs may interact with many therapeutic agents, it is important to warn patients about this issue. It was understood that methods such as psychotherapy, aromatherapy, meditation, acupuncture, homeopathy, relaxation exercises, which were determined to be used frequently in studies conducted in Europe, were less tried for cancer treatment. Also, in case of Turkey, since the patients did not have sufficient knowledge on this subject, the same was perceived.[24]

Since the majority of the patients in our study believed that these treatments were beneficial, they resorted to these methods to cure their diseases and to support the treatment given by their doctors. They started CAMs most often with the suggestion of their friends. Again, the majority of patients stated that these treatments were less effective than their original treatment. These findings were also consistent with the literature.[25] About 38.8% of the patients told like how side effects. However, 61.2% of the patients did not report the use of CAM stating that they did not find it necessary. This situation may be because patients believe that these treatments are innocent and do not have enough information about the toxicities that may develop. Only 5% of the patients stated that they developed side effects related to CAM. This rate was thought to be low because the patients did not attribute the side effects they experienced to CAMs.

The most important limitation of this study is that it is single-centered and cross-sectional. For this reason, it may not reflect the CAM usage of the whole country. It is possible to reach more comprehensive results with a study involving a multicenter design.

Conclusion

Our study showed that the use of CAM was quite high in breast cancer patients. Doctors should question this situation in every patient, and patients should be informed about their decisions. Thus, it may be possible to protect patients from possible side effects and interruption of treatment because of them.

Ethics

The research was conducted out in line with the principles of the Declaration of Helsinki and was approved by the local ethical committee (No. 2020/31), dated 11.06.2020. The patients were included in the study after the written consent form was read and their signed consent was obtained. After oral explanation was given to illiterate patients and their consent was obtained, a questionnaire was administered in the presence of their attendants.

Funding

None.

Conflict of interest

None declared.

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Bleomycin-Induced Flagellate Dermatitis in Indian Patients with Germ Cell Tumors

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Ind J Med Paediatr Oncol 2022;43:278–279.

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Bleomycin is an antibiotic antineoplastic agent commonly used in systemic therapy for Hodgkin lymphoma, germ cell tumor, squamous cell carcinoma, and gestational trophoblastic disease. Bleomycin-induced pulmonary toxicity is well-known and dose-limiting, though skin reactions have also been occasionally reported. Both pulmonary and cutaneous adverse events are attributed to low concentration of bleomycin hydrolase, a metabolizing enzyme.[1] Several dermatologic appearances including palmar–plantar peeling, nail-bed discoloration, hyperkeratosis, Raynaud's phenomenon, and gangrene of digits are described. Flagellate erythema is a less often described but characteristic toxicity; the reported incidence is 8 to 20% but declining use of bleomycin has reduced incidence of this toxicity as well.[2] Indian or tropical skin may mask the erythematous component in many patients, and the lesions are picked up only if involving large areas of skin. The name is derived from the Latin word "flagellare," meaning whipping or flogging, often for religious or sexual gratification purposes, and the rash mimics that appearance. We encountered two consecutive patients with nonseminomatous germ cell tumors (NSGCT), post-high inguinal orchiectomy, who developed flagellate pattern hyperpigmentation without erythema or itching within 4 weeks of starting first cycle of BEP regimen (plan: bleomycin 30 IU intravenously D1, 8, 15, etoposide 165 mg/m^2 D1–3, cisplatin 35 mg/m^2 D1–3 q 3 weeks for 4 cycles). The first patient was an 18-year boy with left testicular NSGCT (intermediate risk) and the second patient was a 27-year-old man with right testicular NSGCT (poor risk). Both were post-orchiectomy and had Karnofsky's performance status of $\geq$70. The first patient developed the characteristic interlacing streaks, most marked over upper back, right inguinal, and right thigh region (►**Fig. 1A, B**). The second patient had limited hyperpigmentation limited to upper back only, though he had palmar–plantar hyperpigmentation and nail changes as well (►**Fig. 1C, D**). Since the patients had good performance status, normal biochemical parameters, and less than 10% of body surface area involved with the rash, chemotherapy was continued on original schedule with weekly monitoring of rash. Both patients completed the planned chemotherapy without further progression of the flagellate rash. The incidence of this rash appears unrelated to cumulative bleomycin dose, or duration of drug administration. It is mostly self-limiting but requires monitoring and possibly bleomycin discontinuation if progressive or extensive. Skin examination should be a routine part of monitoring bleomycin toxicity in addition to pulmonary function testing so that the rash is not missed especially in dark-skinned individuals.

Flagellate erythema, though a characteristic toxicity, may be associated less often with other systemic agents such as doxorubicin, docetaxel, trastuzumab, and bendamustine, as well as following intake of shiitake mushrooms.[3–5] Rheumatologic conditions such dermatomyositis and Still's disease (adult onset) may also have centripetal flagellate erythema as a cutaneous manifestation.[6] Histopathologic examination may be undertaken in doubtful cases when the association with implicated drugs or dietary items is less clear on history and there are no other predisposing rheumatologic conditions, when the appearance of rash is not characteristic, when infective/parasitic etiology has to be ruled out, or when the rash progresses despite discontinuation of the implicated agent and supportive management. Typically, lymphocytic infiltrates in dermis with high number of eosinophils and occasionally lymphocytic vasculopathy may be observed in flagellate dermatitis.[7]

DOI https://doi.org/10.1055/s-0042-1749394.
ISSN 0971-5851.

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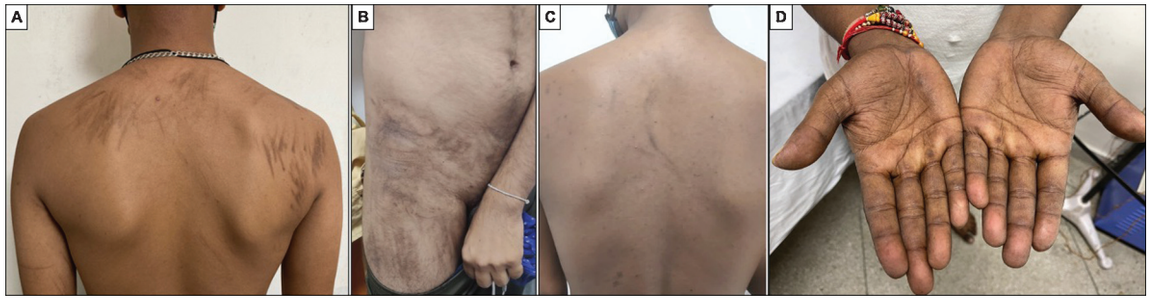

Fig. 1 (**A**) Photograph of patient 1 (18-year boy with intermediate risk nonseminomatous germ cell tumor, NSGCT) with flagellate hyperpigmentation over upper back and (**B**) right thigh and inguinal region. (**C**) Photograph of patient 2 (27-year-old gentleman with poor risk NSGCT) with limited flagellate rash over upper back and (**D**) palmar hyperpigmentation.

Authors' Contributions

S and SG were involved in data collection, literature review, manuscript preparation, and final approval, while KP and RM were involved in manuscript review, revision, and final approval.

Funding

None.

Conflict of Interest

None declared.

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Florence Nightingale Needs Your Attention: A Framework for Improving Pediatric Oncology Nursing in Low- and Middle-Income Countries

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Ind J Med Paediatr Oncol 2022;43:280–284.

Executive Summary

- Children with cancer in low- and middle-income countries (LMIC) succumb to their disease four times more often than those in high-income countries (HIC).[1]
- Ninety percent of all pediatric cancers occur in LMIC.[2]
- In HIC, more than 80% of children with cancer are cured, but in LMIC only 26% survive.[3]
- Nurses play a vital role in the care of children with cancer.
- Causes of low survival in LMIC include shortage of dedicated pediatric cancer centers, trained pediatric oncology team members, inadequate supportive care, abandonment of treatment, excess relapse due to poor adherence, and lack of understanding as well as capacity to implement complex treatment requirements.
- Pediatric oncology nurses play a key role in mitigating these causes of excess treatment failure.[1,4]
- Pediatric oncology nursing in LMIC faces a crisis from workforce shortage and lack of standards.
- The shortage of pediatric oncology nurses in LMIC results from low salaries, lack of career progression, lack of training opportunities, limited structured training programs, long irregular working hours, unsafe working conditions, and in some cases lack of respect for the profession.[5,6]
- Baseline standards for pediatric oncology nursing care are well established, but most hospitals in LMIC do not meet the standards.[7]
- The time for action is now.
- There is an urgent need to ensure that baseline standards for pediatric oncology nurses are met in LMIC to achieve the World Health Organization's (WHO) goal of improving childhood cancer survival in LMIC to 60% by 2030.[8]
- Effective interventions proven to improve pediatric oncology nursing and empower nurses in LMIC include onsite subspecialty oncology nurse education and mentoring, implementation of a career ladder with concrete steps for advancement, and adherence to safety standards for handling of chemotherapy as well as blood products.[7]

Venkatraman Radhakrishnan and Sanjeeva Gunasekera equally contributed to the manuscript (Co-first authors)

DOI https://doi.org/10.1055/s-0042-1748938.
ISSN 0971-5851.

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Table 1 Illustrative case of challenges faced by pediatric oncology nurses in low- and middle-income countries

Case: It is a warm and humid summer night in Southern India and Nurse Mary is the nurse on the night shift along with her colleague in the pediatric oncology ward at a cancer hospital in a big city. These two nurses are taking care of more than 50 children during their shift. Mary has 10 years' experience working in pediatric oncology and her colleague is fresh out of nursing school. Over the next 12-hour shift, they will check the vital signs for all the children, administer chemotherapy and supportive care medications, attend emergencies, assist the doctor with patient care, complete their nursing charts, replace fluid bottles, insert cannulas, draw blood samples, and request for lab tests and radiology. Neither Nurse Mary nor her colleague has received formal training in oncology or pediatrics; all their learning has happened on the job. This is a scenario playing out daily in pediatric cancer centers in low- and middle-income countries.

Introduction

Nurses make up the largest section of the healthcare workforce.[8] According to the WHO, there are ~29 million nurses and midwives in the world. The WHO has given due recognition to the nurses by naming the year 2020 "The Year of the Nurses." There was a shortage of 9 million nurses in the World in 2014 and most of the shortages were in LMICs.[5] The ratio of nurses per 1,000 population varies from 17.5 and 11.1 in Sweden and United States to 1.4 and 2.1 in India and Sri Lanka.[5,9]

Nurses form the backbone of the healthcare system, especially in the hospital setting. They have the most interaction with patients and caregivers among all healthcare professionals. They play a key role in continuous monitoring of patients' condition, implementing care, and act as a patient advocate.

The Burden of Pediatric Cancers

Eighty percent of the 400,000 new pediatric cancers diagnosed in the world every year occur in LMICs.[1] Compared with 80% survival reported in HICs, the survival in LMICs is significantly inferior and ranges from 10 to 50% based on the country.[2] Therefore, it is expected that ~160,000 to 200,000 children with cancer will die in LMICs every year. Lack of adequate nursing services can contribute significantly to this deficit.[2]

Justification for Addressing This Issue

- A systematic review suggests that nurses working in understaffed oncology/hematology units are more likely to suffer from work-related stress and burnout.[12]
- The challenges faced by pediatric oncology nurses in LMICs have been highlighted in ►**Table 2**.
- Although the study was not specific to oncology settings, a recent systematic review clearly showed the association between a higher number of registered nurses employed and lower mortality in tertiary care hospitals.[13]
- In a study done in South America, building a sustainable model of Pediatric Oncology Nursing education proved both possible and financially feasible.[3]

Scope of the Problem

- Nurse to patient ratios in most LMICs is well below the recommended rates even by LMICs standards.[6,9] A nurse to patient ratio of 1:5 is the accepted standard for pediatric oncology wards. However, a survey of 46 LMICs revealed this standard was met only in 28% of centers.[5]
- Forty-eight percent of nurses who work in pediatric oncology centers in LMIC have had no formal training in pediatric oncology before commencing work (see ►**Table 1**).[5]
- Many nurses are frequently rotated out of pediatric oncology units preventing them from gaining the needed skills and expertise.
- Only 52% of nurses had a formal orientation program before they started in pediatric oncology wards. An orientation program of more than 2 weeks was only experienced 30% of the time.[5]
- In Sri Lanka's public hospital system, nurses are rotated every 4 years preventing them from getting the necessary experience and competence by working for an extended period in a pediatric oncology ward. This is a problem that exists in many other LMICs too.[10]
- Trained nurses in India, Sri Lanka, and many other LMICs prefer to migrate to HICs due to economic considerations. This leads to significant manpower and financial loss to the health systems of these countries and discourages governments from investing in training nurses.[11]

Key Steps Needed to Achieve Baseline Standards for Pediatric Oncology Nursing Care in LMIC

- Make the pediatric oncology nurses' roles more attractive and offer career advancement opportunities that may include nontraditional roles in advanced practice nursing and research.
- Establish training programs and fund the position of "Nurse Educator" in pediatric cancer units to provide continuous training and mentoring as oncology nurses are onboarded and nurtured through the course of their career.
- Encourage twinning and regional exchange programs for capacity building of pediatric oncology nurses.
- Conduct periodical reviews to ensure the success of the above interventions using a validated tool.

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Table 2 Challenges with pediatric oncology nursing in low- and middle-income countries

1. High staff attrition, turnover, and mandatory rotations
2. Few dedicated pediatric oncology nursing posts
3. Low salaries
4. Long working hours
5. Lack of training and mentoring
6. Lack of respect and representation in hospital leadership
7. Few opportunities for career progression
8. Migration of specialized nurses to centers in high-income countries in search of better pay, more job security, and improved lifestyle
9. Unsafe working conditions including lack of personal protective equipment, lack of chemotherapy mixing stations with adequate ventilation, exposure to needles as well as blood products, and other potential hazards

Baseline nursing standards in pediatric oncology in LMICs

The International Society of Pediatric Oncology (SIOP) Global Health Nursing Working Group published baseline nursing standards in pediatric oncology.[6] These are the standards any LMIC needs to strive for and some salient features are as follows.

1. A nurse-to-patient ratio of 1:5 for general pediatric oncology units and 1:2 for critical care and transplant units.
2. Training in the form of formal orientation with learning objectives, including theory and practice for all new nurses joining the pediatric oncology department. Nurses should have the required competencies after completing the orientation program.
3. Continuing education and assessment after induction to maintain skills and knowledge. A minimum of 10 hours of training in a year is recommended.
4. Nurses are recognized as core members of the multidisciplinary team involved with the care of children with cancer.
5. Nurses have resources for providing safe and efficient care.
6. The hospital has an evidence-based policy that guides the delivery of quality nursing care.

A survey of nurses from 101 hospitals in 54 countries identified the following factors as predictors of nonachievement of standards mentioned above: low current health expenditure as percentage of gross domestic product, WHO Africa region, United Nations "developing or transition" country classification, countries with fewer than 3 nurses/midwives per 1000 population, and hospitals without bone marrow transplant and/or intensive care units.[14]

Stakeholders and Methods

The major stakeholders involved with pediatric oncology nursing are the nurses, pediatric oncologists, nursing councils, nursing colleges, ministries of health, local ministries involved in education and quality, hospital administrators, recruiters in HICs, and children with cancer and caregivers. This policy brief is the result of input from a policy brief development exercise with the St. Jude Global Nursing and Asia Pacific programs, consultations with the SIOP Global Health Nursing Working Group, discussions with nursing and physician colleagues in India, Sri Lanka, and other LMIC, interactions with international experts, and engagement with the public sector via inputs from CanKids (www.cankidsindia.org). This is the largest pediatric nongovernmental foundation in India dedicated to childhood cancer that provides direct patient support, but also support for training and salary support for key pediatric oncology nurses.

Recommendations to Address These Problems

We propose a framework for improving nurse recruitment, reducing attrition, and providing training to nurses in pediatric oncology (►**Fig. 1**). This framework has been adapted by the authors from the SIOP Global Health nursing working group guidelines[6,15] and integrating perspectives of the health system.

1. Recognizing pediatric oncology nursing as an important specialty

Pediatric oncology nursing requires a unique skill set and is often more demanding than other nursing disciplines. Therefore, their remunerations should reflect on this increased expertise and greater sacrifices. An established career development plan should be established for all recruits. Nurses working in specialized units like pediatric oncology should be given enough time to develop experience and skills without subjecting them to mandatory rotations. Specialized training in pediatric hematology and oncology nursing should be essential for nurses working in these particular units. The hospital administration should ensure that the nurses with these specific competencies be assigned to pediatric oncology patients. It is important to create pediatric oncology nursing networks and nurses should be encouraged to participate in the network.

The important role they play should be recognized at the local level as well as nationally. This can be done through hospital-based functions or media campaigns using traditional and social media nationally. These steps will not only help to attract more nurses to pediatric oncology but also reduce migration and attrition. Establishing and strengthening dedicated pediatric oncology centers will provide additional opportunities for nurses interested in pediatric oncology and create the context for development, training, and retention of sub-specialty nursing expertise. Increasing the numbers of specialized centers with trained multidisciplinary team members will also improve access to care for children with cancer in underserved regions.

2. Using pediatric oncology nurses beyond their traditional role

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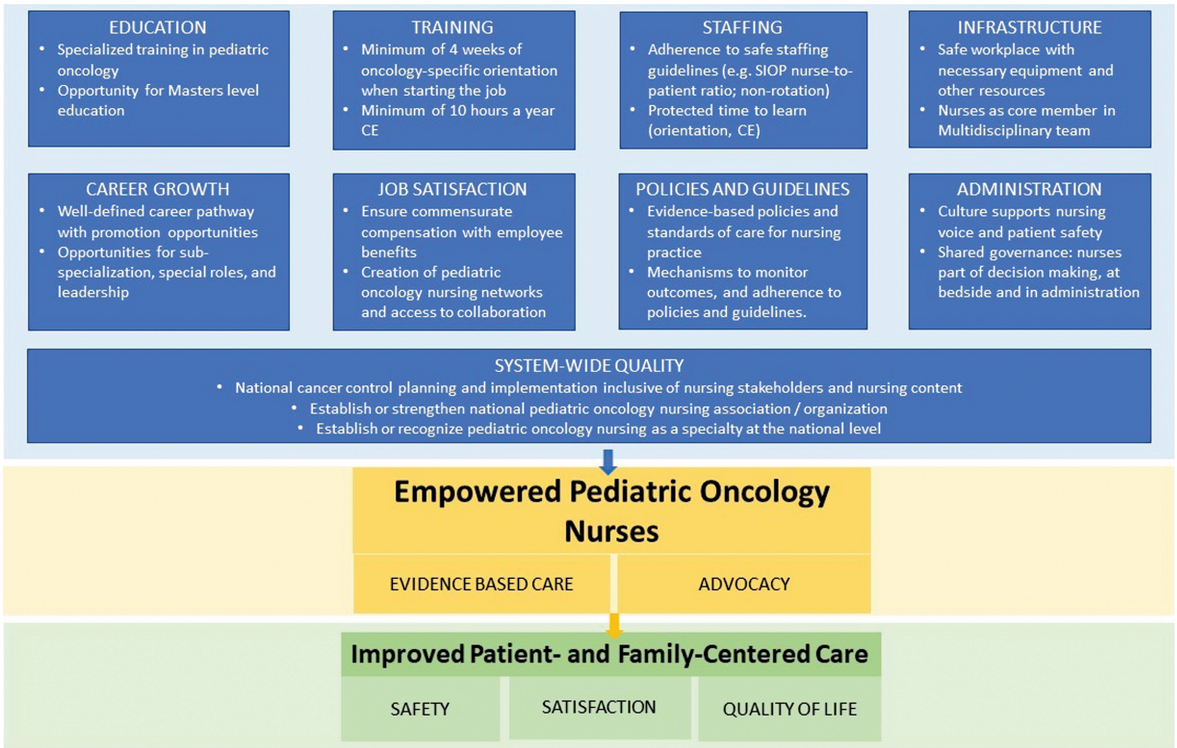

Fig. 1 Framework for empowering pediatric oncology nurses.
Category of needs **(blue)** and outcomes **(yellow/green)** are shown in capitalized headings, with bullet points of recommendations for success. These can all be affected by support/ interventions at a hospital- and/or national level.
CE, continuing education; **SIOP**, International Society of Pediatric Oncology.

A trained pediatric oncology nurse can work in areas that extend beyond their traditional domain of patient care, counseling, and administration of medicines with supportive care. Some of these areas include research and evidence-based medicine, palliative and end-of-life care, and survivorship.[16]

Studies including meta-analysis have shown that oncology nurse-led interventions are effective, lead to better implementation, and improve patient quality of life.[16,17] Engaging nurses in these roles will not only be more cost-effective for the health system but will also broaden the career prospects of nurses.

3. Establishing a formal nurses training program and the position of a "Nurse Educator" in pediatric cancer units

In 2007, the St Jude Children's Research Hospital conducted a study where they employed a full-time nurse educator in a pediatric oncology unit in Guatemala.[3] The nurse educator was trained here and she provided pediatric oncology education for newly hired nurses, teaching courses in chemotherapy administration as well as central venous line care, and providing continuing education and onsite mentoring. Eighty-six percent of nurses employed in the hospital participated in the chemotherapy course and 93% achieved competency, 57% participated in the central line course, and 79% achieved competency. The nurses completed an average of 26 hours of continuing education yearly. The cost of employing the nurse educator was $244/nurse per year and was found to be effective and sustainable for LMICs. A similar study done in a pediatric hematology unit in Tanzania in collaboration with the American Society of Hematology observed that a nurse educator-led training program increased the nurses' confidence, respect, and participation in interprofessional team decision making.[18]

Therefore, a "Nurse Educator" lead in a formal educational program can play a pivotal role in improving nursing services as well as providing new career options to pediatric oncology nurses.

4. Encouraging twinning programs for capacity building of pediatric oncology nurses

Most pediatric oncology nurses in HICs receive extensive training before joining a new job and they continue to receive training while working. Such training is mostly not available to nurses in LMICs and this contributes to the disparity seen in the survival of children with cancer in HICs and LMICs. However, the nurse in HICs can mentor the LMIC nurses to build up competencies, expose them to international best practices, and introduce new technologies. Many such twinning and regional support programs exist in other areas of childhood cancer and can be successfully extended to and sustained for nursing care as well.[19] This will have the added benefit of raising the profile of LMIC pediatric oncology nurses and help in raising the morale of nurses.

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5. Re-evaluate periodically the success of the above interventions

The primary objective of the above interventions is to help institutions and countries achieve Baseline Nursing Standards, and empower nurses as part of broader strategies cognizant of needs across the health system, as summarized in ►**Fig. 1**. A validated instrument to measure achievement of baseline standards for pediatric oncology nursing in LMICs has recently been developed.[20] Using this instrument to benchmark the successes of the above interventions will help countries be more efficient in their endeavors.

Conclusion

There is ample evidence to show that improvement in the pediatric oncology workforce and training can have a positive outcome on children with cancer. There is an urgent need to address the shortage of pediatric oncology nurses and deficient training of pediatric oncology nurses in LMICs. We believe the above steps will go a long way in addressing this deficit.

Conflict of Interest
None declared.

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Access, Affordability, and Sustainability: Barriers to High-Quality Care in a High-Income Country

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Ind J Med Paediatr Oncol 2022;43:285–288.

Introduction

There is a perception among oncologists that the field of global oncology pertains only to matters related to low- and middle-income countries (LMICs). It stems from a perception that considers lack of access to cancer care and unaffordability of therapy as problems that plague the less affluent regions of the world. In this commentary, we aim to shed light on the fact that these issues do not respect the dichotomies of high-income versus low-income countries or the global north versus south.

When physicians from high-income countries were surveyed about the access to cancer medicines deemed essential by the World Health Organization, a large majority of them felt that these medicines, including immunotherapy, were universally accessible (i.e., no substantial out-of-pocket expense for >90% of patients).[1] Unfortunately, the inaccessibility and unaffordability of cancer care are profound even in high-income countries, although we perceive it as otherwise. This inaccurate fact stated by practicing oncologists makes it clear that their current understanding of the accessibility and affordability of cancer care as oncologists is faulty.

Almost 27 million (8.6%) Americans were still uninsured in 2016.[2] A large proportion of cancer survivors experience financial hardships due to cancer.[3] Even if we falsely assume that the out-of-pocket expense for the individual is marginal, the economic burden of cancer care is steadily rising. It is definitely not sustainable for the economy in the long run.

The US Healthcare System: An Eagle's Eye View

In the United States, the government provides two types of health coverage for patients under the supervision of the Center for Medicare and Medicaid Services (CMS). Medicare for patients more than 65 years of age and Medicaid for the disabled. Most private and public sector employers provide health insurance as part of the employee benefits.[4] A private health insurance coverage can be bought for a monthly fee from the marketplace for the self-employed. Health insurance does not cover all healthcare expenses (referred to as "cost-sharing"). Health insurance would start covering the costs after an initial "deductible" is being met by the patient, which can be ranging from hundred to a few thousand dollars depending on the plan. Then, once the patient goes for a doctor visit, he/she may have to pay a small fee (referred to as co-pay) at the respective offices, usually about 25 to 100 dollars.

Even after the patient meets the deductible, most insurance plans pay only a part of the cost, ranging from 60 to 80%. The patient has to pay the remainder of the price ("co-insurance"). All these costs are covered by the patient account for the "out-of-pocket-maximum," which is usually in the order of a few thousand dollars. Once the patient meets the "out-of-pocket- maximum," the subscribed health insurance plan usually covers the remainder of the cost. The "Donut hole" is the gap in insurance coverage when a patient is responsible for the cost of the drugs after an initial period

DOI https://doi.org/10.1055/s-0042-1748798.
ISSN 0971-5851.

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where the plan pays for the medications. If the patient is "uninsured" or "self-paid," they have to depend on the safety net hospitals that may provide some financial assistance.

Pharmaceutical benefits managers (PBMs) manage the prescription drug benefits for private insurers and government health plans.[5] Even though the PBMs were introduced to decrease the cost of prescription medicines, in reality, they work as a middleman, leading to increased cost of drugs, lower value, and increased administrative burden.

The Three-Legged Problem

We can categorize the problems in the American healthcare system into three major parts.

First, it is inaccessible. The inaccessibility of cancer care can be due to multiple reasons—regional, geographic, ethnic, racial, or socioeconomic disparities. For instance, the survival of breast cancer patients is adversely affected by where they live; patients who live in poorer neighborhoods have reported decreased survival rates.[6] The racial disparities, Black, Hispanic, and Native American patients have more inadequate access to cancer care and consequently reported worse survival rates, have been well established in multiple cancers, including prostate cancer,[7,8] cervical cancer,[9] and head and neck cancers.[10] Geographical disparities in cancer care have been well documented in various cancers, including breast cancer, colon cancer, and prostate cancer.[11,12] For instance, geographical differences and socioeconomic deprivation lead to late-stage diagnosis and worse survival in colon cancer.[13] Unfortunately, all of these disparities work hand-in-hand to make timely cancer care inaccessible to the most vulnerable population.

Second, it is unaffordable. Financial toxicity in cancer care is defined as the harmful personal financial burden faced by patients receiving cancer care.[4] Catastrophic health expenditure refers to any medical expense that can threaten the household's financial stability.[14] One in three Americans experiences financial burden as a result of medical care.[15] The risk of a high financial burden is significantly greater in patients with cancer than patients with other chronic medical conditions.[16] Thirteen percent of the nonelderly patients with cancer spend at least 20% of their income, and 50% of the elderly (Medicare beneficiaries) spend at least 10% of their income on cancer treatment-related out-of-pocket expenses.[16,17] Patients with cancer had a nearly threefold more significant risk of declaring personal bankruptcy. Those bankrupt patients had a 79% higher mortality risk than those who did not.[15,18] Zafar et al explained the three possible reasons behind the relationship between financial distress and a higher risk of mortality[15]: poorer subjective well-being,[19] impaired health-related quality of life,[20] and subpar quality of care.[21]

Finally, it is unsustainable. The US healthcare expenditure is almost 3 trillion dollars/year (almost equal to the gross domestic product [GDP] of India in 2021).[22] It is nearly identical to 18% of the GDP of the United States. The cost of healthcare is rising year by year. Cancer care costs are estimated to grow by 34 to 246 billion dollars by 2030.[23] It is unsustainable for the country's economy.

Table 1 Contributing factors for financial toxicity in the United States

1. Overdiagnosis
2. Overtreatment
3. Unnecessary use of diagnostic testing
4. Use of low value practices
5. Injudicious use of expensive treatment modalities
6. Lack of pricing competition and choice
7. High price of innovative therapeutic techniques
8. Use of extended course radiation treatment and indiscriminate use of proton therapy
9. Excess burden of billing and insurance-related administrative cost
10. Lack of awareness of the cost among physicians and the patients
11. Lack of price transparency

Contributing Factors for Financial Toxicity

Multiple factors contribute to financial toxicity in the United States (►**Table 1**). Unnecessary use of diagnostic testing leads to wastage of almost 210 billion dollars per year.[24] Overdiagnosis (when a condition is diagnosed that would otherwise not go on to cause symptoms or death during a patient's lifetime) and overtreatment (when medical services are provided with a higher volume or cost than appropriate) are also pervasive problems.[25,26] It is estimated that up to 30% of the US healthcare cost is wasted money.[27] The use of low-value practices, including the injudicious use of expensive treatment modalities that offer a marginal benefit at best, also leads to substantial financial toxicity. A lack of pricing competition and choice also leads to increased cost of healthcare products and technologies.[28] The CMS is banned from negotiating drug prices which affects the medication cost for millions of Americans. A study that reviewed the cost of cancer medicines (e.g., rituximab and bevacizumab) found that Americans are paying almost twice the price compared with Norway, likely due to the lack of negotiating power for CMS.[28] The high cost of innovative therapeutic techniques is also a contributing factor, especially when used in terminal disease.[28] The use of more extended course radiation treatment and indiscriminate use of proton therapy may also contribute to financial toxicity.[29] Another cause is the excess burden of billing and insurance-related administrative cost—both by the insurer and the provider. It was estimated by a recent study in 2017 by Woolhandler and Himmelstein that the United States spends 1.1 trillion dollars on administrative costs, which is almost one-third of the healthcare expenditure.[30]

Lack of awareness of the cost of various therapies contributes tremendously to financial toxicity. Significant numbers

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of physicians in the United States believe that cancer care is accessible and affordable to the whole population, but in reality, it is not.[1] Physicians' knowledge about the cost of diagnostic tests, medicines, or healthcare visits is poor.[31] It was found that when the data on the fees were provided to the physicians, they cut down the use of ordering tests.[32] So, it is crucial to educate the physician community about this cost of healthcare. Another pervasive problem pertains to the lack of price transparency. It is challenging for patients to determine how much a medical intervention will cost them. Sadly, even physicians are in the same boat.

Solutions

The Institute of Medicine in the United States has called for attention to the "waste in healthcare" and came up with suggestions to provide "best care at lower cost" in 2013.[33] "Choosing wisely" campaign has been initiated as a part of this effort to curtail the use of low-value practices and thereby to decrease the cost of health care.[27] Various organizations of physicians involved in cancer care, like the American Society of Clinical Oncology and the American Society of Radiation Oncology, have come forward with their recommendations to help in this regard.[27,34] These efforts may have improved the awareness of low-value practices among oncologists; but there is no definitive evidence that these have successfully curtailed the cost.

Having the influence and power for negotiation curtails the cost of drugs to some extent.[35] There have been some efforts to control prescription drug pricing, but more efforts are needed at a policy level.[36] Recently, there has been an effort to have online pharmacies that can cut the cost for the patients (e.g., the cost-plus drug company). We believe this will result in competitive pricing among the various PBMs. The medical community and policymakers are having more discussions about the lack of price transparency.[37] Allowing CMS to have the power for price negotiation will help curtail the cost of drugs. At the level of physicians and patients, education efforts are needed to improve the awareness of the problem and the potential solutions.[32]

Take a Leaf Out of the Indian Scene

Cancer care in India is burdened by financial toxicity, much more than in the United States.[14] There are multiple reasons for this, including the lack of insurance, poverty, and lesser spending by the government on healthcare. It is often suggested that the average Indian middle-class family is one medical bill away from poverty. But there are some silver linings in India; there are multiple options for generics and biosimilar drugs, which have helped decrease the cost for the patients.[38] For instance, Nair et al reported that the availability of rituximab biosimilars in India tremendously cuts costs, leading to increased access to this life-saving therapy (35% in 2010 to 95% in 2020).[38] Greater access to generics and biosimilars can help reduce the price of cancer therapy in the United States, with no detrimental impact on outcomes.

Conclusion

There are critical challenges to delivering cost-sensitive cancer care in high-income countries. Understanding the issues and applying best practices in other parts of the world would help address some pervasive problems. We believe that such bidirectional learning would improve patient care and exemplify the true meaning of global oncology.

Conflict of Interest
None declared.

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The Intersection of Tobacco Use, Health Disparities, and Inequalities in Lung Cancer Treatment and Survival

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Ind J Med Paediatr Oncol 2022;43:289–293.

Abstract

Tobacco use and socioeconomic status are related with each other and important determinants of disparities and inequalities to access to care. There is overall reduction in number of smokers but still most number of smokers is represented by people from low socioeconomic status, with less number of these people having an access to the treatment centers. Patients who are tobacco users have shown to be less likely to receive any form of treatment for lung cancer, whether that be chemotherapy, radiotherapy, or surgery. As there is less awareness about signs and symptoms of lung cancer, lower socioeconomic patients are likely to report to hospitals at advanced stages or many times as a medical emergency. We are well aware that patients with advanced lung cancer have lower chances of survival in view of incomplete response to treatment. As there is an intersection between tobacco use, health disparities, and inequalities and lung cancer treatment and survival, this issue needs better focus and attention to minimize disparities and inequalities in access to care and outcomes.

Keywords
- lung cancer
- tobacco
- smoking
- inequalities
- health disparities

DOI https://doi.org/10.1055/s-0042-1750205.
ISSN 0971-5851.

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Introduction

Globally, lung cancer contributes 11.4 and 18% in overall cancer incidence and mortality, respectively, making it one of the leading causes of morbidity and mortality.[1] Not only disparities and inequalities in lung cancer care pose a challenge to increase survival but pattern of tobacco use and availability and affordability of health care facilities add more challenges. Use of tobacco products, mainly cigarette smoking, remains the leading preventable cause of death for all population groups.[2] However, there is a clear socioeconomic divide between the numbers of cigarette smokers.

Socioeconomic, Ethnic, Racial, and Health Disparities

Cigarette smoking as a risk for lung cancer mortality is influenced by many variables like race, socioeconomic status, and gender. Largest socioeconomic disparity has been reported in lung cancer in view of greater environmental exposures, contributing to increase incidence and mortality.[3–5] Poor prognosis is more commonly associated with lower income patients than higher income patients as they are less likely to receive curative treatments.[6] Although there is a decline in the incidence of lung cancer among black men, but still that is higher when it is compared with white men. Female racial smoking pattern is reflected by consistently higher new lung cancer diagnosis in white than black women.[7]

Studies have shown an association between lower socioeconomic status and higher chances for lung cancer with higher chances of presentation at a more advanced stage. This can be well understood with relationship between race, socioeconomic status, lung cancer occurrence, and outcomes.[8,9] Individuals with a lower socioeconomic status, represented by both poverty and lack of education are more likely to be current cigarette smokers.[10] During 2003 to 2011, men with less than a high school education and those below the poverty level had 2.6 times higher lung cancer mortality than their more educated and affluent counterparts. Education and income levels were also inversely related to female lung cancer mortality. Education and income inequalities in lung cancer mortality increased over time.[11]

Ethnic and racial disparities in lung cancer due to tobacco are also significantly marked. Lung cancer mortality is 10% higher for black men, than white men but 31% higher for white women than black women.[12] Using the Surveillance, Epidemiology, and End Results 18 database, Wafa et al recently demonstrated that Asian lung cancer patients exhibits lower incidence and mortality rates, when compared with blacks or whites.[13] There is substantial data that correlates racial discrepancies of lung cancer genes among different populations, hence suggesting "genetics" as an important factor for disparity among populations. Consider the frequencies of epidermal growth factor receptor (EGFR) mutations, its highly prevalent in Asian populations (30%), when compared with whites (7%).[14] Another study observed that African American population harbor 2.4% EGFR mutation, compared with 14.1% in whites.[15] Later, studies do suggest that EGFR mutation rate occurring in these populations was quite comparable.[16–18] However, still EGFR mutation burden is found to be on the higher side in Latin American cohort ($>$ 30%).[19] All these findings suggest that occurrences of genetic alteration among patients of lung cancer of diverse racial backgrounds play important role in lung cancer incidence.

One study indicates that high risk of lung cancer in Latinos and African American may be attributed to use of menthol cigarettes despite prevalence of fewer cigarette consumption on daily basis. Despite fewer cigarette consumption on daily basis, intermittent use of cigarette smoking, and initiation of smoking at later stage of life in comparison with white smokers, black smokers are at increased risk of lung cancer due to peculiar nicotine metabolism.[20,21] Smoking is the cause of nearly 87% lung cancer deaths.[21]

During the past 50 years, landscape for gender-based differences in global lung cancer incidence has vividly shifted. Results from Cancer Incidence in Five Continents (CI5), a 5-year study performed by the International Agency for Research on Cancer demonstrated that Turkey has the highest lung cancer rates followed by European countries, that is, Belarus and Croatia, in men. Among women, highest rates were observed in Denmark, followed by African Americans in U.S. and Iceland.[22] There is a speculation that women are more susceptible to develop lung cancer compared with men, at parallel level of exposure. This distinctness might be due to molecular alterations associated with the disease between the two genders.[23]

Smokers are most commonly disadvantaged citizens socially and economically.[24] A study within the United States showed that the number of smoking-related deaths in middle-aged men who achieved no more than a high school education was twice the amount of that then those who achieved more than a high school education.[25] In fact, within the United States, it has been shown that two of the largest tobacco manufacturers target their advertising to "working class" young people. Further driving the number of young lower-class citizens to start smoking at a younger age.[26] This particular class are also more likely to smoke more cigarettes a day and are less likely to stop smoking in comparison to higher class groups.[27]

The lower socioeconomic class smokers require more support and assistance in smoking cessation as they are more often intensely addicted to nicotine.[28] These people are less likely to seek out and receive adequate medical support, make it a difficult barrier in making services accessible to all.[29] The public health campaigns that have been implemented across Europe have been successful in reducing the number of smokers. However, this reduction has mostly occurred among the middle- and high-income groups.[30] Quitting smoking is also difficult for low socioeconomic classes. Higher level of education contributes significantly in quitting smoking in comparison to other individuals with lower level of education.[21] Further highlighting the disparities within the use of tobacco among socioeconomic classes.

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Disparities in Survival

Lung cancer is one of the most common cancers, and tobacco smoking is the most common and well-established cause for it. Increased use of cigarettes among lower socioeconomic population is attributing to the higher incidence of lung cancer.[5] Lower survival rates among lower socioeconomic groups are reported and this difference in cancer survival rates may be due to division of socioeconomic class.[31] There may be many contributing factors to this situation like patients failing to seek medical treatment on time and report to hospital in emergency with advanced diseases, or primary health care services in deprived area are less effective. Therefore, lower socioeconomic patients are likely to present late or as a medical emergency. Both of which lower their chances of survival. Lower socioeconomic groups are also more likely to start smoking at a younger age, therefore they expose their lungs to carcinogens for a prolonged period of time and are more likely to develop lung cancer in later part of their life.[32]

American Thoracic Society released a statement on health care disparity in lung cancer and found that the current guidelines do not take into account the racial, ethnic, and gender-based differences which do not fully include high-risk individuals. Disparities in availability of health care facilities for rural high-risk patients, insurance cover, status of the individual's education, and financial conditions are among the point found which needs to be addressed.[33] Participation rate of black smokers was comparatively low in the National Lung Screening Trial, while study results show higher rate of mortality reduction among black then in white.[20]

Numerous studies have documented disparities in survival among patients diagnosed with non-small cell lung cancer (NSCLC). In particular, patients who are non-white,[34–36] low income,[37,38] or uninsured[39,40] have a higher mortality rate from NSCLC compared with other patients. Surgical resection, the most successful treatment, is an option only for localized disease[41] and individuals presenting with advanced disease, have fewer options for successful medical intervention. Thus, black patients are less likely to have the option of surgical resection, which may contribute to the lower 5-year survival. Access to chemotherapy and radiotherapy is also very limited.

In spite of the existence of these disparities, stage of the disease and delivery of the treatment on time are more important predictors of survival than race and socioeconomic status.[42] In the delivery of care for patients diagnosed with NSCLC, disparities that pertain to individual characteristics such as race, marital status, education, and age have been reported both in receipt of treatment and survival.[43]

Disparities in Treatment

Socially and economically deprived groups are also deprived of on time treatment and report lower treatment rates.[44] These patients are less likely to receive any form of treatment whether that be chemotherapy, radiotherapy, or surgery.[6] This disparities to receive cancer treatment can be influenced by other mediating factors that include exposure to distinctive environmental conditions linked to residential segregation, genetic differences, resilience factors, nativity/migration, and cultural practices and beliefs, and availability of treatment factility.[45,46]

Tobacco use and socioeconomic status are related to each other and are important determinants of disparities and inequalities to access to care. There are overall reduction in number of smokers but still represented by people from low socioeconomic strata with less number of people having an access to the treatment centers.[47] Prolonged exposure and increased frequency of exposure are important determinants of higher incidence of lung cancer among this population. These patients are particularly difficult to treat in view of late stage of presentation where intent of treatment change to palliative and also mispresumptions are made by medical staff due to their class.[29]

Education inequalities are important factors for tobacco use and lung cancer management. Better survival is reported in many studies among early-stage lung cancer patients who are more educated. A Swedish study reported that early-stage lung cancer patients with high education level had better survival whereas lower survival was observed in high educated stage III lung cancer patients.[48] One study observed higher overall survival in higher educated early-stage disease out of three studies on socioeconomic and educational inequalities in overall survival from lung cancer in England.[49] One study from Denmark discussed the role of educational inequalities in overall survival which were explained by differences in stage of lung cancer at diagnosis, delivery of first-line treatment, comorbidity, and lower cancer survival.[50] Two studies reported worst overall survival in lung cancer patients living in deprived areas in view of difference in receipt of prescribed treatment.[51,52] Higher concentration of deprivation and lower levels of education was associated with decrease in survival in an American study.[43] However, it is unclear how clinical and treatment differences contribute to these survival differences.

Conclusion

Disparities and inequalities in terms of tobacco use and lung cancer treatment and survival have been reported in many studies. Association of these factors have been observed in lower socioeconomic population, socially deprived population, and less educated population and found to be significantly influencing the overall survival of lung cancer patients. More work is required to better educate the lower socioeconomic class to not undertake and to stop smoking as optimal strategy for preventing lung cancer.

Conflict of Interest
None declared.

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Neuroblastoma in India: Closing the Gap

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Ind J Med Paediatr Oncol 2022;43:294–295.

In low- and middle-income countries (LMIC), there is a paucity of childhood neuroblastoma (NB) cases diagnosed in contrast to the expected number, and this pattern is also seen in India.[1] The incidence of NB is notoriously hard to ascertain, given that >30% of patients with NB may have the disease form that is surgically resectable or self-involuting. Patients who have aggressive NB may be confused with other malignancies in the absence of adequate pediatric oncology care services. The concept of "incidence gap" in childhood cancers is well recognized, but is especially problematic in a LMIC.[2] While the expected number of annual cases of NB in India is around 3000, we estimate that under 1,000 children are diagnosed each year; approximately a third of that reported from the Surveillance, Epidemiology, and End Results (SEER) program.[3] These data are derived from the International Incidence of Childhood Cancer report, with data from 7 Indian population-based cancer registries representing 4% of the Indian population.

In addition, for patients with NB who are diagnosed in India, there are gaps in knowledge about biology, presentation, and outcomes. To better understand the landscape of NB in India, we launched the India Neuroblastoma Registration and Biology Study (InPOG-NB-18–01, CTRI/2020/01/023088) to prospectively collect NB registry and biology data across India.[4] Several barriers impacted accrual, including reluctance of Institutional Ethics Committees to permit centralized genomic analysis, difficulties in prospectively consenting as well as capturing registration data in busy pediatric oncology clinics, and the recent pandemic.[5] As a result, after 2 years of effort we had registered less than a dozen cases. In 2021, we made the decision to amend the study, closing down the biology component, and only collecting retrospective anonymized data on NB patients for each center.

In the 6 months since study amendment, we now have data on 90 patients from four centers, with 8 sites expressing an interest and waiting for Ethics Committee Approval. We should reach our target of 400 patients by the end of this year. The initial data gathered is a small sample of the ultimate total but reveals some interesting findings, which will need to be confirmed once all the sites submit data. As expected, there is a male predominance (53/90), and the majority had metastatic (47/90) or unresectable (24/90) disease. Only a minority underwent urine vanillylmandelic acid (VMA) testing (17/90) and/or Iodine-123 metaiodobenzylguanidine (MIBG) testing (10/90). This is presumably due to the difficulty in accessing these tests, since positron emission tomography-computed tomography was still performed in the majority of patients (60/90). Once we accrue data from more patients, we will look at survival outcomes of NB.

If this current approach in data sampling is successful, we will apply it to other childhood tumors, such as rhabdomyosarcoma and Wilms tumor. While this will still not give us an accurate estimate of the incidence of these uncommon childhood cancers in India, the acquired data on presentation and outcomes will help us optimize the required clinical management for the same.

Funding
None.

DOI https://doi.org/10.1055/s-0042-1748801.
ISSN 0971-5851.

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Conflict of Interest
None declared.

Acknowledgment
We wish to express our gratitude to colleagues in the Indian Pediatric Oncology Group, for their efforts involving the study cited, as well as other ongoing initiatives to improve our knowledge about childhood cancer treatment in India.

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Clinical Profile of COVID-Positive Cancer Children across Three COVID Waves: A Tertiary Care Center's Experience

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Ind J Med Paediatr Oncol 2022;43:296–297.

Though coronavirus disease 2019 (COVID-19) infection prevalence among adult cancer patients was reported to be higher than the general population, it was found that children with cancer were less infected and were mostly asymptomatic or mildly infected.[1] We conducted a prospective study of incidence and outcomes of COVID positivity among children with malignancies admitted between March 2020 and February 2022.

All children < 18 years of age with malignancies admitted in this period were included. Institutional ethics committee approval was obtained. All patients underwent COVD testing by reverse transcription polymerase chain reaction method, prior to every admission.

A total of 1,962 admissions were made during this period. Twenty-eight children (1.4%) were found to be COVID positive and 4 of them were newly diagnosed acute leukemia at the time of COVID positivity. Among the 28 children, 14 were acute leukemias, 3 had lymphomas, and 11 had solid tumors. Only 4 (14.2%) of them were symptomatic with fever and upper respiratory infection symptoms. Twenty-two children were managed in home quarantine. Six of the 28 (21.4%) children needed admission. Among the six, three were newly diagnosed leukemias, one was admitted for social reason, one child with intracranial germ cell tumor needed monitoring due to primary disease-mediated hyponatremia and polyuria, and one child was admitted for neutropenia and severe mucositis.

Computed tomography chest was done only in the newly diagnosed acute leukemias prior to starting steroids. No imaging studies or COVID-specific blood investigations like D-dimer were done in the rest of them. Chemotherapy was delayed for all COVID-positive children for an average period of 7 to 10 days. None of our children received COVID infection-directed medications. None of the children with COVID positivity developed any complications related to COVID or primary disease or their treatment. All of them recovered completely. Only one child was monitored in the intensive care unit for 24 hours for febrile neutropenia with features of early shock. No long-term sequelae were reported in any of them till this date. Among the 28 children, 11 were positive during the first wave, 6 during the second wave, and 11 turned positive during third wave.

Bansal et al have reported that a higher number of children and adolescents were affected during the second wave in India and were symptomatic with fever, diarrhea, cold, and cough when compared with the first wave.[2] Iftimie et al from Spain and Brookman et al from London also have reported a high prevalence of infections among children and young people but they were not associated with any severe illness or any complications, similar to the first wave.[3,4] We reported the lowest number of COVID positivity during the second wave and two of the six were symptomatic during this period. The highest number of positive cases was actually seen during the third wave, when we had 11 positivity in 4 months, whereas during the first wave, 11 children were positive during a period of 9 months. This study supports

DOI https://doi.org/10.1055/s-0042-1750203.
ISSN 0971-5851.

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that children with cancer when infected with COVID do not warrant additional COVID-directed investigations, imaging studies, or therapy if they are asymptomatic or present with milder infections. All the 28 children were followed up for a period ranging from 2 years to 2 months (during the third wave). Our study is very encouraging for developing countries with limited resources for supportive care to continue cancer-directed treatment for children with cancer without unnecessary interruptions.

Presented in Conferences
None.

Funding
None.

Conflict of Interest
None declared.

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Pembrolizumab Weight-Based Dosing: Conviction and Lacunae in Adopting a Cost-Saving Approach—A Survey Report

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Ind J Med Paediatr Oncol 2022;43:298–303.

Abstract

Introduction Use of immunotherapy drugs has increased leaps and bounds in the last decade with promising results in some of the cancers. The use is limited in low- and middle-income countries due to cost constraints. Weight-based dosing is one measure adopted by Canada and Israel to reduce cost burden and improve access to immunotherapeutic drugs.

Objective We conducted a survey among medical oncologists from India to understand challenges faced in accepting the weight-based dosing of pembrolizumab.

Materials and Methods Questionnaire covering various aspects related to use of immunotherapy drugs was made and it was circulated across various social media platforms. Medical oncologists practicing across India were invited to participate in this survey. The issues like access to drugs and awareness about weight-based dosing of pembrolizumab were covered in the survey. Also, the impact of international guidelines on accepting the weigh-based dosing was studied.

Results Ninety-nine medical oncologists across India participated in the survey. Only 60% medical oncologists are aware about weight-based dosing of pembrolizumab practiced in other countries. Further, 70% of medical oncologists could not prescribe immunotherapy due to cost factor in majority (90%) of their patients. More than 90% agreed that they will use weight-based dosing of pembrolizumab if the Drug Controller General of India, National Comprehensive Cancer Network, or European Society of Medical Oncologists guidelines endorses weight-based dosing.

Conclusion Weight-based dosing of pembrolizumab would be accepted if policy makers and Indian medical oncology societies come together and formulate guidelines. Such guidelines will improve accessibility to immunotherapy drugs and lead to huge cost savings.

Keywords
- DCGI India
- pembrolizumab
- survey
- weight-based dose

DOI https://doi.org/10.1055/s-0042-1745814.
ISSN 0971-5851.

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Introduction

Immunotherapy is a major development in the field of cancer care and therapeutics in the last decade. First immunotherapy drug ipilimumab got approval in 2011 for advanced melanoma after showing improved survival in phase 3 trial (NCT00324155).[1] Since then, these drugs are used in almost all cancers. It has improved outcome in few of the advanced cancers like lung, kidney, and liver. At any given time, hundreds of trials of immunotherapy drugs are ongoing across the world. These drugs are slowly being introduced into both adjuvant and neoadjuvant settings. This has led to accelerated approvals for these drugs in various advanced and early stage cancers. But this progress is limited to high-income countries. In an era of global cancer equality, patients from low- and middle-income countries (LMICs) are not able to access these drugs due to cost constraints. Health insurance coverage (both government and private) is limited in LMIC. In India, in 2014, the mean out-of-pocket expenditure for cancer treatment was Indian rupee (INR) 57,232. The expenditure is catastrophic for 79% of households (>10% of household consumption expenditure) and for 43% of them it is distress financing, meaning forced sale of house or land, borrowing money, or getting contributions from friends or families.[2] The study from Tata Memorial Hospital, Mumbai, revealed that only 1.6% of patients received immunotherapy.[3] Efforts are needed to reduce the cost of cancer therapy in LMIC. Various ways to reduce the cost for immunotherapy drugs need to be explored.

Use of weight-based dosing of pembrolizumab is one such way. Pembrolizumab was used by the manufacturing company in initial trials as 2 mg per kg every 3-weekly dose.[4–6] At that time, both 100 mg and 50 mg vials were available. But after few years, the company withdrew the 50 mg vial from the market. They also changed the dosing to fixed dose of 200 mg given 3-weekly. Now, this has led to the use of extra dose of drug especially for those patients who have average weight of 50–60 kg. It is wastage of money as same patient will need less doses in weight-based dosing as compared to a fixed-dose schedule. The pharmacokinetic studies done on pembrolizumab have shown that the dose of 2 mg per kg and 200 mg are equivalent in effect.[7–9] The dose of drugs is carefully decided after phase 1 studies. Both pharmacokinetic and pharmacodynamic properties of drug along with toxicity profile are taken into consideration while deciding final approved dose of the drug. The final maximum dose chosen for phase 3 clinical trials and subsequent drug approval is generally the one with better efficacy and with lesser toxicity. This is an old concept and needs revision in present time of targeted therapy and immunotherapy.[10]

According to a Canadian Agency for Drugs and Technologies in Health report, the Canadian authorities have approved the 2 mg/kg every 3-weekly dose of pembrolizumab across all tumors based on the basis of initial pembrolizumab clinical trials and modeling based studies.[8] With the establishment of the equal result of 2 mg/kg every 3 weeks and 200 mg every 3 weeks, there is potential of large cost savings on adopting the 2 mg/kg every 3 weeks as compared to the 200 mg flat dose.[9] The regulatory authorities have considered such weight-based strategies in Israel and Denmark. Many countries might follow the same in future. Indian regulatory guidelines from the Drug Controller General of India (DCGI) lack such recommendations.[11] To initiate similar efforts in India, we did this survey as to understand the difficulties faced by Indian medical oncologists (IMOs) in adopting weight-based immunotherapy.

Materials and Methods

We used Google Forms to conduct this survey and framed the questions according to the medical oncologist's perspective (►**Table 1**). The survey was circulated through social media apps from August 1, 2021, to August 30, 2021. Only medical oncologists from across the country were included as survey participants. Survey participation was voluntary. Social media apps like WhatsApp and platforms such as Indian Society of Medical and Pediatric Oncology (ISMPO), the only official organization of medical oncologist in India, were used to circulate the survey questionnaires. All the responses to survey were collected in an Excel spreadsheet and analyzed. The questionnaire mainly focused on the primary objective of assessment of awareness of weight-based dosing of pembrolizumab among IMOs and understanding lacunae in adopting the same. Secondary objective was the assessment of knowledge of global efforts to reduce cost of immunotherapy drugs.

Statistical Analysis: It was done using descriptive statistics.

Results

A total of 103 responses were received from August 8, 2021, to August 15, 2021. Among these, 99 responses were from medical oncologists and only these were taken into consideration for the analysis.

The survey results are depicted in ►**Table 1**. The responding 44, 24, and 31 of the 99 IMOs have had 1 to 5 years, 6 to 10 years, and >10 years of practice, respectively. Majority of them, that is, 74% are practicing in metropolitan cities, followed by 14% in districts, and 11% in towns.

Seventy percent of IMOs reported that 90% of their patients do not receive immuno–oncology drugs due to the cost factor. Sixty four percent ($n = 64$) of IMOs responded that the lack of recommendation by scientific organizations and/or recommendation by regulatory authorities prohibited them from using weight-based dosing of pembrolizumab. Twenty-three (24%) IMOs do not use mg/kg dosing in view of lack of studies comparing 2 mg/kg every 3 weeks versus 200 mg every 3 weeks. Only three IMOs are already using weight-based dosage of pembrolizumab as they stated that nothing prohibited them. Five IMOs did not answer this question (►**Fig. 1**).

Eighty five percent ($n = 85$) of IMOs agreed that there was no rationale for using only 200 mg every 3 weeks in subsequent trials of pembrolizumab. Sixty percent ($n = 60$) were not aware of the fact that countries like Canada, Israel, and Denmark have adopted the weight-based dose of pembrolizumab. Ninety percent IMOs would change their practice to weight-based dosing if DCGI recommends mg/kg dosing. Similarly, 93% and

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Table 1 Questionnaire and results—pembrolizumab weight-based dosing: conviction and lacunae in adopting a cost-saving approach (n= 99)

S. no	Question	Answers (options)	Results: *n* (%)
1	How many eligible patients of immunotherapy do not receive IO drug due to cost factor?	1. >90%	69 (69)
		2. 50–90%	22 (22)
		3. <50%	8 (8)
2	Until 2015, pembrolizumab was studied at 2 mg/kg every 3 weeks in metastatic melanoma and mNSCLC. There is no rationale for 200 mg flat dose schedule for consequent trials. Do you agree?	1. Yes	85 (85)
		2. No	5 (5)
		3. Do not know	9 (9)
3	What prohibits you from using pembrolizumab as mg/kg?	1. Lack of recommendation by regulatory authorities	15 (16)[a]
		2. Lack of recommendation from scientific organizations	6 (6)
		3. Both options 1 and 2	43 (46)
		4. Lack of studies comparing 2 mg/kg versus flat 200 mg dose	23 (25)
		5. Others	7 (7)
4	Are you aware of the fact that Canada, Israel, and Denmark have approved pembrolizumab as 2 mg/Kg every 3 weeks?	1. Yes	39 (39)
		2. No	60 (60)
5	If DCGI agrees to change its recommendation, would you change your practice to mg/Kg?	1. Yes	89 (89)
		2. No	3 (3)
		3. Not sure	7 (7)
6	If NCCN adds its recommendation on mg/kg, would you change your practice?	1. Yes	93 (93)
		2. No	1 (1)
		3. Not sure	5 (5)
7	If ESMO adds its recommendation on mg/kg, would you change your practice?	1. Yes	94 (94)
		2. No	1 (1)
		3. Not sure	4 (4)
8	Are you a medical oncologist?	1. Yes	99 (100)
		2. No	0 (0)
9	How many of years of practice in medical oncology?	1. 1–5 years	44 (44)
		2. 6–10 years	24 (24)
		3. >10 years	31 (31)
10	Where do you practice?	1. Metro city	74 (74)
		2. District	14 (14)
		3. Towns	11 (11)

Abbreviations: DCGI, Drugs Controller General of India; ESMO, European Society of Medical Oncologists; IO, immuno-oncology; mNSCLC, metastatic non-small-cell lung cancer; NCCN, National Comprehensive Cancer Network.
[a]For question no 3, responders were: n = 94.

94% of IMOs would change their practice if National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncologists (ESMO) add mg/kg recommendation of pembrolizumab in their guidelines (►**Fig. 2**).

Discussion

Most of the LMIC countries have no individual guidelines for cancer management.

Oncologists from LMICs depend heavily on NCCN or ESMO guidelines for treatment decisions in absence of any country-specific guidelines. As shown in our survey, almost all of the oncologists were reluctant to change the practice unless NCCN or ESMO guidelines recommend to do so. NCCN guidelines generally do not take into consideration financial stress caused by treatment, which is a vital deciding factor for treatment in LMIC patients. Recently, NCCN added the mg/kg dosing of pembrolizumab and nivolumab for malignant

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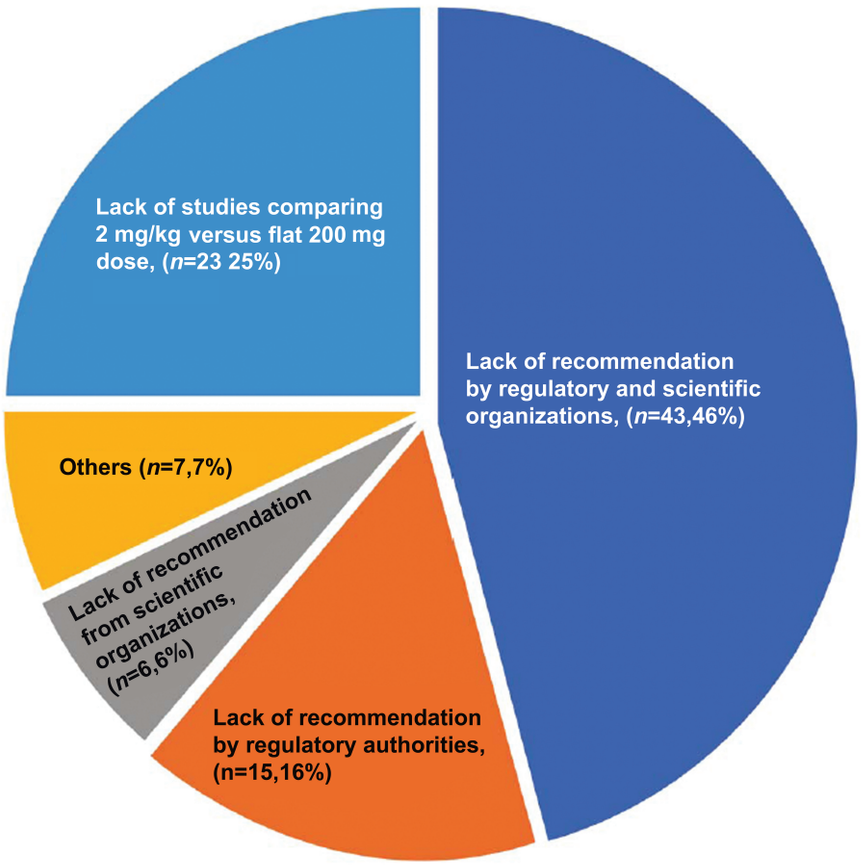

Fig 1 Survey among Indian medical oncologist on factors prohibiting use of mg/kg dosing of pembrolizumab ($n = 94$).

melanoma patients;[12] however, restricting such recommendations for other cancer indications is not well understood. This is a very important issue for change of practice at grassroots level. We also found that if Indian regulatory authorities, that is, DCGI, endorse such a recommendation, 90% of IMOs would change the practice. Hence, a coordinated effort is required between scientific organizations and drug approval authorities like Indian Council of Medical Research

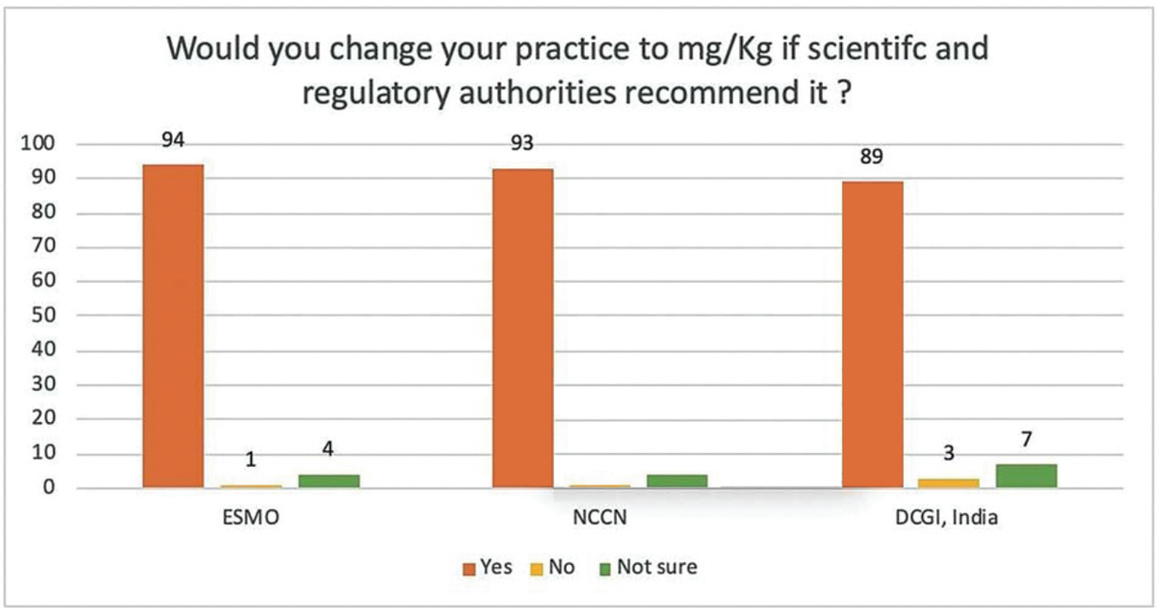

Fig. 2 Survey among Indian medical oncologists ($n = 99$) on changing the practice to using mg/kg dosing of pembrolizumab. ESMO, European Society of Medical Oncologists; NCCN, National Comprehensive Cancer Network; DCGI, Drugs Controller General of India.

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(ICMR) and the Central Drugs Standard Control Organization (CDSCO). The World Health Organization acknowledged the issue of lack of cancer treatment guidelines and lack of cost negotiations with the companies in LMICs.[13]

When pembrolizumab was launched, both the 100 mg and 50 mg vials were available. This was useful for administrating weight-based dosing. In 2017, the parent company withdrew 50 mg vial for reasons less understood. In fact, prescribing information for pembrolizumab provided by the company still has mention of 50 mg vial.[14] The average weight of an Indian lung cancer patient is lower as compared to western patients.[15,16] For a mean weight of 55 kg, almost double dose of pembrolizumab is used if we use flat dose. Both pembrolizumab and nivolumab have shown comparable outcomes of weight based with a flat dose.[17–19] As per report published in 2017, pembrolizumab flat dosing leads to wastage of nearly 1 billion US dollar (USD) per year as 100 mg vial costs around INR 235,000 without access (USD 3,118).[9] The economic impact of weight-based dosing of pembrolizumab and nivolumab has been studied extensively and cost benefits are enormous including in the USA and European countries.[20–22] Negotiations must be done with the company for availability of 50 mg vial by the concerned regulatory authorities.

In our survey, IMOs that represented India's situation in medical oncology belonged to a diverse group of professionals from various social strata. They have faced the obstacle of limited access to the use of immunotherapy drugs. The results of such surveys as this can be useful for scientific organizations and also policy makers.

Limitations

Our survey is limited by the number of responders. India has almost 250–300 new medical oncologists coming into clinical practice every year and this survey was exclusive to them.

Conclusions

Weight-based dosing of pembrolizumab would be accepted if policy makers, regulative authorities, and IMOs come together and formulate the required guidelines. Such guidelines will improve accessibility of immunotherapy drugs and lead to huge cost savings. A coordinated effort is needed among scientific organizations like ISMPO, ICMR, and CDSCO (DCGI) to formulate India-centric guidelines on the use of pembrolizumab with weight-based (mg/kg) dose.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
We thank all IMOs who participated in this survey. We are grateful to Dr. Daniel Goldstein for his support on sharing his experience on weight-based dosing of pembrolizumab. We also thank Dr. Navneet Singh for sharing his studies on body mass index in lung cancer.

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Rightsizing the Dosing of Modern Oncology Drugs: Mind the Gap

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Ind J Med Paediatr Oncol 2022;43:304–305.

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What could be more controversial than using lower than recommended doses of approved drugs, particularly for a life-threatening disease? But that is exactly what should be done for many anticancer drugs approved by global regulatory agencies. There are two potentially justifiable reasons for using lower doses: (1) reducing the risk and/or severity of adverse events and (2) reducing the cost of care. While not true of all marketed oncology drugs, it is expected that modern oncology drugs (e.g., kinase inhibitors, immunotherapy) would often be maximally effective at doses well below the maximally tolerated dose (MTD).[1] In contrast, the vast majority of dose-finding studies in oncology are simply phase 1 studies aimed at determining the MTD, rather than randomized dose-ranging trials to determine the optimal dose, as recommended by the International Committee on Harmonization E4 guideline.

Despite rapid evolution and advances in antineoplastic drug discovery, clinical trial paradigms have had only minor changes. Debate has focused on the optimal way to define the MTD, without considering whether or not the MTD is even relevant.[2] (To emphasize the point of lack of relevancy, the MTD of remdesivir, the first drug approved for coronavirus disease 2019, has never been ascertained). Furthermore, oncology drugs are often given in combination, which further complicates the challenges of dosing, if the optimal dose of the individual drugs has never been determined.

Historically, cytotoxic chemotherapy was usually administered parenterally, and thus, oncologists did not often have to consider the complexity of oral drug delivery, and certainly not the issues pertinent to many modern compounds, such as amphiphilic kinase inhibitors. While it was well known that food could increase drug absorption, the development of many oral oncology drugs has relied on fasting administration, perhaps due to a misperception that cancer patients might not be able to reliably take oral drugs with food.[3]

This mislabeling—at least from the perspective of a clinical pharmacologist—led to suggestions that some drugs could be administered at a fraction of the labeled dose, if administered off-label with food. Furthermore, a patient that did not strictly follow the labeled regimen (e.g., eating breakfast 30 minutes after the morning dose), could potentially suffer the consequences of an effective overdose due to greater absorption than in the clinical trials.[4,5] This has even led to the Food and Drug Administration (FDA) to require a black box warning in the U.S. nilotinib prescribing information for the risk of food causing sudden death, if consumed within 2 hours prior to or 1 hour after taking the drug.

The notion of using lower doses for the primary purpose of cost reduction has been dubbed "interventional pharmacoeconomics." [6] While regulatory agencies have occasionally required postmarketing studies of lower doses because of concerns regarding the safety of the initially approved dose, interventional pharmacoeconomic studies have rarely been initiated. As one example, Szmulewitz et al conducted a small prospective randomized study of low- dose abiraterone (25% of the standard dose administered off-label with food), which demonstrated that the lower dose—as expected based on the known effect of food to increase bioavailability of this agent—was essentially equivalent (and in fact noninferior) to the standard dose.[7] This reduced dose regimen, a 75% cost savings, was subsequently incorporated into the National Comprehensive Cancer Network guidelines as an acceptable alternative.

In India, abiraterone currently costs nearly INR 8,400 (US $110) per bottle of 120 tablets (250 mg), ostensibly a 1-month supply.[8] This is much cheaper than other oral

DOI https://doi.org/10.1055/s-0042-1748490.
ISSN 0971-5851.

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anticancer agents, as abiraterone is manufactured and sold by multiple generic pharmaceutical companies. Yet, the annual cost of this generic drug is nearly 70% of the Indian per capita gross income.[8] Needless to say, new patent-protected agents are even less affordable, generally 5 to 10 times higher in monthly cost. The U.S. is no different, with some new agents having a list price of over US$30,000 (INR 2.3 million) per month, over US$360,000 (INR 27.4 million) per year (more than five times the U.S. per capita gross income).

While the notion of reducing the cost of abiraterone by 75% (i.e., stretching a 1-month supply to 4 months) is attractive, it is likely feasible to administer even lower doses per month, perhaps administering the drug as infrequently as weekly.[9] However, further studies are required before this strategy can be recommended.

While abiraterone is an excellent example of an overdosed drug, sotorasib may even be more egregious, approved in May 2021 by the FDA, but with a formal postmarketing requirement for Amgen to compare the labeled dose of 960 mg (administered as eight 120 mg tablets) to 25% of the labeled dose.[1] This requirement is justified due to a lack of a relationship of drug dose to both plasma concentrations and antitumor activity, which was evident at the lowest dose studied, 180 mg. Notably, an even lower dose (e.g., 120 mg) may be equally effective, as based on Amgen's preclinical data.

There are many other examples of both oral and parenteral drugs for which interventional pharmacoeconomic studies are indicated. There is no evidence of a dose–response relationship for ibrutinib, and the therapeutic index may be greatly enhanced by reducing the dose to 140 mg once daily (from 420 or 560 mg).[10] Multiple immune checkpoint inhibitors are also labeled at excessive doses, and reduction of dose and/or frequency will certainly reduce costs, and potentially toxicities as well.[11]

We have made great advances in the treatment of cancer, and now the pharmaceutical industry is holding the world economically hostage—at least for payers and patients seeking access to their modern drugs. While companies should be appropriately incentivized to discover, develop, and commercialize drugs, physicians and patients should expect, if not require, that drug doses be optimized, particularly for those drugs that can cause significant toxicities interfering with patient quality of life. While the FDA has taken the lead on requiring dose optimization for new drugs, governments also need to enable and support (if not require) dose optimization studies for already marketed drugs, particularly if there is evidence that the marketed dose is excessive.

This is an important global gap in oncology clinical research and best practices. Instead, patients in wealthier countries receive unnecessarily high—and often toxic—doses of drugs, whereas patients in low- and middle-income countries often do not have access to modern drugs at all.

Conflict of Interest
None declared.

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Pembrolizumab weight based dosing – A call for policy change

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Ind J Med Paediatr Oncol 2022;43:306–310.

Introduction

Immuno-oncology (IO) drugs are now approved for use in metastatic, adjuvant, and/or neoadjuvant setting for a growing list of cancers including non-small cell lung cancer, small cell lung cancer, melanoma, urothelial cancer, renal cell carcinoma, head and neck squamous cell carcinoma, esophageal cancer, gastric cancer, cervical cancer, endometrial cancer, hepatocellular cancer, Merkel cell carcinoma, microsatellite instability-high or mismatch repair deficient colorectal cancer and other cancers, tumor mutational burden-high cancer, cutaneous squamous cell carcinoma, triple-negative breast cancer, classical Hodgkin lymphoma, and primary mediastinal large B cell lymphoma. This list continues to expand at an impressive speed. The benefits in improving progression-free survival (PFS) and overall survival are a welcome advance beyond the plateau that we seem to have reached with conventional chemotherapy treatment. The biggest challenge is to identify biomarkers that would help select the 20 to 40% patients who respond to immunotherapy drugs, thereby limiting treatment to those most likely to benefit, avoiding toxicity among the patients unlikely to respond. This has very important pharmacoeconomic implications, especially because immunotherapy drugs are very expensive.

The important question is whether we can do something substantial to address unnecessary wastage of expensive medicines. The answer is yes. It is based on a long established principle of using dose according to the individual's weight/surface area. It is based on avoiding "flat" dosing—a flawed strategy that leads to unnecessary wastage of expensive medicines and subjects our patients to avoidable toxicity. There is a strong rationale to integrate the concepts of pharmacoeconomics.[1] We present here our policy brief on rational use of pembrolizumab that optimizes patient benefit as well as utilization of resources.

Pharmacokinetics and Pharmacodynamics of Pembrolizumab

Pembrolizumab is a completely humanized monoclonal antibody immunoglobulin G 4 against the programmed

DOI https://doi.org/10.1055/s-0042-1742651.
ISSN 0971-5851.

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death-1 tumor-derived antigen. Similar to other monoclonal antibodies, it has peculiar pharmacokinetics and pharmacodynamics (PK PD) properties such as a very long half-life, linear clearance at doses above 0.3 mg/kg, and steady-state levels being achieved after 18 weeks of therapy.[2] Using the half-life of 23.72 days for pembrolizumab, the complete washout period will be 237 days.[3] Washout period is generally 10 half-lives.[4] In phase 1 pharmacokinetic study of pembrolizumab, the complete interleukin 2 target engagement was seen at doses of 1 mg/kg and above.[5] Durability of this action was documented till day 21 in all the three-dose cohorts, that is, 1, 3, or 10 mg/kg and responses lasted beyond stopping the drug.[5] The modeling-based studies by Chatterjee et al in melanoma and metastatic non-small cell lung cancer (mNSCLC) provided additional evidence that 2 mg/kg q3 weeks was the optimal dose.[6,7] The use of pembrolizumab beyond 2 mg/kg q3 weeks has not shown to improve response rates. Safety, adverse effects, and activity of pembrolizumab were studied at 2 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, and 10 mg/kg every 3 weeks in advanced or mNSCLC.[8] It is important to note that, in this study, the response rate was highest for the dose of 2 mg/kg every 2 weeks (33.3%; albeit with limited data from 6 patients). Also, it was identical for pembrolizumab 10 mg/kg q3 weeks (19.2%; $n = 287$) and 10 mg/kg q2 weeks (19.3%; $n = 202$) schedules, irrespective of histology.

The phase 2/3 KEYNOTE-010 study enrolled 1,034 patients of previously treated mNSCLC across 24 countries. Pembrolizumab 2 and 10 mg/kg (doses selected on the basis of the previous studies—vide supra) was compared with docetaxel. Overall survival was the primary end point, being 10.4, 12.7, and 8.4 months in pembrolizumab 2 mg/kg, 10 mg/kg, and docetaxel groups, respectively. Hazard ratios (HRs) were 0.71 (2 mg/kg q3w) and 0.61 (10 mg/kg q3w) in comparison with docetaxel. In patients with 50% and more programmed death ligand 1 (PD-L1) expression, HRs were 0.54 and 0.50 for overall survival in pembrolizumab 2 and 10 mg/kg groups, respectively. The authors therefore had sufficient evidence to support the dose of 2 mg/kg q3 weeks for pembrolizumab.[9]

Similarly, a phase 2 randomized trial in ipilimumab refractory metastatic melanoma studied pembrolizumab at 2 and 10 mg/kg every 3 weeks. The HR for PFS was 0.57 and 0.50 in 2 and 10 mg/kg dose and 6-month PFS rate was 34 and 38%, respectively. The authors recommended the minimal effective dose of 2 mg/kg q3 weeks for further use, although the trial was not designed to compare outcome between the two dose schedules.[10]

Factors known to affect the metabolism of pembrolizumab include age, sex, serum albumin, and performance status.[2] Turner et al's PK PD study concluded that patients with slow clearance have almost double the overall survival as compared with those who had rapid clearance, with identical benefit in cohorts of 2 and 10 mg/kg dose.[11] With all this evidence, 2 mg/kg every 3 weeks is an optimal dose.

Standard of Care and Approved Dosing

In the landmark KEYNOTE-024 trial of pembrolizumab in advanced lung cancer,[12] the flat dose of 200 mg was used every 3 weeks, citing pharmacokinetic modeling by Freshwater et al. Freshwater et al used data from population-based pharmacokinetic properties based on 2 and 10 mg/kg and compared them to data from newer trials using fixed doses. In fact, they found no difference between weight based and flat dose regimens.[13]

Food and Drug Administration approved pembrolizumab 400 mg dose every 6 weeks across all indications. This approval was based on pharmacokinetic modeling study which compared 6 weekly 400 mg schedule to 200 mg 3 weekly and 2 mg/kg 3 weekly schedules and concluded that the three schedules were expected to produce similar efficacy and safety across all diseases.[14] This work was supported by Merck Sharp & Dohme Corp. The authors specified that a fixed dose of 200 mg q3 weeks would be more convenient by reducing cost in respect of logistics (reducing cost of manufacturer and hospitals). They conveniently missed the adverse implication on payors (patients, insurance companies, government) by shutting out the weight-based schedule of 2 mg/kg. Further phase 3 trials continued to propagate flat doses of 200 mg across various cancer groups—without any efficacy, safety, or cost–benefit rationale.

The present standard of care for dose differs with different indications. Based on the patent holding company's dossier submission to Indian drug regulatory authorities (Drug Controller General of India), pembrolizumab has been approved since 2016 for use in lung cancer and melanoma at the dose of 2 mg/kg q3 weeks (in previously treated patients of mNSCLC and melanoma). In contrast, for treatment naïve patients of mNSCLC, the submission dossier recommended a flat dose of 200 mg q3 weeks.[15] National Comprehensive Cancer Network recommended 2 mg/kg every 3 weeks for malignant melanoma in addition to flat dose of 200 mg.[16]

Weight-Based versus Flat Dosing of Pembrolizumab

The flat dose of 200 mg every 3 weeks was derived from the modeling-based study.[13] The Canadian Agency for Drugs and Technologies in Health (CADTH) extensively reviewed the pharmacokinetics and modeling-based studies of pembrolizumab and nivolumab[3] and derived that 2 mg/kg every 3 weeks is the optimal dose of pembrolizumab. In CADTH report, blood levels of pembrolizumab for a patient of 70 kg patient were identical between the four cohorts viz. 98% at the dose of 2 mg/kg q3 weeks; 97% for 4 mg/kg q6h weeks dosing; 99.31% at 200 mg q3 weeks; and 98.16% for 400 mg q6 weeks.[3]

Studies have shown that pembrolizumab is well tolerated up to doses of 10 mg/kg q2 weeks. Toxicities are similar between weight-based (2 mg/kg q3 weeks) and fixed-dose (200 mg q3 weeks) schedules. Recent meta-analysis showed that 2 mg/kg dose of pembrolizumab was better tolerated. Interestingly, in this meta-analysis, pembrolizumab discontinuation rate was higher (9.2%; 95% CI: 6.9–12%) in flat 200 mg dose as compared with weight-based dosing schedule (6.5%; 95% CI: 4.8–8.8%).[17]

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Real-World Studies

Mukherjee et al studied the flat dose versus weight-based dose of pembrolizumab and nivolumab. A total of 60/137 patients received weight-based dosing. There was no difference in overall survival, even after adjusting for other study variables.[18] In a similar study from Singapore, 100 mg (low dose) of pembrolizumab was compared with 200 mg dose in mNSCLC. Sixty-five patients received 100 mg pembrolizumab and 49 patients received 200 mg flat dose. Again, there was no difference in response rate, PFS and overall survival.[19]

Goldstein et al analyzed the cost implications for United States if pembrolizumab is used with weight-based 2 mg/kg dose in PD-L1-positive lung cancer treatment. They estimated savings of $82.5 million every year without compromising patient outcomes in any way.[20] Using this approach for all labeled indications of pembrolizumab would multiply this saving many folds, saving billions of dollars every year in the United States alone. Another publication also supported the weight-based 4 mg/kg every 6 weeks schedule during coronavirus disease 2019 (COVID-19) pandemic, with additional benefits. It would deliver similar results (efficacy and safety), save cost, and reduce the risk of COVID-19 exposure by reducing hospital visits.[21]

Worldwide Challenges and Solutions

The 23rd expert committee of World Health Organization on use of essential medicines has considered cost as a major factor for nonconsidering the application for pembrolizumab as essential medicine and also stated that mg/kg dosing may be preferred to flat dose without compromising on disease outcomes.[22] CADTH is an independent organization which helps the Canadian authorities by providing objective evidence on optimal use of dose, devices, and procedures.[3] It has recommended use of pembrolizumab as 2 mg/kg (with 200 mg capping dose) for first line in NSCLC and melanoma. Vial sharing option was suggested specifically as the 50 mg vial was not available. Recently, Israel and Denmark approved weight-based dosing of pembrolizumab.

Access to Immuno-oncology Drug in Indian Setting

In a real-world study of more than 9,000 patients, only 1.61% of eligible patients received immunotherapy from 2015 to 2018. The cost remains a major deterrent for access to costly medicines.[23] Average weight of Indian lung cancer patients is 55 kg as compare with 75 kg of average American patients.[24,25] The average weight of Indian male is 59.6 kg and female is 52.5 kg.[26] In studies from north Indian lung cancer patients, almost 45% of patients were underweight (body mass index <18.49 kg/m^2 and at 70 percentiles, weight was less than 60 kg).

The cost of pembrolizumab is around INR 235,000 per 100 mg vial (with one vial free). This price might differ marginally across various states and institutions. Cost of 100 mg, that is, one vial of pembrolizumab is more than India's per capita gross domestic product. A 100-mg vial is ideal for a patient weighing 50 kg, saving a vial for a vial. If conventional doses are used, there is huge monetary loss to the payers. For patients, more than 60 kg, vial sharing remains an option and same vial can be used multiple times as drug is available in liquid form.

Practical Challenges and Remedies for Practicing the mg/kg Dosing

The Dose Banding

Dose banding is a well-established methodology wherein the weight-based calculations are simplified by rounding off, taking into consideration available vial size/strength. Ogungbenro et al have shown how this strategy in the usage of pembrolizumab and nivolumab is cost effective.[27] In fact, the National Health Service of the United Kingdom has adopted the strategy of dose banding for nivolumab and pembrolizumab.[28,29] They round off to allow 10% variation. Thus, for a typical 45 to 55 kg patient, the dose range would be 90 to 110 mg of pembrolizumab and one vial of 100 mg would be sufficient, and for majority of Indian patients, the cost of treatment will be halved.

Stability of IO Drugs

Stability has been studied at 2 to 8°C, at 40°C, and using freezing/thawing cycles. This has been documented for both 10 and 2 mg/mL concentrations. Pembrolizumab is stable in normal saline 0.9% at 2 to 8°C for up to 7 to 14 days in polyolefin infusion bags.[30,31] Nivolumab is stable at 2 to 8°C for 30 days and at 40°C for 7 days.[32]

The Implications of the 50-mg Vial

Key advantage of weight-based dosing is dependent on the availability of a 50-mg vial. Curiously, the 50 mg vial was withdrawn from the U.S. market, while continuing to be available in certain European countries. In the absence of the 50 mg vial, the application (and resultant cost saving) of weight-based dosing disappears in most countries. It would still be possible (but shall increase complexity) in countries that permit vial sharing, where a central pharmacy prepares chemotherapy infusions. Weight-based dosing is the only way of using pembrolizumab in the pediatric population—approved dose being 2 mg/kg q3 weeks.[33] This is applicable to several cancers including classical Hodgkin lymphoma, primary mediastinal B cell lymphoma, metastatic Merkel cell carcinoma, and high-level microsatellite instability tumors.[34] For a 25-kg child, the dose of 50 mg is adequate. The nonavailability of the 50 mg vial in countries where pediatric use is licensed results in wastage of up to half the drug.

Recommendations by the Authors

1. Pembrolizumab is recommended as 2 mg/kg every 3 weekly or 4 mg/kg every 6 weekly across all indications

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in cost constraint situations, and 200 mg every 3 weeks schedule remains an option.
2. The 50 mg vial of pembrolizumab should be made available in all countries to reduce cost and prevent wastage.
3. Sharing of vials will provide additional saving and should be used where feasible, especially when the government is the payor.

Conclusion

The usage of IO drugs is expected to rise exponentially in coming years. We provide existing evidence and rationale for usage of pembrolizumab in a manner that optimizes benefit, minimizes toxicity, and prevents unnecessary wastage of resources. These recommendations needs to be implemented and governing authorities are requested to take the case forward.

Methodology

We initially surveyed the challenges associated with practice of mg/kg dosing of pembrolizumab. We discussed this issue with imminent and various medical oncologists of India. We formulated a group of 14 medical oncologists representing nationwide academic and nonacademic institutes, corporate and government hospitals. First author wrote the initial manuscript and the manuscript was circulated to all members of the group through emails. The consensus was accepted and approved unanimously.

Conflict of Interest
None declared.

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Case for More Autologous Transplants in Myeloma in Resource-Constrained Settings

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Ind J Med Paediatr Oncol 2022;43:311–313.

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Abstract

Multiple myeloma is characterized by a near universal risk of relapse. Autologous stem cell transplantation provides a significant progression free survival benefit but is under utilized worldwide. We provide a small snapshot of why ASCT assumes greater importance in resource-constrained settings.

Keywords

- hematology
- medical oncology
- myeloma
- transplant

Multiple myeloma is a malignant plasma cell disorder that has witnessed a steady improvement in survival over the past two decades. The overall survival (OS) in the past 20 years has nearly doubled due to the progress in supportive care, drug therapy, and the increasing use of autologous stem cell transplantation (ASCT).[1,2] Although ASCT alone has directly not led to an increase in OS, for all eligible patients, the choice of first-line of treatment includes induction therapy, followed by high-dose melphalan and ASCT.[3]

However, the role of ASCT as first-line therapy has been questioned with advances in drug therapy for myeloma. Novel agents are associated with unprecedented response rates, including very good partial response (VGPR) or better responses in over 70% of patients on bortezomib/lenalidomide-based triplets.[4] Newer agents, including carfilzomib and daratumumab, have enabled minimal residual disease negativity as a viable target in a significant majority of patients, questioning the need for upfront transplantation.[5–8]

We provide a snapshot of data affirming the utility of ASCT in the current era and highlight how the importance of ASCT is further amplified in resource-constrained settings.

A few randomized trials have compared ASCT with chemotherapy alone for eligible patients. The randomized IFM2009 trial published in 2017 compared lenalidomide–bortezomib–dexamethasone (RVD) alone versus RVD with autoSCT and found significantly better progression-free survival (PFS) and measurable residual disease (MRD) negativity in the autoSCT arm.[9] The phase 3 HO95 study also found an improvement in the 3-year PFS with autoSCT compared with chemotherapy alone.[10] Randomized control trials (RCTs) comparing *newer* novel agents (daratumumab, carfilzomib, pomalidomide) with ASCT are expected in the near future. Randomized data comparing ASCT with chemotherapy alone has been evaluated by two meta-analyses, both of which included similar studies. The first study from China included four RCTs of ASCT versus novel agents and found a significant improvement in the PFS (hazard ratio [HR]: 0.56, 95% confidence interval [CI]: 0.44 to 0.73) with no significant change in OS.[11] A meta-analysis published in JAMA in 2019 found similar results and concluded that even in the absence of an OS benefit, autoSCT in the first remission should be preferred due to high rates of deeper responses including MRD negativity, low treatment-related mortality (TRM), and PFS benefit.[12] As of now, no treatment option has shown enough benefits to replace ASCT as the standard of care, which must be used for all eligible newly diagnosed patients.[13]

DOI https://doi.org/10.1055/s-0042-1743504.
ISSN 0971-5851.

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Nevertheless, the utilization of ASCT for myeloma worldwide has been less than ideal but is slowly increasing with time. Data from the USA over 1995 to 2010 indicate the utilization rates of less than 15%, being higher for younger patients.[14] Current data, derived from the SEER database, indicate a slight increase in the utilization rate to ~30% (8,371 transplants out of 30,000 newly diagnosed patients in 2018). The Worldwide Network for Blood & Marrow Transplantation (WBMT) registry also recorded a 107% increase in worldwide transplant activity for myeloma during this period.[15] Increasing the use of first-line ASCT, even in settings with easy access to newer drugs, indicates ongoing clinical benefits in the eligible patients. Additionally, safety and reducing TRM with ASCT for myeloma over the past two decades has allowed easier adoption of this treatment modality. The TRM in most centers in India is less than 5% and typically averages 2 to 3%.[16]

In the absence of direct studies evaluating the utilization of ASCT for myeloma in India, it is easy to realize that very few eligible patients proceed to transplant. However, in resource-constrained settings, proceeding to transplant rather than continuing on newer drugs has several tangible benefits.

Economic concerns and access to newer drugs play a significant role in treatment decisions in low- and middle-income countries (LMICs). Compared with continued administration of newer novel agents, ASCT is more cost-effective in the long run. ASCT has been found to incur a cost of approximately Rs. 334,433 per QALY gained in India, and data from India have demonstrated that it can be made more cost-effective with early initiation of treatment.[18] Bortezomib and lenalidomide are now available as generics and available at a cost of approximately USD 90 and USD 30 for a month of therapy, respectively.

However, the cost of newer agents such as carfilzomib and daratumumab is still formidable. For instance, autoSCT in a public-sector hospital in India has been documented to cost approximately INR 395,527 (USD 6,085), compared with approximately USD 33,000 for 16 doses of daratumumab and USD 9,333 for 6 months of carfilzomib alone (communication with the drug company). The introduction of biosimilars or generic formulations may make newer agents more cost-effective in the future but would need a detailed cost-effectiveness analysis to guide the same.

Therefore, the best option for most patients is an early ASCT, with an aim to stall a relapse for as long as possible. Eliminating a very effective treatment option such as an ASCT is not a viable option for a resource-constrained setting such as India.

Another novel approach includes the use of outpatient transplantation, which now demonstrates results similar to conventional transplants with a careful patient and site selection.[19] Various models of outpatient transplant, including total outpatient, mixed inpatient–outpatient, or delayed admission can be adopted in an attempt to markedly reduce costs by reducing the duration of hospital admission.

ASCT utilization is expected to be lower than Western data in India due to a multitude of reasons including concurrent medical illness, lack of expertise or infrastructure for ASCT at various centers, and financial factors, which can lead to withholding this useful and cost-effective treatment for many patients. Inferring from daily practice, several patients do not undergo this effective treatment due to the fear of complications or after being advised against by family members and primary physicians.

Therefore, it is essential to compile collaborative data illustrating the rates of the utilization of ASCT for myeloma and delineation of underlying reasons for the same so that this efficacious and cost-effective therapy is provided to as many eligible patients as possible.

Conflict of Interest

None declared.

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Xanthogranulomatous Oophoritis in the Setting of Post-IVF Twin Pregnancy with History of Endometriosis: A Rare Case Report with Review of Literature

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Ind J Med Paediatr Oncol 2022;43:314–317.

Abstract

Xanthogranulomatous inflammation is an uncommon, nonneoplastic, chronic process in which the affected organ is destroyed by massive cellular infiltration of foamy histiocytes admixed with multinucleated giant cells, plasma cells, fibroblasts, neutrophils, and foci of necrosis. The organs most commonly affected by this entity are kidney and gallbladder. Only a few cases involving the ovary have been reported. The etiology of this entity is unknown, but the associated risk factors are infection, inappropriate antibiotic therapy, use of intrauterine contraceptive device, abnormalities in lipid metabolism, endometriosis, leiomyoma, and recurrent pelvic inflammatory disease. The current case was a 31-year-old female with post-in vitro fertilization (post-IVF) twin pregnancy, who presented with pain in the abdomen, provisionally diagnosed as ovarian mass with suspicion of malignancy. Patient was treated with antibiotics and an elective lower segment cesarean section was planned, due to lower abdominal pain and the presentation of both fetuses being breech. Patient underwent exploratory laparotomy with right oophorectomy and left double-J stenting, in view of left hydronephrosis. Diagnosis of xanthogranulomatous oophoritis was established on histopathological examination. There is only a single case; previously documented from India, in the setting of primary infertility. The present case report stresses that the condition may affect women of any age group and may be encountered in pregnancy, as has been observed in this case. Hence, thinking about this differential diagnosis in the cases presenting with similar complaints, would be of great value to avoid misdiagnosing them.

Keywords

- pathology
- xanthogranulomatous oophoritis
- foamy histiocytes

Introduction

Xanthogranulomatous inflammation is an uncommon form of chronic inflammatory process that is destructive to the involved organs.[1] The usual sites of involvement are the kidneys and gallbladder, though it can affect the anorectal area, bone, stomach, and testis.[2] The involvement of female genital tract is uncommon and if involved, it generally affects the endometrium.[3] Only a few cases affecting the vagina, cervix, fallopian tubes, and ovaries have been described.[4] The

DOI https://doi.org/10.1055/s-0042-1748489.
ISSN 0971-5851.

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characteristic massive infiltration of tissues by foamy histiocytes along with the plasma cells, lymphocytes, and polymorphonuclear leukocytes is evident on histopathology. The rare but unique histopathological appearance of this entity, noted in the pregnant female with post-in vitro fertilization (post-IVF) twin conception, warranted the case report of the said patient.

Case Report

A 30-year-old female (a primigravida, who was treated for infertility using short protocol using gonadotrophin-releasing hormone antagonist injection cetrorelix, with post-IVF-embryo transfer [ET] conception with diamniotic dichorionic twins—period of gestation being 35 weeks) reported to the emergency department of a tertiary care hospital with complaints of moderate to severe pain in lower abdomen, increased frequency of urination, and bleeding, while passing urine.

She was a known case of endometriosis and had presented earlier at the beginning of second trimester with endometrioma, for which she had undergone an emergency exploratory laparotomy, right salpingectomy, and right ureteric double-J (DJ) stenting, in view of hydroureteronephrosis. She was also a known case of hypothyroidism, anemia in pregnancy, receiving thyroid hormone replacement therapy, and hematinics.

Patient was hemodynamically stable. On per abdominal examination, 36 weeks gravid uterus was noted with a tense anterior abdominal wall, without tenderness. Cardiac activity of both the fetuses was also noted. On per vaginal examination, mass was noted in the pouch of Douglas. The patient was found to be having leukocytosis (total leucocyte count 14,700/mm_3). Other hematological and biochemical parameters were found to be within reference limits. Urine culture was positive for *Escherichia coli*, sensitive to amikacin, cotrimoxazole, nitrofurantoin, fosfomycin, and minocycline. The magnetic resonance imaging showed a large heterogeneous mass in the right adnexa, measuring 102 × 89 × 108 mm (anterior-posterior × transverse × craniocaudal), superiorly extending from the level of L3–4 to the level of coccyx inferiorly. The lesion appeared to be originating in the right adnexa and extending to the pouch of Douglas. Tumor markers like human epididymis protein 4, alpha-fetoprotein, cancer antigen 125 (CA 125), CA 19–9, and carcinoembryonic antigen were not elevated.

Patient was treated with antibiotics and an elective lower segment cesarean section (LSCS) was planned, due to lower abdominal pain. Both fetuses were having breech presentation. The exploratory laparotomy was planned along with right oophorectomy and left DJ stenting, in view of left hydronephrosis. During LSCS, two live preterm fetuses, a female and a male, weighing 2.2 and 1.9 kg, respectively, were delivered and required neonatal resuscitation. About 1.8 L of foul-smelling purulent discharge was drained from the right adnexal mass and was sent for microbiological investigations. Ziehl–Neelsen staining was negative for acid-fast bacilli, and the pus culture did not grow any pyogenic bacteria. Appendectomy was performed due to unhealthy appearance of the same. The left DJ stenting was performed, as planned.

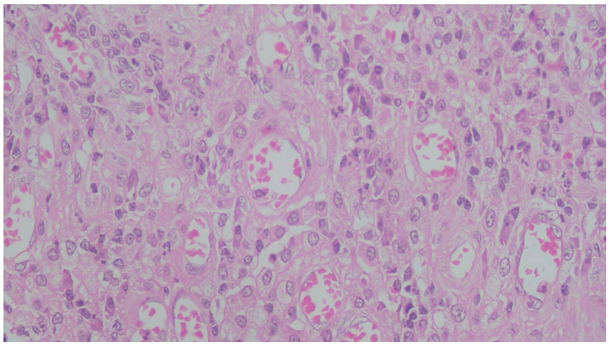

Fig. 1 The presence of large number of foamy histiocytes admixed with plasma cells, lymphocytes, and occasional neutrophils, is seen, which is pathognomonic feature of xanthogranulomatous oophoritis (hematoxylin and eosin staining; magnification 100x).

The oophorectomy and appendectomy specimens were sent for histopathological examination (HPE). On gross examination, right ovarian mass, measuring 15 × 13 cm, showed lobulated and congested external surface. On cutting open the specimen, two cysts were noted of size 12 × 9 and 10 × 6 cm, with the smaller cyst showing the presence of pus.

On microscopic examination, the cyst wall was seen to be comprising of fibrocollagenous tissue, infiltrated by sheets of foamy macrophages, lymphocytes, plasma cells, and neutrophils (►**Figs. 1–3**). Proliferating blood vessels were noted. Few areas showed fibrosis with hemosiderin-laden macrophages. Endometrial glands or stroma was not seen. The features like atypia and dysplasia were characteristically absent. The appendix showed normal histomorphology with periappendiceal inflammation. CD68 immunohistochemistry confirmed the presence of foamy histiocytes (►**Figs. 4**, **5**), while pan-cytokeratin was negative. Diagnosis of xanthogranulomatous oophoritis was made, based on the histomorphological features.

Postoperative recovery of the patient was uneventful.

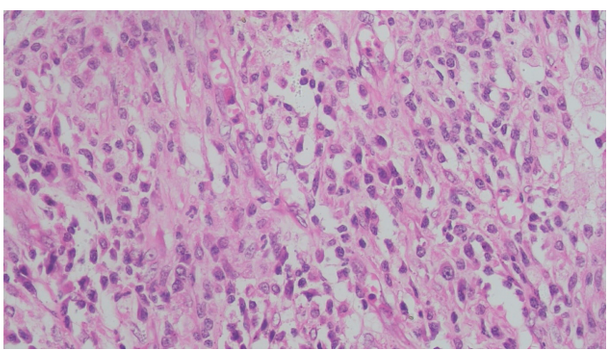

Fig. 2 The presence of large number of foamy histiocytes admixed with plasma cells, lymphocytes, and occasional neutrophils, is seen, which is pathognomonic feature of xanthogranulomatous oophoritis (hematoxylin and eosin staining; magnification 100x).

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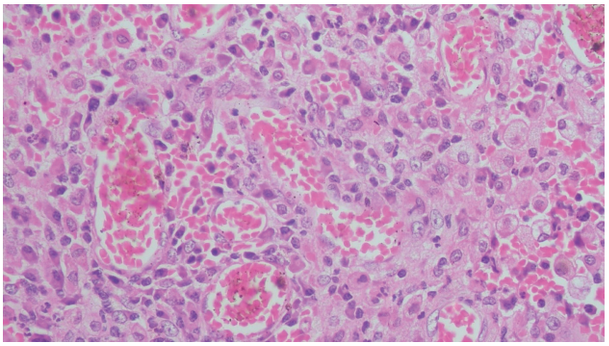

Fig. 3 The presence of large number of foamy histiocytes admixed with plasma cells, lymphocytes, and occasional neutrophils, is seen, which is pathognomonic feature of xanthogranulomatous oophoritis (hematoxylin and eosin staining; magnification 400x).

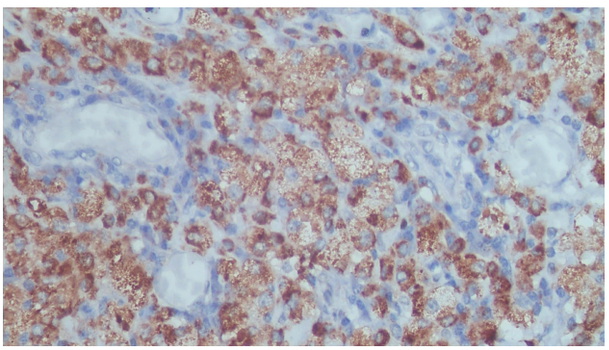

Fig. 5 The foamy histiocytes show positivity by immunostaining with CD68. (CD68 antibody staining; magnification 400x).

Discussion

Xanthogranulomatous inflammation is a rare benign inflammatory disease—commonly noted in the kidney and gallbladder.[5–8] It has also been found in other sites like bones, testis, and small intestine.[5,9,10] The involvement of the female genital tract is somewhat less common, which can present as endometritis, oophoritis, and salpingitis.[4,11,12] The ovarian involvement sometimes has been referred to as ovarian fibroxanthoma.[4] The average age of presentation is 38.5 years (commonly cases reporting between 23 and 72 years), though there has been a case report stating the occurrence of the disease in a 2-year-old child.[2,13] The disease can present, either unilaterally or bilaterally.[13] About 32 cases have been reported from India and the incidence seems to be more in the developing countries than the developed countries.[14]

The predisposing factors thought of, are pelvic inflammatory disease (PID), endometriosis, and inadequate antibiotic therapy.[15–17] Abnormal lipid metabolism has also been considered as one of the predisposing factors.[18,19] Previously, cases have also been reported with infertility and this can be considered as one of the predisposing factors.[16] The pathogenesis of this condition remains unidentified,[20] with various proposed mechanisms like ineffective clearance of bacteria by phagocytosis or as late sequalae of PID.[2] In cases of endometriosis, sites of bleeding along with the

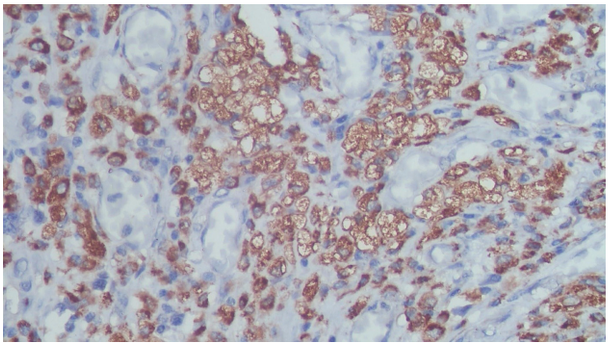

Fig. 4 The foamy histiocytes show positivity by immunostaining with CD68. (CD68 antibody staining; magnification 100x).

obstruction remain to be the fertile soil for the growth of multitude of microorganisms, which is then followed by tissue necrosis and the subsequent release of cholesterol and other lipids, which further leads to increased number of tissue macrophages, trying to phagocytose these products.[21] It has been also considered by some that xanthogranulomatous oophoritis may be the rare aggressive form of the commonly occurring endometriosis.

Common presentations include abdominal pain, adnexal tenderness, pelvic mass, menorrhagia, fever, etc. On hematological investigations, leukocytosis is a consistent finding with raised erythrocyte sedimentation rate.[4] The radiological investigations, confirm the ovarian mass, which is well-defined and often raises the suspicion of malignancy.[4] Bacterial infection is seen in many cases, the causative organisms commonly noted being *E. coli*, *Proteus spp.*, *Staphylococcus aureus*, *Bacteroides fragilis*, *Salmonella typhi*, *Actinomyces*, *Streptococcus faecalis*, *viridans streptococci*, etc.[21] The pus culture is negative for acid-fast bacteria. The antibiotic therapy alone is not sufficient and operative treatment is necessary in the form of salpingo-oophorectomy, depending on the site of lesion.[3,4,22]

The gross appearance of the specimens may show cystic degeneration, foci of necrosis, and hemorrhage, in grossly enlarged ovary. The microscopic examination shows the presence of foamy histiocytes, along with a mixture of inflammatory cells like lymphocytes, plasma cells, and occasional neutrophils.[21] Foamy histiocytes, the so-called "xanthoma cells," are histiocytes with abundant lipid-laden cytoplasm having a vacuolated appearance. These impart the yellowish color to the specimen, when seen on the gross examination. There is no cellular atypia, abnormal mitoses, or any other microscopic feature suggestive of malignancy.

CD68 immunostaining shows characteristic staining of foamy histiocytes, which confirms the diagnosis.[23] The differential diagnoses of this condition include malakoplakia, chronic infections like tuberculosis, etc. This rare condition should be included in the differential diagnosis of ovarian cysts/tumors and endometrioma abscesses.

In our case, the mass in the right adnexa, though previously thought to be of either neoplastic or infective etiology, the HPE revealed the actual diagnosis, which was crucial in further patient management. Though the entity is overall

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rare and cannot be diagnosed without the HPE, it is imperative to consider this entity in the differential diagnoses for patients presenting with similar complaints especially in cases having predisposing conditions like PID, endometriosis, inadequate antibiotic therapy, infertility, etc.

Conclusion

Xanthogranulomatous inflammation, occurring in female genital tract, is extremely rare. The presence of this entity, should always be paid due attention, as meticulous HPE is the key in its diagnosis. This case report, which is the first documented report of occurrence of xanthogranulomatous oophoritis, in a pregnant female with post-IVF ET pregnancy, having history of endometriosis and infertility, stresses the fact that the condition can present in varied settings and high level of suspicion is of paramount importance for the diagnosis.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal their identity.

Conflict of Interest

None declared.

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A Rare Case of Life-Threatening Extensive Mucocutaneous Adverse Reaction Induced by Docetaxel in a Breast Cancer Patient: Toxic Epidermal Necrolysis, a Case Report with Review of Literature

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Ind J Med Paediatr Oncol 2022;43:318–321.

Abstract

Fever and extensive necrosis with 30% or more epidermal involvement along with mucous membrane is known as toxic epidermal necrolysis (TEN). It is a life-threatening mucocutaneous disease and is usually drug induced. We report a rare case of docetaxel-induced TEN. A patient with metastatic breast carcinoma received single agent docetaxel and developed severe skin and mucous membrane reaction involving more than 30% of the skin, and managed conservatively in intensive care unit but she succumbed to her illness. Although common toxicities reported with docetaxel include alopecia, nail damage, myelosuppression, and erythema multiforme major, TEN after docetaxel is very rare and can be a life-threatening complication as in our case.

Keywords
- docetaxel
- toxic epidermal necrolysis
- breast cancer
- case report

Introduction

Docetaxel is derived from the needles *Taxus baccata* (European yew tree). It binds to microtubules and enhances tubulin polymerization leads to inhibition of mitosis and cell division. Reported cutaneous toxicities include alopecia, hypersensitivity with skin rash, pigmentation, onycholysis, palmar–plantar erythrodysesthesia, cutaneous lupus, and erythema multiforme. In our case, patient developed toxic epidermal necrolysis (TEN) following administration of docetaxel, which is a rare side effect of docetaxel.

Case Report

A 39-year-old woman was diagnosed with metastatic breast cancer (liver and lung metastasis). She was on palliative chemotherapy docetaxel 75 mg/m^2 with trastuzumab (8 mg/kg in first cycle followed by 6 mg/kg in consecutive cycles) on a 3-weekly schedule. She tolerated two cycles of planned therapy. Nine days after third cycle of docetaxel and trastuzumab on August, 08, 2021, she presented with complaints of blisters that later ruptured with excoriation of skin over both hands, feet and back, oral mucositis with difficulty in swallowing, sticky eyelids with conjunctival redness,

DOI https://doi.org/10.1055/s-0042-1743125.
ISSN 0971-5851.

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multiple episodes of vomiting, loose motions, shortness of breath, and low-grade intermittent fever.

On examination, her Eastern Cooperative Oncology Group performance status was 4, pulse rate 125/min, feeble, rhythmic, normovolumic, hypotension (90/60 mm Hg), tachypnea (respiratory rate >21/min), afebrile, saturation of peripheral oxygen 80%, and Grade III oral mucositis. Dermatological examination showed extensive erythematous desquamation with ruptured blisters involving skin of hands, lips, feet, vulva, perianal region, and lower back involving more than 30% of body surface was noted with mucosal involvement (►**Fig. 1**). Crepitations was present in both lower zones of lung. Patient was admitted in intensive care unit. Laboratory evaluation showed hemoglobin of 9.4 g/dL (11–14), total leukocyte count 32.27×10^9/L ($4–10 \times 10^9$) with 82% neutrophils, 11% lymphocytes, 7% monocytes, and platelets of 2.84 lakh/mm^3, creatinine 1.1 mg/dL (0.5–1.5 mg/dL), and blood urea 102 mg/dL (15–40 mg/dL). Bilirubin of 4.11 mg/dL (0.5–1.5 mg/dL), serum glutamic oxaloacetic transaminase 54 U/L (0–40 U/L) and serum glutamic-pyruvic transaminase 40 U/L (0–45 U/L), random blood sugar 164 mg/dL, pH 7.20 (7.35–7.45), bicarbonate 16 mEq/L (22–26 mEq/L) and rest other investigations were within normal limits. Chest X-ray showed dense homogenous opacity in left hemithorax obscuring left costophrenic angle suggestive of left-sided pleural effusion.

Punch biopsy taken from the lesions on the left forearm and left medial foot, on hematoxylin-eosin-stained specimen, light microscopy features suggested TEN (►**Fig. 2**). Diagnosis of docetaxel-induced TEN was confirmed and managed with intravenous fluids, vasopressors, steroids, antibiotics, and total parenteral nutrition with hypothermia prevention. Secondary infection control and skin care were instituted. Unfortunately, patient died on the sixth day of hospitalization.

Discussion

Docetaxel a microtubule inhibitor got first approved in 1996 for the treatment of metastatic breast cancer patients who relapsed after anthracycline-based chemotherapy.[1,2]

Side effects of docetaxel include neutropenia, anemia, thrombocytopenia, and minor rash to severe anaphylaxis reactions, which are reversible on stopping treatment. In literature, various skin reactions reported includes maculopapular drug rash, alopecia, nail hyperpigmentation and destruction, onycholysis, palmar–plantar erythrodysesthesia, cutaneous lupus and scleroderma,[3] photolichenoid eruption,[4] erythema multiforme major,[5] and persistent serpentine supravenous hyperpigmented eruption.[6]

Only a few cases of life-threatening TEN-like adverse reaction due to docetaxel have been reported till date.

As per Gell and Coombs system,[7] docetaxel causes delayed onset T-cell-mediated type IVc hypersensitivity reaction, and can occur days to weeks after exposure.

Immunophenotype study of lymphocytes in blister fluid of TEN lesions suggested a cell-mediated cytotoxic reaction against keratinocytes leading to apoptosis.[8] Further studies showed that cytotoxic T cells are drug specific, human leukocyte antigen (HLA) class I restricted, and directed against the native form of the drug rather than against a reactive metabolite.[8–11] Drugs directly bind to major histocompatibility complex class I and the T cell receptor leading to stimulation the immune system, clonal expansion of drug-specific cytotoxic T

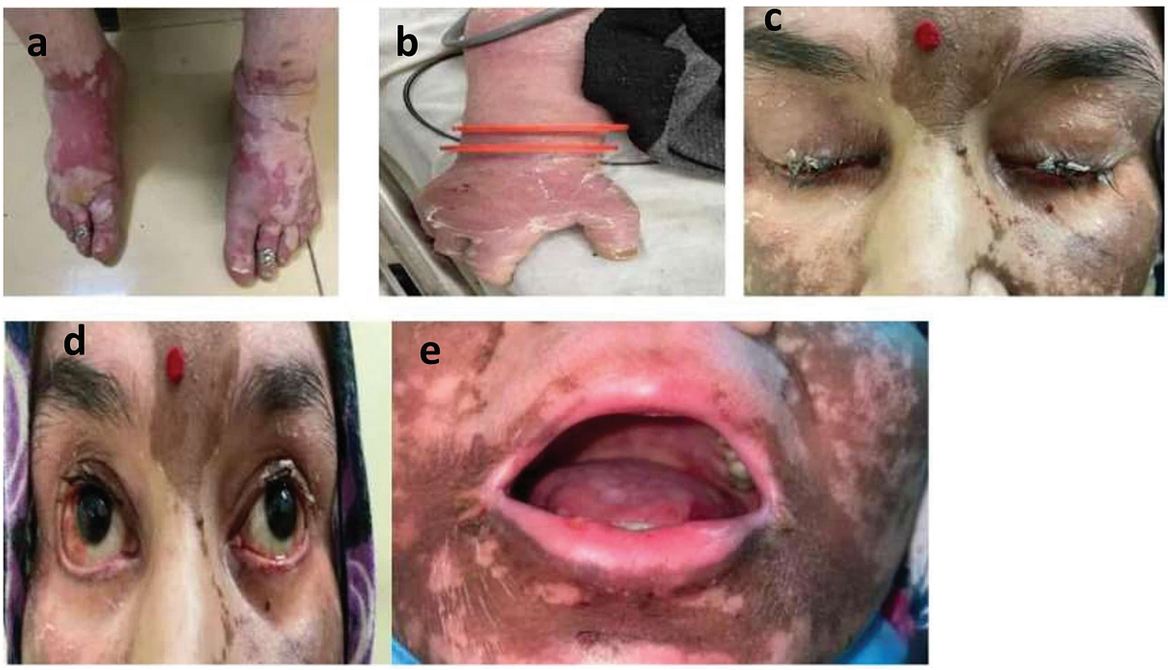

Fig. 1 (a) Photograph of erythematous bullous eruptions over feet. (b) Photograph of hand with skin excoriation with erythema after rupture bullous lesion. (c) Both eyelid skin excoriation. (d) Conjunctival hemorrhage. (e) Mucosal lesion of lips and tongue.

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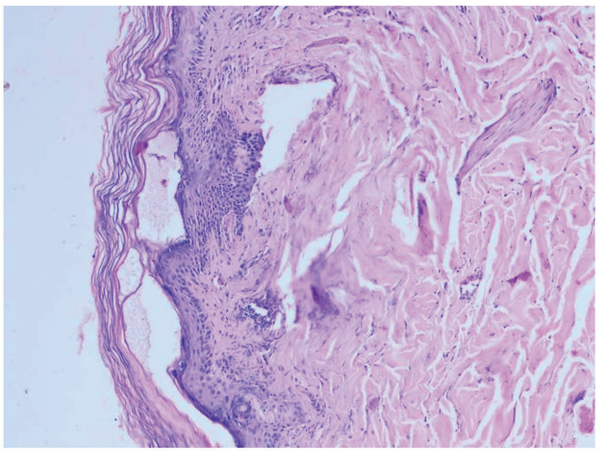

Fig. 2 Biopsy images and pathology report: microscopic examination of the skin (hematoxylin and eosin stain) was performed. The punch biopsies from the edges of both lesions (left forearm and left medial foot) show similar morphologic features (1) orthokeratosis of epidermis, (2) follicular plugging, (3) subcorneal separation and small vesicle formation, (4) basal vacuolar changes, (5) superficial dermis shows perivascular lymphoplasmacytic infiltrate, (6) papillary dermis shows mild edematous changes, and (7) interstitium shows increased mast cells. The histologic features are consistent with toxic epidermal necrolysis/Stevens–Johnson's syndrome.

cells, killing of keratinocytes via release of soluble death mediators, including granulysin.[12]

Drugs directly bind to the HLA class I peptide pouch,[13] and change the repertoire of peptides recognized as foreign[14] and make the HLA–drug complex recognized as foreign.

Medications are most common cause for TEN. TEN involves sloughing of more than 30% of the body surface area. It starts with malaise, fever, and involvement of mucous membranes in nearly all cases.[15] Toxic epidermal necrosis is distinguished from Stevens–Johnson's syndrome (SJS) by severity and percentage of involvement of body surface area.

The skin lesions, that is, erythematous macules, patches, and almost 50% of cases start with erythema lead to full-thickness epidermal necrosis and skin resembles that of extensive thermal injury as seen in our patient. TEN is a potential life-threatening adverse reaction with risk for complications such as secondary infections, dehydration renal, gastrointestinal involvement, and finally scarring with cosmetic and functional problems.

Anticancer medications reported to cause severe cutaneous adverse reactions (SJS and TEN), alkylating agents (treosulfan, chlorambucil, temozolomide, procarbazine), plant alkaloids (paclitaxel, docetaxel, etoposide), anthracyclines (doxorubicin), antimetabolites (methotrexate, cytarabine, fludarabine, gemcitabine), antitumor antibiotics (bleomycin), epidermal growth factor receptor inhibitor (afatinib, cetuximab, panitumumab), immune checkpoint inhibitors (nivolumab, pembrolizumab), etc.

Prevention of adverse effects can be with premedication, which can be started from a day before infusion up to 5 days. Once TEN is established, management involves multispecialty supportive care with critical care, skin specialist, plastic surgery, nutrition specialist and infectious disease physicians involved in fluid and electrolyte management, wound care, nutritional support, and treatment of superinfection. Data regarding use of corticosteroids are mixed, as their use may increase risk of sepsis in TEN.[16]

The Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) prognostic scoring system is applied to rapidly evaluate individual patient on admission. Overall mortality rates of 25 to 35% have been seen with TEN using SCORTEN prognostic scoring system which is used to determine prognosis on days 1 and 3 of hospitalization.[17]

Mortality rate (%) as follows:

- 0 to 1 = 3.2% (confidence interval [CI]: 0.1–16.7)
- 2 = 12.1% (CI: 5.4–22.5)
- 3 = 35.3% (CI: 19.8–53.5)
- 4 = 58.3% (CI: 36.6–77.9)
- ≥ 5 = > 90% (CI: 55.5–99.8)

The SCORTEN score in our case was 5, which suggests > 90% risk of mortality. The occurrence of TEN after third cycle of docetaxel-based therapy in our case should caution us toward the rarity and unpredictability of this toxic reaction (►**Table 1**).

Table 1 Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN)

Risk factors	Score		Patient
	0	1	
Age	< 40 y	≥ 40 y	39 y
Associated cancer	No	Yes	Breast cancer
Heart rate	< 120	> 120	125 beats/min
Detached or compromised body surface area	< 10%	≥ 10%	>30% of body surface area
Serum blood urea nitrogen	≤ 28 mg/dL (10 mmol/L)	> 28 mg/dL (10 mmol/L)	102 mg/dL
Serum bicarbonate	≥ 20 mEq/dL (≥ 20 mmol/L)	< 20 mEq/dL (≥ 20 mmol/L)	16 mEq/dL
Serum glucose	≤ 250 mg/dL (≤ 13.88 mmol/L)	> 250 mg/dL (≤ 13.88 mmol/L)	164 mg/dL
			SCORTEN score 5

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Conclusion

Docetaxel-induced TEN is a rare but fatal complication. Early recognition and intensive management with supportive care by team of specialist can limit this life-threatening complication of a commonly used cytotoxic drug in cancer management.

Ethics

The authors certify that they have obtained an Ethics committee approval for publication (ECR/748/Inst/MP2015-EE/18, dated: 22 October 2021) from the institutional ethics committee of Sri Aurobindo Institute of Medical Sciences.

Funding

None.

Conflict of Interest

None declared.

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Ind J Med Paediatr Oncol 2022;43:322.

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IJMPO family is indebted to our peer reviewers. Structuring a good review is time-consuming and effort-intensive. We deeply value the inputs of all the reviewers who volunteer their time and expertise to provide essential feedback and suggestions to the authors as well as the editorial board and ensure the quality of research published in IJMPO. We would like to thank the following reviewers for contributing to this issue:

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DOI https://doi.org/10.1055/s-0042-1753456.
ISSN 0971-5851.

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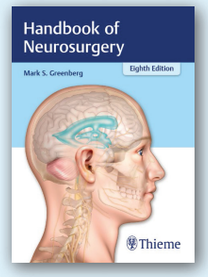

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