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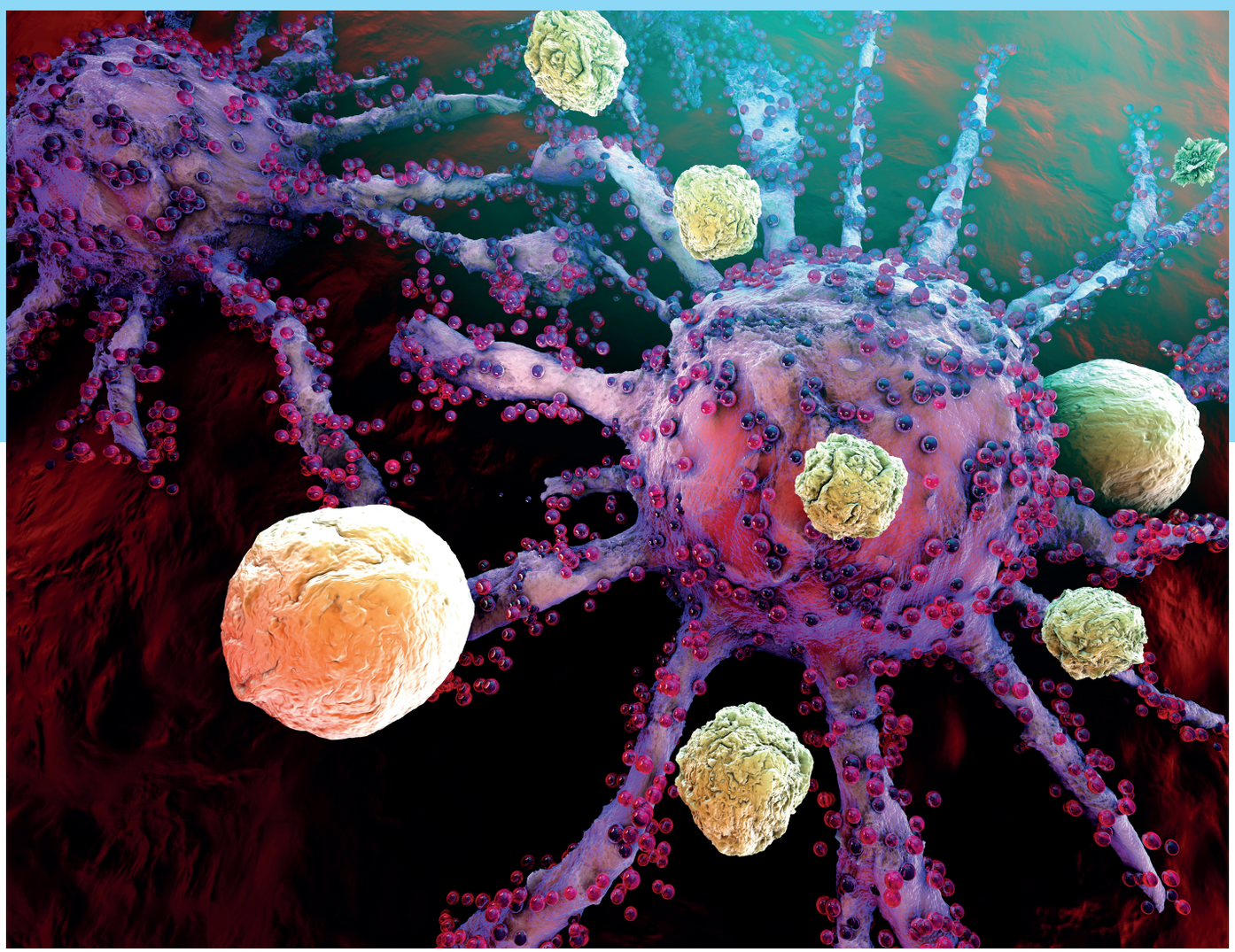

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Cutting-Edge Developments in Oncology Research

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Abstract

The field of oncology research has made many successful advances, and new discoveries have started making headlines. As an example, the identification of immune checkpoint inhibition mechanisms in carcinogenic cells led to the development of immunoassays, which have helped many cancer convalescents recover. This article covers the most advanced cutting-edge areas of cancer research: exosomes, microbiomes, immunotherapy, nanocarriers, and organoids. Research on exosomes advances cancer detection and treatment modalities, as well as further understanding of mechanisms that regulate carcinogen cell division, proliferation, invasion, and metastasis. Microbiome consents the researchers to understand the disease cancer. Immunotherapy is the third method in the treatment of cancer. Organoid biology will be further expanded with the aim of translating research into customized therapeutic therapies. Nanocarriers enable cancer specific drug delivery by inherent unreceptive targeting phenomena and implemented active targeting strategies. These areas of research may also bring about the advent of the latest cancer treatments in the future. Malignant infections are one of the leading grounds for demise in the society. Patients are treated with surgery, radiation, and chemotherapy. In chemotherapy, the malignant cells are destroyed and the tumor burden is reduced. However, in most cases, resistance to chemotherapy develops. Therefore, there is a constant need for new additional treatment modalities and chemotherapeutic complex rules. Due to the rapid development in cancer research, I can only mention a few goals and treatment options that I have chosen; However, this review specializes in new and admirable significant strategies and compounds.

Keywords

- cancer treatment
- chemotherapy
- exosome
- immune checkpoint
- immunotherapy
- medical oncology
- microbiome
- nanocarriers
- oncology
- organoid

Introduction

Considerable advancement has been done in the ground of cancer research through the use of state-of-the-art gear and technologies. Next-generation sequencing (NGS) is an example of cutting-edge technology. Besides specified to as high-throughput sequencing, NGS is the universal designation accustomed to explain numeral single leading nucleic acid sequencing technologies.[1] Liquid biopsy, or fluid phase biopsy, is the scrutiny of liquid body fluid tissue, frequently blood.[2] It provides a broad range of opportunities in the field of oncology and carcinogen treatment and is used as a

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singular manner to detect cancer. Hence, liquid biopsies can be accomplished more habitually and could be used to monitor carcinoma expansion, track a patient's response to treatment, or as a "scrutiny" method for people who have completed the treatment but are at high risk of their disease recurring.[1] This approach can be used to authenticate the efficacy of a malignancy treatment drug by analyzing a couple of liquid scintigraphy tissue sections in the duration of a limited number of weeks.[1] These techniques permit for a great deal faster and less expensive sequencing of nucleic acids, that is, DNA and RNA in comparison with the formerly used Sanger sequencing (dideoxy chain termination sequencing), and thus have reformed the field of genetic makeup and cell biology. NGS additionally permits on behalf of less complicated exposure of transmutations in mutagen sections, which leads to improvement in numerous novel proxies that can be used to treat the patients.[1] Innovative maneuvers, medicines, and drugs have been devised and advanced for cancer treatment. Keyhole surgery using robotics has advanced and has made it feasible to envisage the motion of the tongs in three dimensions. This approach is at present utilized in esophageal, gastrocolic, and celiac cancer surgical procedures.[3–5]

Currently, immunotherapy have become a further approach for handling cancer patients. Honjo and Allison detected the insusceptible checkpoint, which brought the improvement in insusceptible checkpoint inhibitors.[6] Notwithstanding these advances, gastrointestinal cancer malignancy is still a prime hassle in the way of latest treatment techniques. In this review article, the introduction and description describe five new regions of cancer research that could make contributions to cancer treatment in the upcoming times: exosomes, microbiome, immunotherapy, nanocarriers, and organoids. Despite its accepted application in medical oncology, clinicians and biomedical scientists are nevertheless struggling with an incredibly low degree of expertise of diverse cellular and subcellular techniques and understanding of treatment mechanisms of chemotherapeutics already utilized in medical oncology.[1] There is no uncertainty that the certification of innovative chemotherapy-sensitive target molecules can optimize treatment success in clinical oncology.

The Role of Exosome Investigation in Oncology

An exosome is a minor molecule (micro vesicle) that is oozed out from cells. Its outer face has macromolecules derived from cellular membranes that measure between 15 and 150 nm in proportions. In addition, proteins and nucleic acids are determined in the matrix of exosomes.[7] In recent times, several scholars have concluded that exosomes are concerned in numerous ailment mechanisms.[1] Exosomes, which contain microRNAs, mRNAs, and proteins, have proven useful for retaining a wide range of practical amalgams.[8,9]

Countless cells practice the secretion of exosomes to express each other, and those exosomes also serve the goal of reaching remote cells. Malignant cancer cells can also release exosomes that incorporate particles that are conducive to cancer progression. Exosomes initiated by cancer cells can also destroy the blood-cerebral barricade, which subsidizes brain tumor.[10,11] Malignant cancer cells are additionally influenced via exosomes that surround normal cells.[12] Thus, in addition to the tumor microenvironment and premetastatic niche development, exosomes become deeply involved in cancer cell division, propagation, incursion, and metastasis.[13]

Exosomes can also be applied to identify most cancers. Categories which are established in numerous body fluids, including blood, plasma, and urinal fluids. The identification and interpretation of exosomes from most malignant cancer cells are used to make detections on the occurrence of the disease.[14] In the meantime, innumerable vesicles, such as many proteins (nucleotides), DNA, and microRNAs, are present in exosomes from ordinary cells; it is essential to separate them for most of them are associated with cancer.[1] Currently, exosome exposure strategies are being developed for exosomes within the plasma of many periampullary and hepatopancreatic cancer patients, with exosomes constant in the bladder of most cancer patients. Therefore, the similarity of the mechanisms that control most cancer cell division, proliferation, invasion, and metastasis, along with improvements in most cancer detection and treatment techniques is strongly influenced by exosome research.[1] While the discharge of exosomes from most malignant cancer cells can be restricted, the tumor microenvironment and signal transduction that facilitate the formation of the premetastatic region of interest cannot be achieved. Research is currently underway converging on the elimination of most cancerous exosomes.[15,16]

Implementation of Microbiome in Cancer Research

Different variety of pathogens live in the human anatomy out of which bacteria have the maximum essential association with the human anatomy. Bacteria can survive at any place inside the human anatomy, such as the digestive system, respiratory system, and oral cavities.[17] In particular, the bacteria in the gut are abundant in types and amounts.[1,18–20] The average populance of different bacteria observed in the mortal gut is called the microbiome.

Modern improvements with NGS have produced even more specialization to the duodenal microbiome.[21] Bacteria in human microbiome primarily belong to four files: *Firmicutes*, *Bacteroides*, *Proteobacteria,* and Enterobacteriaceae. Of these, the most prominent species are *Firmicutes* and *Bacterioidetes*.[22] Dysbiosis is a circumstance where the multiplicity of the microbiome is abridged. Dysbiosis has been reported to be related with several ailments, comprising seditious bowel disease, colorectal cancer, diabetes, and allergic diseases.[23] *Atopobium parvulum* and *Actinomyces odontolyticus* proliferate with size in the early stages of colorectal cancer (adenoma or intramuscular) over the course of the cancer advancement.[2,24] This suggests that a specific microbe may be related with the primary junctures

of colorectal cancer remission, which may be convenient for understanding premature exposure of cancer.

Countless researches have likewise been led to clarify the connection among the microbiome and the human immune system.[25] Immunoglobulin A (IgA) antibodies, one of the utmost essential factors in the intestinal resistant system, are assumed to have a function in removal of pestilent microbes and restoring the intestinal environment. IgA antibodies detect, eradicate, and counteract infectious bacteria and toxins. It additionally preserves a mutual association by opening and capturing the host's typical microbiome.[26] Recent research has identified W27IgA antibodies, which have the ability to bind to many bacteria.[27] This antibody called W27IgA apprehends to a portion of serine hydroxymethyl transferase, an enzyme intricated in bacterial growth. W27IgA antibodies bind to them and suppress the growth of *Escherichia coli*. The W27IgA antibody, however, does not attach to bacteria that overpower enterocolitis, including bifidobacteria and lactic acid bacteria.[27] Thus, the microbe is intensely concerned with the resistance of the human gut. Lately, it has been installed that besides being involved in the intestinal immune system, microbiome also plays a broader role in the human immune system.[1]

As the exploration of the microbiome progresses, its links to pathophysiology of numerous ailments such as cancer as well as its supervision of the human immune system become clear. It is, moreover, associated with lymph node metastasis, hepatocellular carcinoma, and remote metastasis.[28,29] The research and study of the microbiome provide some evidence in improving and treating gastrointestinal cancer.

The Growth of Immunotherapy in Cancer Treatment

For the last few decades, surgery, chemotherapy, and radiation therapy have been the primary techniques of therapy for most cancers. Along with to these treatment options, immunotherapy has freshly fascinated universal interest.[30] An individual's immune system is stimulated by the cancer antigens to attack cancerous cells under typical conditions. Nevertheless, occasionally the immune system does not treat cancer cells as nonself or is unable to assault them. Even though therapies that prompt the immune system to counter against cancer cells have been analyzed for a long time, the usage of an affected person's own immune system to treat cancer has not been recognized. Lately, the immunoassay center has demonstrated the effectiveness of both immunosuppressive measures and chimeric antigen receptor (CAR)-T cell therapy.[31]

There are two main fundamental reasons why it may be problematic to prove the effectiveness of anticancer therapy for some time. Signal transduction by immune checkpoint compounds, including Programmed death 1 and CTLA4, overpowers cytotoxic T lymphocytes (CTLs).[32] Suppression of immune checkpoint molecules that neutralize antibodies can initiate the subdual of cancer-specific CTLs which instantly activate the immune system and promote cancer eradication. Immunoassay has been shown to be effective and clinically applicable in many solid cancers, including melanoma,[33] lung cancer,[34] gastric cancer, and esophageal cancer.[35] In addition to PD-1 and CTLA4, new immunoassay molecules containing LAG3 T cell Ig and ITIM domain and Signal regulatory protein α are also being actively studied.[36] Although this treatment is favorable, cancer cases that answer to these treatments are narrow. This is due to the fact that the use of this treatment calls for the incidence of cancer-specific CTLs in the patient's body.

A second problem with immunotherapy is that T cells do not apprehend the exact cancer cell antigens and the immune accelerators are very weak. By delivering CTLs to the victim's body that recognize the exact cancer cell-specific antigen, CAR-T cells strengthen the immune accelerator. The CAR is made up of single chain Fv antigens (CD28, 4–1BB) and constitutive molecules (CD3z, 4–1). Next, CAR is instigated into T cells taken from cancer patients and CAR-T cells cells are generated. CAR-T cells secrete a specific antigen of cancer cells and are activated to damage these cells. The CAR-T cells link with high antibody specificity to cancer-specific antigens, as well as to cancer cells that are very proliferative and possess strong cytotoxic activity. The CAR-T treatment is operative in leukemia, including B-cell acute lymphoblastic leukemia and myeloma.[37] While CAR-T cell therapy has a high beneficial effect, an obstinate and severe malignant singularity known as cytokine release syndrome has been acknowledged in some patients.[32] The recent treatment for microsatellite instability-high colorectal cancer includes nivolumab and ipilimumab. The progression-free survival rates (9 months) and 12-month survival rates (71%) for the Nivolumab Plus Ipilimumab Cohort of Checkmate-142 were 87 and 85%, respectively.[38]

Therefore, it is predicted that the further specialization of the cancer immune system and the improvement of different immunotherapies will subsidize to momentous improvements in cancer treatment. One hassle with immunotherapy is that there is no conclusive extrapolative biomarker.[1] To find the new biomarker, we assess cytolytic activity (CYT) ratings. CYT rating is based on GZMA and PRF1 mRNA expression levels as a new measure of cancer immunity.[1] Advances in biomarker novelty may assist many gastrointestinal cancer patients.

Use of Organoids in Cancer Research

The three-dimensional (3D) organoid arrangement is a biological culture-based, innovative, and physically applicable cellular stage.[39] The organoid is a small and abridged model of an organ that is fashioned in vitro in 3D and represents the actual microscopic anatomy. With a few cells cultured from the tissue or cultivated cells as the preliminary substance, the organoids nurture and transmit into the vault membrane cellular pool, which subsidizes to their self-regenerative and distinction capabilities.[39] A wide variety of cancer tissues and cells can also be studied to determine the traits of the stem embryonic stem cells or prompted pluripotent stem cells.[40]

The organoid structure is commonly referred to in 3D[39] for the growth of stem cells or their innate cells. The

phylogeny and practical properties of diverse varieties of cancer tissue have been replicated in single-cellular suspensions or organoids generated from cell masses. In addition to culture-propagated cancer cells, these masses are quarantined from murine embryonic cells and humanoid tissues or cultured cells. The arrangements of organoids display the capability of cancer cells to self-regenerate, proliferate, and differentiate, and offer insight into important molecular pathways and biome elements in many cancer treatment.[40] Organoid systems have also been applied to the analysis of many genetic and biological processes, including locomotion, pressure reaction, cellular-cellular communiqué, and cell exchanges with a wide variety of cells, including fibroblasts, endothelial cells, and inflammatory cells.

Organoids, although not a complex and convenient technology, do require precise media, enhancements, and several intricate techniques,[41] and their solicitation is mainly dedicated to the treatment of cancers (colorectal, prostate, breast, ovary, and esophageal cancer).[40,42] The keratinocyte serum-free medium was modified to produce endoscopic esophageal biopsies, commemorated human esophageal epithelial cells, and 3D organoids from the murine esophagus.[2,43]

3D organoid systems have materialized as a sturdy apparatus in basic fundamental research over the past few years that can be used for customized medication.[44] In maximum circumstances, it may be beneficial to organize the patient's organoid to investigate the susceptibility of new therapeutic agents to the treatment of cancer.[44] Therefore, it seems that organoid biology is becoming more broaden with the purpose of interpolating research into customized medicine.

Nanocarriers: Cutting-Edge Antineoplastic Drug Carriers in Cancer Treatment

Biological nanocarriers are frictional nanomaterial systems that can deliver small molecular weight drugs or macrocellular anticancer agents, such as genes or proteins, to subcutaneous tissues during targeted treatment and accumulate in tumors in the same way as molecular carriers like antibodies and peptide-drug conjugates do.[45] Furthermore, nanocarriers attenuate dilapidation, lessen renal absorption, extend its half-life in the bloodstream, aggregate the payload of cytotoxic drugs, reverse the kinetics of anticancer drugs, and increase the solubility of insoluble anticancer drugs.[45] In most cancers, angiogenesis produces new blood vessels for the tumor, but these new vessels have enlarged permeability or enhanced permeability and retention (EPR) effect, resulting in inactive nanocarriers as well as poor lymphatic drainage of the tumor tissue by delivering the release of chemotherapeutic agents into the tumor homeostat.[46] To take advantage of the abnormalities of tumor vascularization, nanocarriers must have a sufficiently diffuse half-life to target the tumor environment passively, inhibiting the movement of the mononuclear phagocyte system (MPS) and reticuloendothelial system by transporting anywhere in the bloodstream and releasing anticancer drugs into the tumor.[47] For this resolution, the nanocarrier size to exit MPS should not exceed 400 nm and is more effective by the EPR effect in tumors less than 210 nm[48] in diameter. Moreover, the surface of these nanoscale carriers must be hydrophilic and neutral or simply ionic to escape plasma proteins (opsonins) and stop macrophage attack.[49] This is accomplished by coating the carrier exterior with hydrophilic polymers such as polyethylene glycol (PEG)[50] or synthetic copolymers of polyethylene oxide (hydrophilic block) and propylene oxide (hydrophobic block).[51] Further, blood vessels and cells contain negatively charged molecules that can repel nanocarriers with negatively charged exteriors. Therefore, one must use slightly negative or positive exteriors.[52] On the surface of nanocarriers for containing active targeting, chemotherapeutic drugs are present by a combination of various components, such as monoclonal antibodies, antibody fractions, peptides, and growth factors.[53]

In fact, nanocarriers permit the inclusion of multiple pursuing ligands due to the surface-to-area-to-volume ratio that comes with many binding options.[45] The active targeting target does not increase the total tumor accretion of cytotoxic drugs at the site, but submissively allocates cytotoxic drugs in superior quantities than the consolidated systems to the tumor because the preliminary accretion of nanocarriers in the tumor affects the consequence of EPR before the target is formed.[42,54] Nevertheless, the active cellular target enhances healing efficiency by reducing specificity and increasing the intake.[45] Moreover, the use of peptides aims to defeat the multicellular resistance of nanocarriers and avoid the restrictions of sedentary targets, as in some hypovascular tumors.[55,56] Active targeting nanocarriers can intensify antitumor capacity several times compared with nontargeting carriers.[57–59] From tumor vasculature penetration, it can be accredited to this clinical failure because there are fundamentally certain restrictions on the procurement and entry of cancer cells.[60] Furthermore, in budding tumors, cancer cells are close to the endothelial barrier and bind to receptors that initially penetrate the rest of the tumor, targeting nanocarriers. In this cutting-edge world, specific techniques have been defined to address these defects that reduce the transport of nutrients and oxygen to the tumor and increase the antitumor potential of nanocarriers by releasing less molecular anticancer drugs near the tumor vasculature.[59–61] An extra drawback that contributes to the state-of-the-art clinical miscarriage of dynamic targeting nanocarriers is the inclusion of target in nanocarriers, which have enhanced immunogenicity and plasma protein absorption, reducing their blood flow time and their capability to passively target tumors.[59] Among nanocarriers, there are polymer therapeutics (polymer-protein and polymer-drug conjugates) in which the drug is nonpolarly bonded or conjugated to the polymer, and particulate drug nanocarriers, in which the drug is trapped inside specific structures made from specific materials like polymers (polymeric micelles, dendrimers, and polymeric nanoparticles [NPs]) or organometallic compounds (chiral and zigzag carbon nanotubes).[2,62]

Polymer Therapeutics: Explicit Biomarkers for Cancer Treatment

In polymer therapeutics, there are polymer–protein conjugates and polymer–drug conjugates, which are, among other things like nanosized linear water-soluble polymeric macromolecular structures that are joined to antitumor proteins and anticancer peptides by cleavable linkers proteins or small molecules that can be united with anticancer drugs and are constant for the transference period of the cytotoxic component and discharges anticancer drug into the tumor.[63] The synergistic combination of anticancer proteins with polymers diminishes its immunity and escalates its constancy and diffusion interval in the blood,[64] but in the case of polymer-drug amalgamations, the polymers deliver improve the circulating time in blood for cytotoxic drugs, with improved aqueous solubility. Passive beleaguered delivery to tumors and low toxicity increase the remedial value of the anticancer drug.[63,65] In both cases, these constructions can be measured as "new chemical entities" with a penchant for drug carriers, with low drug loading and limited potential for active targeting due to the limited number of compound sites available in the polymer.[64] In combination, PEG-L-asparaginase (pegaspargase or Oncasper), a polymer-protein conjugates, is administered intravenously.[66,67] Pegaspargase is a primary polymer-protein conjugate authorized through the U.S. Food and Drug Administration (FDA) in 1990s for the treatment of acute lymphoblastic leukemia.[43] Recent research does not have any new FDA approvals for cancer treatment, but there are enzymes (arginine deaminase) and bio biological response modifiers (interlukin 2, interferon-, and antibody fragments).[68,69] Research on polymer-drug compounds for the cure of age-related,[54] cancer currently consists of at least 20 compounds (most of which are in closed state)[62] and are mainly used Instead of conventional cytotoxic drugs, for instance, platinates,[70] doxorubicin, camptothecin, paclitaxel, methotrexate, and irinotecan. In phase III clinical trials, Xyotax (CT-2103 or OPAXIO), a polyglutamic acid (PGA)-paclitaxel conjugate, and NKTR-59, a polymeric conjugate of irinotecan, are close to commercialization.[53,71]

In 1994, a manmade polymer-drug conjugate based on N-(2-hydroxypropylene) methacrylamide-doxorubicin became the key component in medical trials. Since then, no further polymer-drug conjugates based on artificial polymers such as HPMA, PGA or PEG have been submitted for medical trials. Additionally, numerous natural polymers can be classified as polymer-drug conjugates, though only some polysaccharides, hyaluronic acid, human serum albumin, and dextran have reached the stage of clinical trials.[53] The most notable breakthrough in the direction of medical use of polymer-drug conjugates is the docosahexaenoic acid—paclitaxel conjugate (Taxol), which has recently entered the phase III clinical trials of cancer treatment.[2,72] Although nearly all polymer-drug conjugates use passive targeting, active mechanisms with targets such as antibodies, peptides, and folate have evolved over the years.[53] Polymer-drug conjugates[53] are also being researched for their potential to inhibit specific kinases, accelerate apoptosis, or reduce angiogenesis (polycystic ovary syndrome).[73]

Conclusion

As the exosomes enter the bloodstream or urinal tract, if the apprehending system is in place, it will become a much less intrusive test to make out cancer.[1] Since exosomes contain not only DNA but also other genetic material and proteins, it is a novel instrument for cancer research that includes the early prognosis of cancer. Normal mobile homeostasis is predicted by the interchange of genetic biological substances across the membrane and enables such transport by vessels that transport the cargo to the suitable destination. They are immersed in the ubiquitous external environment and are featured by specific capabilities contingent on the secreted cell of the foundation.[1] Exosomes contribute to the technique of chemo-organotropic metastasis and additionally involve extra essential chemooncogenic indicators in integrating the selection and function of the analogous exosome in chemo-organotropic metastasis. Ultimately, to detail the complex mechanisms of regulation and cross-communication that exist between cancer and stromal cells, further research is needed. Furthermore, the origin and biological impact of diversity in exosomes continue to be largely unknown due to the deficiency of analytical platforms and accessible equipment. The standard features of the human immune system such as accurate detection and removal of cancer cells, adaptation to the developing tumor, and memory of the immune system appear to be an excellent aggregate to develop an effective defense for long-term cancer regulation.

Microbiome may be an addition in advanced cancer prognosis and treatment. Exposure of a particular microorganism in the gastrointestinal tract can envisage particular cancer proliferation. Microbiome is extraordinarily essential for human health; at contemporary times its function in the context of cancer is clear. Microbial outcomes vary from improving cancer immunity and cancer treatment efficiency to promoting cancer advancement and preventing treatment effectiveness. These broad implications have prompted researchers to analyze these specific interfaces, along with how vicissitudes in the microbiome augment the survival and treatment potential of most cancers. For cancers such as gastric cancer, these interactions have been well established; however, they are rarely understood in other cases. Since nonsmall cell lung cancer is the bulk of lung cancer cases and one of the pinnacle causes of cancer deaths globally, the specificity of the mechanisms that affect microbiome evolution is compulsory for measures and treatment to prolong patient's endurance and treatment reaction.

As the field of cancer immunotherapy has evolved, the focus of treatment has lifted from handling the disease site to treating specific tumor biological symptoms and its relations with the patient's internal cancer autoimmunity set-point. Because the immune system has the ability to recollect and detect and destroy tumor forms, immunotherapy always has integral benefits compared with other therapies that do not have these two main indications. Finding out why

immunotherapy treatments work best in some cancers and in some patients is even more thought-provoking, while in others tumors that were once sensitive to treatment may become resistant. To be particularly effective, cancer immunotherapy must discover conducts to change the immune system in patients who show a low or no immune response to their tumors, even to the tumor microenvironment without tumor-infiltration T-cells. Despite the promise of immunotherapy for cancer treatment, only a minority of cancers respond to some of these treatments.

Nanotechnology is pragmatic in cancer treatment and has ushered a new era in cancer treatment. A variety of NPs, including organic and inorganic NPs, are already widely used in the medical treatment of a wide variety of cancers. Furthermore, nanocarrier delivery systems make available better platforms for combination therapy, which can help drug resistance to hypoxia, including flux transporter overexpression, defective apoptotic pathways, and hypoxia in the tumor microenvironment. The use of nanovaccine and synthetic antigen presenting cells has demonstrated greater effectiveness than conventional immunotherapy; however, the medical effectiveness of this treatment is unsatisfactory, and its safety and permissibility must be explored further. Furthermore, the development of immunomodulatory factor-loaded NPs enhances the efficacy of inoculations for immunotherapy.

Organoids can also help solve the problem of drug resistance and lead to the advancement of modified therapies. However, the preparation of organoids takes time and may take even take longer to test for drug resistance. Present-day advances in in-vitro 3D culture technological expertise, comprising organoids, have opened new opportunities for the development of unique, more physical human cancer models. The genetic modification of organoids allows disease modelling in a setting that accesses the biological environment. In addition, organoids can be raised from patient-derived healthy and highly functional tumor tissue, undoubtedly allowing for patient-accurate drug testing and improving personalized treatment regimens. If we can overcome these problems, research on organoids can help overcome cancer. Therefore, these five new cancer research fields will make a significant difference to the diagnosis and treatment of most cancers.

Conflict of Interest
None declared.

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Management of Relapsed and Refractory Multiple Myeloma: Recent advances

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Abstract

Multiple myeloma (MM) accounts for ~10% of total hematologic malignancies worldwide. In India, the incidence of MM has increased two-fold with marked heterogeneity. Significant improvements in terms of clinical outcomes have been observed in the management of MM in recent years. However, most patients develop a disease relapse with the first or subsequent treatments. A combination of immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (PIs; bortezomib) has been the mainstay for the therapeutic management of relapsed/refractory multiple myeloma (RRMM). This review highlights the management of RRMM with newer agents such as belantamab, carfilzomib, daratumumab, elotuzumab, ixazomib, mafadotin, selinexor, panobinostat, and venetoclax, with more focus on PIs. As a single agent and in combination with other drugs including dexamethasone and carfilzomib has been studied extensively and approved by the United States, European Union, and India. Clinical trials of these newer agents, either alone or in combination, for the treatment of RRMM in Western countries indicate survival, improved outcomes, and overall well-being. However, evidence in Indian patients is evolving from ongoing studies on carfilzomib and daratumumab, which will ascertain their efficacy and safety. Currently, several guidelines recommend carfilzomib-based, daratumumab-based, and panobinostat-based regimens in RRMM patients. Currently, with more accessible generic versions of these drugs, more Indian patients may attain survival benefits and improved quality of life.

Keywords

- relapsed/refractory multiple myeloma
- carfilzomib
- Ixazomib
- daratumumab
- elotuzumab
- panobinostat

Introduction

Multiple myeloma (MM) is a chronic and rare cancer affecting plasma cells in the bone marrow. It is the next most prevalent blood cancer after leukemia,[1] affecting ~138,500 individuals worldwide every year.[2] According to the Globocan 2018 data, the global incidence and mortality of MM are 159,985 and 106,105, respectively,[3] and are expected to rise in the future.[4] Asia has a high incidence, mortality, and 5-year prevalence of MM compared with Europe and North America.[3] In India, the estimated incidence in 2018 is 12,923 new cases; mortality is 9,900 cases, and the 5-year prevalence estimate is 24,375 cases. These figures are almost two times higher compared with 2012 data.[5] Further, there is apparent heterogeneity in the incidence of MM in India across age, sex, and geography.[6]

Despite advancements in induction and maintenance therapies, most patients eventually experience relapse and refractoriness requiring further treatment.[7] Over the years, novel therapeutic strategies, such as bortezomib,[8] thalidomide,[9] and lenalidomide,[10] have been used for MM. However, several studies have highlighted the poor prognosis of

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patients who have been refractory to the currently used drugs.[11,12] Over the last few years, there has been a visible shift in the treatment of relapsed and/or refractory MM (RRMM). Several newer agents or combinations of agents targeting various relapse phases are currently available with improved patient survival and quality of life. This review focuses on clinical trial results of second-generation proteasome inhibitors (PIs), ixazomib and carfilzomib, and also provides an overview on other novel therapies, including daratumumab, isatuximab, elotuzumab, belantamab mafodotin, and panobinostat, for the management of RRMM.

Definition of RRMM

RRMM is characterized as cancer that becomes progressive within 60 days of receiving the most recent therapy in those who attained a minimal response or improved on previous treatment or cancer that is nonresponsive while on salvage treatment.[13] While in the nonsecretory subtype, relapse of myeloma is characterized as an absolute rise in the bone marrow plasma cells by $\geq$ 10%.[14]

Biology of Resistant MM

Relapsed MM is a biologically and genetically advanced heterogeneous cancer.[15] There are several reasons for relapse in MM cells, including the clonal evolution of MM cells and decreased capacity to adapt to the bone marrow microenvironment changes,[16] old age,[17] comorbidities,[18] and high-risk cytogenetics.[19] The International Myeloma Workshop Group (IMWG) defines the type of relapse based on clinical aggressiveness. In biochemical relapse, the disease progression correlates with an increase in M protein levels in an asymptomatic patient, whereas clinical relapses are accompanied by symptoms with or without organ dysfunction and an increase in M protein levels. A quick onset of symptoms characterizes aggressive relapse, widespread malignancy on laboratory, radiographic, or pathologic findings, and rapid organ dysfunction. The other high-risk features include unfavorable cytogenetic defects, high β2M (>5.5 mg/L) or low albumin (<3.5 g/dL), hypodiploidy, extramedullary disease, International Staging System stage II/III at relapse, and isotype makeover (hyposecretory disease, light chain escape). The presence or re-emergence of one or more CRAB characteristics (calcium, renal impairment, anemia, and destructive bone lesions) or a swift and consistent biochemical relapse is indicated for relapse treatment.[14]

The evolution of RRMM is dependent on the modifications in the intrinsic biology of tumor cells, tumor microenvironment, and host-specific factors. The tumor-specific molecular events contributing to RRMM development include accumulating cytogenetic aberrations (chromosomal translocations, gains, and deletions), alterations in signaling pathways (NF-κB, RAS-MAPK, JAK-STAT3), mutations in genes related to tumor suppression and drug resistance (*TP53, RB1, CRBN, CUL4B*), and epigenetic aberrations (DNA methylation, histone modification).[20] Primary cytogenetic abnormalities, such as trisomies and IgH translocations, occur early when the normal plasma cell transitions to a clonal, premalignant stage. Secondary cytogenetic abnormalities, including Del 17p, Del 1p, t (14:16), and t (14:20), occur during the progression of the malignancy to RRMM.[21]

RRMM Treatment

Treatment selection for RRMM is based usually on previous therapy, duration of disease, transplant status, performance status, cancer-associated factors, such as nature of relapse, disease risk, genomic abnormalities, and overall disease burden, and patient-related factors, such as patient preferences for drug intake, age, and comorbidities, including renal insufficiency.[22] With the introduction of immunomodulatory drugs (IMiDs), such as thalidomide, pomalidomide and lenalidomide, second-generation PIs, and more recently monoclonal antibodies targeting CD38, treatment options have been expanded for RRMM management.[23] Currently, new treatment strategies, such as oral HDAC6 inhibitors, bispecific T cell engager antibodies, chimeric antigen receptor T cell (CAR-T) therapy, and cyclin-dependent kinase inhibitors, are being studied in clinical trials. Novel agents, such as second-generation PIs, are generally well-tolerated with a better quality of life (QoL) among adults.[24] In a meta-analysis comparing all available agents for RRMM, PIs were the most efficient treatment options with the lowest toxic effects.[25] The National Comprehensive Cancer Network guidelines list 8 preferred regimens and more than 20 optional regimens constituting carfilzomib and daratumumab for previously treated MM.[22]

However, as the prevalence of MM in elderly patients is expected to increase in the future, optimal care should focus on improving outcomes while preserving the QoL.

In the following section, we will briefly discuss relevant studies and the clinical utility of carfilzomib, ixazomib, daratumumab, isatuximab, elotuzumab, belantamab mafodotin, panobinostat, and selinexor in the management of RRMM exposed to IMiDs and bortezomib.

Carfilzomib

The US Food and Drug Administration (FDA) approved carfilzomib in 2012 as a treatment for individuals with advanced MM, who have used at least one or more prior therapies.[26] Unlike bortezomib, carfilzomib selectively and irreversibly inhibits the 20S proteasome's chymotrypsin-like activity and is less susceptible to drug resistance.[26] Later, it was approved as a combination with lenalidomide plus dexamethasone or with dexamethasone for the treatment of RRMM, with less than or equal to three lines of prior treatment. In RRMM patients, the FDA recently expanded the prescribing information for carfilzomib to include weekly administration in combination with dexamethasone (Kd70 once weekly).[27] Combination of carfilzomib and lenalidomide plus dexamethasone was approved in 2015 by the European Medicines Agency (EMA) for adults with MM who have had at least one previous treatment.[28] In 2017, the Drugs Controller General of India approved carfilzomib and dexamethasone combination or carfilzomib and

lenalidomide plus dexamethasone combination for RRMM patients who have received at least one previous treatment.

Carfilzomib and its Combinations

The efficacy and safety of carfilzomib in combination with dexamethasone were determined in clinical studies (►**Table 1**).[29–32] Based on these findings, the USA and European countries have approved the combination of low-dose dexamethasone and carfilzomib. Safety and tolerability of carfilzomib in combination with lenalidomide and low-dose dexamethasone were determined in phase 1b dose-escalation,[33] phase 2 dose-expansion[34] (PX-171–006), and phase 3[35] studies (►**Table 1**). A randomized phase 3 study investigated the efficacy of carfilzomib versus low-dose corticosteroids with optional cyclophosphamide in RRMM (FOCUS trial) (►**Table 1**).[36]

A meta-analysis by Shah et al analyzed carfilzomib-based medicines for the treatment of RRMM (2906 patients); seven trials used carfilzomib plus other agents: dexamethasone (4 studies), lenalidomide plus dexamethasone (2 studies), and panobinostat (1 study).[37] The pooled overall response rate (ORR) and clinical benefit rate (CBR) were 45% (95% CI: 29–62) and 56% (95% CI: 41–71), respectively. In a separate analysis of three RCTs (ENDEAVOR, FOCUS, and ASPIRE), ORR and CBR improved significantly in the carfilzomib group compared with the control group. There was no difference between carfilzomib and low-dose corticosteroids alone for overall survival (OR) or progression-free survival (PFS) in patients who had received five previous regimens of low-dose corticosteroids for RRMM; this suggests that carfilzomib needs to be combined with certain drugs and used as first-line chemotherapy (FOCUS trial).[37] Compared with a single therapy, combination therapy showed improved ORR and CBR. Further, the treatment response in terms of ORR improved significantly with a more dose of carfilzomib ($>20/27\ mg/m^2$) compared with the normal dose (65% versus 35%, $p = 0.03$). While cardiotoxicity and hypertension were significantly high, peripheral neuropathy events were similar between the two groups.[37] In another meta-analysis of eight clinical studies (1,446 patients), Chen et al presented four trials of carfilzomib (monotherapy) for RRMM, two trials of lenalidomide and dexamethasone in combination, and two trials with or without dexamethasone. The pooled ORR and CBR with carfilzomib were 0.44 (95% CI, 0.18–0.69; $p = 0.000$) and 0.54 (95% CI, 0.33–0.76, $p = 0.000$), respectively.[38] In another meta-analysis of 24 studies (10,853 patients), Luo et al identified the time to progression, OS, and PFS of 21 different regimens and recommended triplet therapy of carfilzomib, daratumumab, and elotuzumab or ixazomib, plus dexamethasone and lenalidomide as the preferred choice in patients with RRMM.[39] In another meta-analysis of 20 prospective studies (2,220 patients) by Liu et al, the ORR and very good partial response were found to be 61% and 29%, respectively, with the carfilzomib combination regimens in 1,211 RRMM patients.[40] Several other studies have also determined the safety and efficacy of carfilzomib with dexamethasone and pomalidomide,[41] ibrutinib and dexamethasone,[42] and daratumumab and dexamethasone.[43] In the subgroup analysis of Asian patients, carfilzomib treatment caused increased cardiovascular toxicities (grade 3 or higher) (ARROW and ENDEAVOR trials).[44]

Safety of Carfilzomib

Polyneuropathy

In a pooled analysis of four phase 2 studies, 71.9% of 84.8% of patients at baseline experienced polyneuropathy (PNP) of grade 1 or 2. PNP grade 3 occurs in ~1.3% of patients.[45] However, the ENDEAVOR trial has reported a lower incidence of PNP with carfilzomib versus bortezomib,[31] whereas the ASPIRE trial observed a similar incidence of PNP between the lenalidomide and dexamethasone (Rd) and carfilzomib, lenalidomide, and dexamethasone (KRd) groups.[35]

Cardiotoxicity

Carfilzomib can cause chest pain, myocardial infarction, cardiac failure, hypertension, and peripheral edema. In a meta-analysis of 24 prospective studies ($N = 2594$), adverse cardiovascular events of any grade were seen in 18.1% of patients and of high degree (≥ 3) in 8.2% of patients. The incidence of these events was two times higher than the control group.[46] In another meta-analysis of 29 studies (4,164 patients), incidences of high-grade and any-grade cardiotoxicity were found to be 4.92% and 8.68%, respectively. The carfilzomib group had significantly higher odds of developing cardiotoxicity than the control group (OR, 2.03; 95% CI, 1.19–3.46; $p = 0.010$ for any grade and OR, 2.04; 95% CI, 1.31–3.17, $p = 0.002$ for high grade). The incidence of cardiotoxicity was similar in recently diagnosed compared with RRMM and in a high dose compared with a standard dose of carfilzomib.[47] However, the risk seems to be high with the addition of IMiDs compared with without addition (6.54% vs. 4.35%, $p = 0.033$). Clinicians need to be aware of these adverse events, and more research is required to develop risk mitigation strategies.[46]

Renal Toxicity

Acute kidney injury is another crucial adverse event of carfilzomib, especially in individuals with RRMM. In a recent meta-analysis of four RCTs (2,954 patients), renal toxicities were reported to be 21.3% for any grade and 8.3% for high grade in the carfilzomib group. The risk of renal toxicity was significantly high in the carfilzomib group compared with the control group ($p < 0.001$) (pooled relative risk [RR], 1.79; 95% CI, 1.43–2.23 for any grade and RR, 2.29; 95% CI, 1.59–3.30 for high grade). The incidence of renal toxicities did not differ based on carfilzomib dose, infusion duration, and treatment setting.[48]

Ixazomib

The safety and tolerability of oral ixazomib and its maximum tolerated dose were determined in a phase 1 trial.[49] The efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone,[50] as well as pomalidomide and dexamethasone,[51,52] were investigated in different clinical studies. (►**Table 1**).

Table 1 Clinical evidence on advancements in relapsing and refractory multiple myeloma treatment

Study title	Study type	No. of patients	Intervention	Outcomes
Carfilzomib				
Phase 1 study of 30-minute infusion of carfilzomib as a single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma[29]	Phase 1 study	33	*Carfilzomib and dexamethasone* carfilzomib (initial dose of 20 mg/m^2 and gradually raised to 70 mg/m^2) in combination with dexamethasone (40 mg per week)	• CBR and ORR for carfilzomib monotherapy were both 48% and 52%, respectively • The addition of dexamethasone increased the CBR and ORR to 64% and 55%, respectively, with acceptable tolerability
A phase 2 single-center study of carfilzomib 56 mg/m^2 with or without low-dose dexamethasone in relapsed multiple myeloma[30]	Investigator-initiated, phase 2, single-arm, single-center, open-label study	44	*Carfilzomib and dexamethasone* carfilzomib was administered for the first two cycles (20 mg/m^2) and 56 mg/m^2 thereafter. Dexamethasone (20 mg) was administered in six patients who progressed with carfilzomib monotherapy	• Partial response was achieved in 55% (23/42) of patients with carfilzomib for the first two cycles • Median DOR was 11.7 months and median OS and PFS were 20.3 and 4.1 months, respectively • In patients with dexamethasone added, 67% (4/6) achieved a partial response
Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomized, phase 3 trial[31]	Phase 3, open-label, randomized controlled trial (ENDEAVOR trial)	929	*Carfilzomib or* bortezomib *and dexamethasone* The initial dose of carfilzomib was 20 mg/m^2 for the first two days of cycle one and was increased to 56 mg/m^2 in further cycles and bortezomib 2 mg SC or IV was administered weekly twice. Dexamethasone (20 mg oral or intravenous infusion) was given on different days after the first two days in the carfilzomib group and bortezomib group.	• Median OS was 47.6 months in the carfilzomib group versus 40.0 months in the bortezomib group ($p = 0.010$)
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomized, phase 3, open-label, multicenter study[32]	Randomized, phase 3, open-label, multicenter study		*Carfilzomib or* bortezomib *and dexamethasone* Carfilzomib (20 mg/m^2 on days 1 and 2 of cycle 1; 56 mg/m^2 thereafter; 30-minute intravenous infusion) and dexamethasone (20 mg oral or intravenous infusion) or bortezomib (1.3 mg/m^2; intravenous bolus or subcutaneous injection) and dexamethasone (20 mg oral or intravenous infusion)	• Median PFS was 18.7 months in the carfilzomib group versus 9.4 months in the bortezomib group at a preplanned interim analysis ($p < 0.0001$)
Phase 1b dose-escalation study (PX-171–006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma[33]	Phase Ib dose-escalation study (PX-171–006)	40	*Carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd)* CRd was administered on 28-day dosing cycles: carfilzomib 15–27 mg/m^2 on days 1, 2, 8, 9, 15, and 16; lenalidomide 10–25 mg on days 1–21; and dexamethasone 40 mg weekly.	• ORR was 62.5%, and clinical benefit response rate was 75.0% • Median DOR and PFS were 11.8 and 10.2 months, respectively
Phase 2 dose-expansion study (PX-171–006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma[34]	Phase 2 dose-expansion study (PX-171–006)	52	*Carfilzomib, dexamethasone plus lenalidomide* Carfilzomib was given initially at a dose of 15 mg/m^2 and slowly increased to 27 mg/m^2 combined with lenalidomide (10 mg/day to 25 mg per day for 21 days in a 1-month cycle) and low-dose dexamethasone in a dosage of 40 mg/week	• Median ORR and PFS of 76.9% and 15.4 months, respectively, with a median DOR of 22.1 months • Patients who were resistant to lenalidomide had a median PFS of 7.9 months and a mean ORR of 70% with a median DOR of 10.8 months

(*Continued*)

Table 1 (*Continued*)

Study title	Study type	No. of patients	Intervention	Outcomes
Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma[35]	Phase 3, multicenter trial (ASPIRE trial)	792	*Carfilzomib, dexamethasone plus lenalidomide* In patients receiving carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group), carfilzomib was administered as a 10-minute infusion (starting dose, 20 mg/m^2 on days 1 and 2 of cycle 1; target dose, 27 mg/m^2 thereafter), lenalidomide and dexamethasone were given at 25 mg and 40 mg, respectively	• The median PFS was significantly higher in the carfilzomib group than in the control group (26.3 months compared with. 17.3 months; $p < 0.001$) • The OS and ORR at 2 years were significantly high in the carfilzomib group compared with the control group (73.3% versus 65.0% and 87.1% versus 66.7%, respectively, $p < 0.0001$) • The median DOR was also high with the carfilzomib versus control group (28.6 months versus 21.2 months)
A randomized phase 3 study of carfilzomib versus low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS)[36]	Randomized, phase 3, open-label, multicenter study (FOCUS)	315	*Carfilzomib monotherapy versus low-dose corticosteroids and optional cyclophosphamide* Carfilzomib (10-minute intravenous infusion; 20 mg/m^2 on days 1 and 2 of cycle 1; 27 mg/m^2 thereafter) or a control regimen of low-dose corticosteroids (84 mg of dexamethasone or equivalent corticosteroid) with optional cyclophosphamide (1400 mg) for 28-day cycles	• Median OS was 10.2 (95% CI, 8.4–14.4) versus 10.0 months (95% CI, 7.7–12.0) with carfilzomib versus control (HR = 0.975; 95% CI, 0.760–1.249; $p = 0.4172$). • PFS was similar between groups • ORR was higher with carfilzomib (19.1% versus 11.4%)
Ixazomib				
Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed or refractory multiple myeloma[49]	Open-label, dose-escalation phase 1 study	60	Ixazomib was administered orally on 3 days of a 28-day cycle for up to 12 cycles or until disease progression or unacceptable toxicity	• Among 30 response-evaluable patients treated at the MTD, 8 achieved a PR for an ORR of 27%
Final overall survival analysis of the TOURMALINE-MM1 phase 3 trial of ixazomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma[50]	Double-blind, placebo-controlled, phase 3 study (TOURMALINE-MM1)	722	Ixazomib (4 mg) plus lenalidomide (25 mg) and dexamethasone (40 mg) (ixazomib-Rd) or matching placebo (placebo-Rd)	• Median OS was 53.6 months in the ixazomib-Rd arm and 51.6 months in the placebo-Rd arm (HR, 0.939; $p = 0.495$)
A phase 1/2 study of ixazomib, pomalidomide, and dexamethasone for lenalidomide and proteasome inhibitor refractory multiple myeloma[51]	Phase 1/2 study (Alliance A061202)	29	*Ixazomib/pomalidomide/dexamethasone* 4 mg dose of pomalidomide and ixazomib and 20/40 mg dose of dexamethasone	• ORR (partial response or better) was 51.7% with a median DOR of 16.8 months • Median PFS and OS were 4.4 months and 34.3 months, respectively
A phase 1/2 study of ixazomib (Ix) pomalidomide (POM) dexamethasone (DEX) in relapsed or refractory multiple myeloma: initial results[52]	Phase 1/2 study	21	*Ixazomib/pomalidomide/dexamethasone* Ixazomib 3 mg, pomalidomide 4 mg, dexamethasone 40 mg, or ixazomib 4 mg with identical pomalidomide/dexamethasone for 28-day treatment cycles	• CBR was 67% and ORR was 40%

Table 1 (*Continued*)

Study title	Study type	No. of patients	Intervention	Outcomes
Daratumumab				
Targeting CD38 with daratumumab monotherapy in multiple myeloma[55]	Open-label, multicenter, phase 1/2, dose-escalation and expansion study (GEN 501)	104	In the dose-escalation period, daratumumab was administered at 0.005 to 24 mg/kg, and in the dose-expansion period, the starting dose of daratumumab is 8 or 16 mg/kg	• The ORRs of patients receiving 16 mg/kg and 8 mg/kg of daratumumab were 36% and 10%, respectively • Median PFS was 5.6 months for 8 mg/kg
Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial[56]	Open-label, multicenter, phase 2 study (SIRIUS)	106	Intravenous daratumumab 8 mg/kg or 16 mg/kg in part 1 of the study. In part 2, patients received 8 mg/kg or 16 mg/kg	• Overall responses were noted in 31 patients (29.2%) • Median DOR and PFS were 7.4 months and 3.7 months, respectively
Daratumumab, bortezomib, and dexamethasone for multiple myeloma[57]	Phase 3 study (CASTOR)	498	*Daratumumab with bortezomib plus dexamethasone* Bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg/m^2) (daratumumab group)	• Median PFS was not reached in the daratumumab group and was 7.2 months in the control group ($p < 0.001$) • ORR was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, $p < 0.001$)
Daratumumab, lenalidomide, and dexamethasone for multiple myeloma[58]	Randomized, open-label, multicenter, phase 3 study (POLLUX)	569	*Daratumumab with lenalidomide plus dexamethasone* Daratumumab (16 mg/kg IV infusion), lenalidomide (10 mg or 25 mg), and dexamethasone (20 mg) or dexamethasone plus lenalidomide	• Kaplan–Meier PFS rate at 12 months was higher in the daratumumab group compared with control group (83.2% versus 60.1%) • ORR in the daratumumab group was higher than that in the control group (92.9% versus 76.4%, $p < 0.001$)
Elotuzumab				
Elotuzumab therapy for relapsed or refractory multiple myeloma[63]	Phase 3, randomized, open-label trial (ELOQUENT-2	646	*Elotuzumab with lenalidomide plus dexamethasone* Elotuzumab (IV; 10 mg/kg) plus lenalidomide (oral; 25 mg/day) and dexamethasone (elotuzumab group) or lenalidomide and dexamethasone alone (control group). Dexamethasone was administered orally at 40 mg during the week without elotuzumab and 8 mg IV plus 28 mg oral on the day of elotuzumab administration	• Median PFS in the elotuzumab group was 19.4 months versus 14.9 months in the control group ($p < 0.001$) • ORR in the elotuzumab group was 79% versus 66% in the control group ($p < 0.001$)
Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma[64]	Multicenter, randomized, open-label, phase 2 trial (ELOQUENT-3)	117	*Elotuzumab with pomalidomide plus dexamethasone* Elotuzumab (IV; 10 mg/kg) plus pomalidomide (oral; 4 mg/day) and dexamethasone (elotuzumab group) or pomalidomide and dexamethasone alone (control group). Dexamethasone was administered orally at 40 or 20 mg during the week without elotuzumab and 8 mg IV plus 28 or 8 mg oral on the day of elotuzumab	• Median PFS was 10.3 months in the elotuzumab group and 4.7 months in the control group • ORR was 53% in the elotuzumab group as compared with 26% in the control group

(*Continued*)

Table 1 (*Continued*)

Study title	Study type	No. of patients	Intervention	Outcomes
Belantamab mafodotin				
Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomized, open-label, phase 2 study[65]	Open-label, two-arm, randomized, phase 2 study (DREAMM-2)	196	2.5 mg/kg or 3.4 mg/kg belantamab mafodotin via IV infusion	• 31% of patients in the 2.5 mg/kg cohort and 34% in the 3.4 mg/kg cohort achieved an overall response
Panobinostat				
Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter, randomized, double-blind, phase 3 trial[66]	Multicenter, randomized, placebo-controlled, double-blind, phase 3 trial (PANOROMA I)	768	*Panobinostat with bortezomib plus dexamethasone* Panobinostat (20 mg) plus bortezomib (IV; 1.3 mg/m^2) and dexamethasone (oral; 20 mg) or placebo plus bortezomib and dexamethasone	• Median PFS was significantly longer in the panobinostat group than in the placebo group (11.99 months versus 8.08 months; $p < 0.0001$) • Median OS was 33.64 months for the panobinostat group and 30.39 months for the placebo group
Selinexor				
Oral selinexor/dexamethasone for triple-class refractory multiple myeloma[69]	Phase 2b trial (STORM)	122	*Selinexor and dexamethasone* Oral selinexor (80 mg) plus dexamethasone (20 mg)	• Partial response or better was observed in 26% of patients • Median DOR was 4.4 months, and median PFS and OS were 3.7 months and 8.6 months, respectively
Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomized, open-label, phase 3 trial[70]	Randomized, open-label, phase 3 trial (BOSTON)	402	*Selinexor with bortezomib and dexamethasone* Once per week selinexor (100 mg), bortezomib (1.3 mg/m^2), and dexamethasone (20 mg) or twice per week bortezomib and dexamethasone	• Median PFS was 13.93 months with selinexor, bortezomib, and dexamethasone and 9.46 months with bortezomib and dexamethasone ($p = 0.0075$)
Venetoclax				
Efficacy of venetoclax as targeted therapy for relapsed/refractory t (11; 14) multiple myeloma[71]	Phase 1 study	66	Venetoclax was given daily from 300 mg up to 1200 mg	• ORR was 21%, and 15% achieved ≥VGPR • 86% of responses were reported in patients with t(11;14), and ORR was 40% in this group
Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t (11; 14) multiple myeloma[72]	Real-world data	10	Venetoclax was initiated at 400 mg for 1 week and then titrated to 800 mg	• ORR was 78% • Kaplan–Meier 6-month OS and PFS were 77% and 28%, respectively
Phase 1 study of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, in patients with relapsed or refractory multiple myeloma with and without t (11; 14)[73]	Multicenter, dose-escalation and dose-expansion, phase 1 study	48	*Venetoclax with daratumumab and dexamethasone with or without bortezomib* Venetoclax (800 mg) with daratumumab (1800 mg SC) and dexamethasone (40 mg) (VenDd) and VenDd with bortezomib (1.3 mg/m^2) (VenDVd)	• ORR was 96% with VenDd and 92% with VenDVd • The 18-month PFS rate was 90.5% with VenDd and 66.7% with VenDVd

Table 1 (*Continued*)

Study title	Study type	No. of patients	Intervention	Outcomes
Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomized, double-blind, multicenter, phase 3 trial[74]	Randomized, double-blind, multicenter, phase 3 trial (BELLINI)	291	*Venetoclax with bortezomib and dexamethasone* Venetoclax (800 mg) or placebo with bortezomib (1.3 mg/m^2) and dexamethasone (20 mg)	• Median PFS was 22.4 months with venetoclax and 11.5 months with placebo ($p = 0.010$) • ORR was 82% with venetoclax and 68% with placebo ($p = 0.0081$)
Teclistamab				
Teclistamab, a B cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicenter, open-label, single-arm, phase 1 study[77]	Open-label, single-arm, phase 1 study (MajesTEC-1)	157	Teclistamab was given injected as IV (range, 0.3–19.2 µg/kg [once every 2 weeks] or 19.2–720 µg/kg [once per week]) or as SC (range, 80–3000 µg/kg [once per week]) in different cohorts, with step-up dosing for 38.4 µg/kg or higher doses	• Recommended phase 2 dose (RP2D) was identified as once per week subcutaneous administration of teclistamab at 1500 µg/kg after 60 µg/kg and 300 µg/kg step-up doses • ORR at RP2D was 65% (95% CI, 48–79) • Median DOR was not reached at RP2D
Teclistamab in relapsed or refractory multiple myeloma[78]	Phase ½ study (MajesTEC-1)	165	Teclistamab was given subcutaneously (1.5 mg/kg body weight) every week after receiving step-up doses of 0.06 mg and 0.3 mg/kg	• ORR was 63%, with complete response in 39.4% of patients • Median DOR was 18.4 months (95% CI, 14.9 to not estimable) • Median duration of PFS was 11.3 months (95% CI, 8.8–17.1)

Abbreviations: CBR: Clinical benefit rate; DOR: Duration of response; IV: Intravenous; MTD: Maximum tolerated dose; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SC: Subcutaneous; VGPR: Very good partial response.

Daratumumab

The FDA in 2015 approved daratumumab, a first-in-class human IgG1j monoclonal antibody against CD38, in patients treated before for MM. In 2016, it was authorized in the combination of dexamethasone and bortezomib or dexamethasone and lenalidomide. In 2017, the combination with dexamethasone and pomalidomide was approved for RRMM.[53] The EMA has approved a combination of dexamethasone and daratumumab plus either lenalidomide or bortezomib with a minimum of one previous treatment in MM patients or as monotherapy with previous treatment of a PI and an immunomodulatory agent, and who had disease progression on previous therapy in adult RRMM patients.[54]

Daratumumab Monotherapy and Other Combinations

The efficacy and safety of daratumumab monotherapy[55,56] or its combination with bortezomib and dexamethasone,[57] as well as lenalidomide plus dexamethasone,[58] were investigated in different clinical trials (►**Table 1**).

In one of the meta-analyses, out of 18 therapy choices, daratumumab/lenalidomide/dexamethasone combination was found better in PFS (HR, 0.13; 95% CI, 0.09–0.19) and likely to be the very best option (99% of the simulations).[59] In comparison to dexamethasone/bortezomib/dexamethasone, and lenalidomide/dexamethasone, this combination reduced progression or death by 87%, 81%, and 63%, respectively.[59] In another meta-analysis of 27 RCTs, both daratumumab/lenalidomide/dexamethasone and daratumumab/bortezomib/dexamethasone were found likely of being the best treatment options and were associated with the minimum chance of progression or mortality versus other FDA-authorized therapy of MM.[60]

Safety of Daratumumab

Daratumumab is generally well tolerated. In a pooled analysis (GEN501 part 2 and SIRIUS), anemia, cough, fatigue, nausea, back pain, neutropenia, upper respiratory tract infection, and thrombocytopenia were commonly reported adverse events.[56] The most frequent adverse events (grade 3/4) listed in the CASTOR and POLLUX trials were thrombocytopenia, neutropenia, and anemia. In both trials, neutropenia events (grade 3/4) were higher in the daratumumab than in the control group (13% vs. 4% in CASTOR and 52% vs. 37% in the POLLUX trial). CASTOR trial participants with daratumumab experienced more thrombocytopenia events (grade ¾) than those with control medication (45 vs. 33%).[57,58]

Elotuzumab-Based Combinations in RRMM

It is a humanized immunostimulatory monoclonal antibody against signaling lymphocytic activating molecule family member 7. The FDA has approved it in combination with either lenalidomide or bortezomib and dexamethasone after a minimum of one line of failed therapy in the appropriate setting.[61,62] Its combination with dexamethasone and lenalidomide[63] or pomalidomide and dexamethasone[64] showed a significant relative reduction in the risk of disease progression or death in patients with RRMM (►**Table 1**).

Belantamab Mafadotin

It is an anti-B-cell antigen bound to monomethyl auristatin, a microtubule inhibitor that, in the phase 2 DREAMM-2 study, produced an overall response in 31% and 34% of patients, respectively, in the 2.5 mg/kg and 3.4 mg/kg cohorts of highly pre-treated patients with RRMM. Thrombocytopenia, anemia, and rarely keratopathy were common adverse events (►**Table 1**).[65] The FDA has approved it for RRMM after four lines of failure (including an IMiD, PI, and anti-CD38 monoclonal antibody).

Panobinostat

The PANOROMA I trial evaluated the outcomes of a combination of panobinostat (a pan-histone deacetylase [HDAC] inhibitor) and bortezomib/dexamethasone and suggested that panobinostat could be beneficial for patients with RRMM who had a minimum of one previous treatment.[66]

In a recent meta-analysis of 19 trials (2,193 patients), the pooled ORR for panobinostat-treated patients was 0.64, whereas, for HDAC inhibitor-treated bortezomib- or lenalidomide-refractory patients, ORRs were 0.36 and 0.46, respectively.[67] The US FDA and EMA authorized the combination of panobinostat and bortezomib/dexamethasone in patients who had a minimum of two previous treatments, containing IMiD and bortezomib.[68] The same combination was approved in India in 2016. The FDA has approved panobinostat for RRMM patients with failed response to lenalidomide and bortezomib.

Safety of Panobinostat

The commonly found hematologic adverse events (grade 3/4) were neutropenia, thrombocytopenia, and anemia.[66] The most frequent nonhematologic adverse events with panobinostat were gastric-related.[68]

Selinexor

The safety and efficacy of selinexor, a nuclear export inhibitor inducing apoptosis, were evaluated in a phase 2b trial (STORM),[69] which led to its approval by the FDA for use with dexamethasone in RRMM following four lines of therapy failing IMiDs, PIs, and two monoclonal antibodies. A phase 3 trial (BOSTON) revealed significant improvement in PFS with the addition of selinexor to bortezomib and dexamethasone in patients who had previously received treatment for MM (►**Table 1**).[70]

Venetoclax

A phase 1 study revealed an acceptable safety profile and effectiveness of venetoclax (a BCL-2 inhibitor) monotherapy in patients with RRMM harboring t(11;14).[71] Real-world

data on the safety and efficacy of venetoclax-based regimens in RRMM patients harboring t(11;14) showed an overall response rate of 78%.[72] The efficacy and safety of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, were evaluated in patients with RRMM with and without t(11;14)[73] and those of venetoclax plus bortezomib and dexamethasone were evaluated in patients with RRMM (BELLINI trial)[74] as shown in ►**Table 1**.

Teclistamab

Teclistamab is an under-investigation fully humanized IgG4 bispecific antibody that targets both the T cell receptor CD3 and the B cell maturation antigen (BCMA). It works by rerouting CD3+ T lymphocytes to promote T cell activation and lysis of myeloma cells that express BCMA.[75] The safety and efficacy of teclistamab in patients with RRMM who have received at least three other lines of therapy are being studied in ongoing clinical studies (►**Table 1**). Additionally, two trials are investigating its effectiveness and safety in combination with other agents for the treatment of patients with RRMM.[76] Common adverse events include cytokine release syndrome, neutropenia, and thrombocytopenia.[77,78]

Treatment of Patients with RRMM in India

In India, most of the patients receive bortezomib, lenalidomide, or thalidomide-based medications as treatment for RRMM.[79] The market for generic medications is growing in India. The cost of these medications is relatively lower because of the stiff competition among many generic drug manufacturers in the country. Thus, the development of generic versions of medications, such as pomalidomide and carfilzomib, makes them more accessible and affordable for cancer patients.[80] Since 2017, generic pomalidomide has been available in India. The results are comparable to those reported in the literature for the original molecule. Hence, it is considered an effective treatment choice for those with RRMM, as well as a less expensive alternative to original pomalidomide in India and other developing countries where affordability is an issue.[81,82] ►**Table 2** shows data from clinical studies that investigated the efficacy and safety of drugs or their combinations for the treatment of RRMM patients in the Indian setting.[82–87]

The CAR-T therapy is a novel and emerging therapy for MM. Global clinical trials have demonstrated that CAR-T treatment is beneficial in RRMM patients. Although this technology has a great deal of therapeutic potential for cancer patients, it is still not available in India because of the exorbitant cost. In this regard, researchers at the Department of Bioscience and Bioengineering, IIT, Mumbai, designed and manufactured the country's first CAR T cells using lentiviral technology.[88] In June 2021, India's first CAR-T therapy was done at the bone marrow transplant unit at Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Hospital, Mumbai.[88] Furthermore, the first CAR-T product HCAR19 showed favorable efficacy and less toxicity with no relapse in 10 lymphoma

Table 2 Clinical evidence of relapsed and refractory multiple myeloma treatment in India

Study title	Study type	No. of patients	Intervention	Outcomes
Retrospective study of carfilzomib/pomalidomide/dexamethasone in relapsed or refractory multiple myeloma patients in a tertiary care hospital in India[83]	Retrospective study	69	*Carfilzomib/pomalidomide/dexamethasone* Carfilzomib was given intravenously at 20 mg/m^2 on days 1–2 and thereafter at 27 mg/m^2 from week 2 (cycle 1) and from cycle 2 onward (biweekly regimen) IV carfilzomib was given at 20 mg/m^2 on day 1 and day 2 followed by 36 mg/m^2 in weekly doses (once weekly) Pomalidomide (4 mg) was given on days 1–21 and dexamethasone (IV; 20 mg weekly) was given in 28-day treatment cycles	• ORR was 65.2% • Relapse was observed in 24 patients (34.8%) • Estimated median PFS and median OS were 11.3 months (95% CI, 8.3–14.2) and 28 months (95% CI, 20.4–35.5)
Study to evaluate safety, tolerability, and efficacy of Kyprolis (carfilzomib) in relapsed or refractory multiple myeloma[84]	Prospective, open-label, noncomparative, multicenter, phase 4 study	100	*Carfilzomib plus dexamethasone and carfilzomib plus lenalidomide with dexamethasone* Carfilzomib 20 mg/m^2 on days 1 and 2, and if tolerated, escalated to a target dose of 56 mg/m^2 or 27 mg/m^2 starting on day 8 of cycle 1 and thereafter Dexamethasone 20 or 40 mg taken by mouth or intravenously Lenalidomide 25 mg is taken orally on days 1–21	• Ongoing trial, so results are awaited

(*Continued*)

Table 2 (*Continued*)

Study title	Study type	No. of patients	Intervention	Outcomes
Real-world outcomes with generic pomalidomide in relapsed refractory multiple myeloma—experience from a tertiary care cancer center[81]	Retrospective analysis	81	Generic pomalidomide (2 mg/3 mg/4 mg daily dose) Generic pomalidomide and dexamethasone (doublet)	• ORR was 58.7% and 65.2% in those who received doublet • Five patients (6.7%) achieved CR; VGPR was seen in 13 patients (17.3%), and PR in 26 patients (34.7%) • Median PFS was 5.5 months and the median OS was not reached
A study of DARZALEX (daratumumab) in Indian participants with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent[85]	Prospective, single-arm, multicenter, pragmatic phase 4 trial (NCT03768960)	150	Daratumumab is given intravenously (16 mg/kg) every week in cycles 1 and 2 (days 1, 8, 15, and 22) and every 2 weeks in cycles 3–6 (days 1 and 15) in 28-day treatment cycles	• Ongoing trial, so results are awaited
Daratumumab plus carfilzomib: an optimistic approach in relapsed/refractory multiple myeloma[86]	Prospective analysis	19	*Daratumumab plus carfilzomib and dexamethasone* Daratumumab (16 mg/kg IV) was administered weekly during cycles 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter Carfilzomib was administered as a 30-minute infusion weekly on days 1, 8, and 15 of each 28-day cycle Patients received an initial carfilzomib dose of 20 mg/m^2 on days 1 and 2; 27 mg/m^2 on days 8, 9,15, and 16 of cycle 1, which increased to 70 mg/m^2 on days 1, 8, and 15 from cycle 2 onward if found tolerable Dexamethasone was given at a fixed dose of 40 mg weekly	• PFS was 95%, and median PFS was not reached
Real-world experience with "generic" pomalidomide in relapsed/refractory multiple myeloma[82]	Real-world study	24	Most of the patients (17/24) received generic pomalidomide plus dexamethasone (doublet therapy) and the remaining seven patients received a third drug (carfilzomib, bortezomib, or melphalan) additionally (triplet therapy). Furthermore, many (16/24) received generic pomalidomide at a starting dose of 4 mg daily for 21–28 days	• ORR was 50% • Median PFS was 6 months (95% CI, 0.2–15.3 months)
Bortezomib in newly diagnosed patients with multiple myeloma: a retrospective analysis from a tertiary care center in India[87]	Retrospective analysis	41	Patients who received bortezomib (1.3 mg/m^2 of the body surface area as an intravenous bolus twice weekly for 2 weeks, on days 1, 4, 8, and 11 in a 21-day cycle or weekly in a 28-day cycle) as first-line therapy were enrolled into the study All patients received dexamethasone (40 mg with bortezomib)	• ORR to bortezomib was 88.5% with CR at 31.4%, VGPR at 34.2%, and PR at 22.8% • At a median follow-up of 9 months, the median PFS was not reached

Abbreviations: DOR, Duration of response; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; PR, Partial response; VGPR, Very good partial response.

patients in a phase 1 clinical trial conducted at ACTREC, Mumbai. A phase 2 trial involving 40 patients is currently underway.[88] The researchers were able to significantly reduce the cost through this innovation, making it affordable and accessible to patients.

Guideline and Cancer Group Recommendations for RRMM

Patients with relapsed myeloma who have failed to respond to bortezomib and lenalidomide should be treated with pomalidomide or carfilzomib (IMWG). Carfilzomib must be taken along with low-dose dexamethasone and lenalidomide. The working group also recommends a combination of panobinostat, bortezomib, and dexamethasone for those with a few treatment options and who have a positive performance status.[89] According to the ESMO guidelines on the clinical management of MM, treatment options at second or subsequent relapse include daratumumab monotherapy or a combination of pomalidomide with dexamethasone plus daratumumab.[90] According to the Mayo Stratification for Myeloma and Risk-Adapted Therapy guidelines, daratumumab, bortezomib, and dexamethasone (DVd) for IMiD refractory; daratumumab, lenalidomide, and dexamethasone (DRd) for PI refractory; carfilzomib, lenalidomide, and dexamethasone (KRd) or carfilzomib, pomalidomide, and dexamethasone (KPd) for dual refractory to bortezomib/ixazomib and lenalidomide; daratumumab, pomalidomide, and dexamethasone (DPd) or daratumumab, pomalidomide, cyclophosphamide, and dexamethasone (DPCd) for triple refractory to carfilzomib, lenalidomide, and bortezomib/ixazomib; daratumumab based or PI and panobinostat for triple refractory to lenalidomide, bortezomib/ixazomib, and pomalidomide have been recommended.[91] The FDA had authorized selinexor in association with dexamethasone for adult RRMM patients who had a minimum of four previous treatments and whose disease is refractory to a minimum of two PIs, two IMiDs, and an anti-CD38 monoclonal antibody.[92]

Conclusion

The approval of PIs, IMiDs, and mAbs in patients with RRMM has considerably modified the treatment options of RRMM in the last few years. Several randomized clinical trials have demonstrated favorable outcomes of these novel drugs in combination therapies. Further studies evaluating the long-term safety and efficacy of combination therapies are warranted. The availability of less expensive generic versions of carfilzomib, daratumumab, and panobinostat in India should pave way for a change in the outlook of patients with improved outcomes, survival, and QoL.

Authors' Contributions

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Measuring Satisfaction in Breast Cancer Patients Receiving Ambulatory Care: A Validation Study

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Abstract

Introduction Patient satisfaction constitutes a vital service quality indicator. It provides a measure of the gap in health-care requirements and patients' expectations.
Objective The aim of this study was to perform linguistic validation of the questionnaire assessing satisfaction with outpatient care.
Materials and Methods A tool for measuring patient satisfaction was developed and validated at our institute in the English language. This tool was translated into Hindi and Marathi. Subsequently, 339 patients diagnosed with breast cancer consulting in the outpatient department from the different parts of India and having diverse linguistic and socioeconomic backgrounds were enrolled. Patients were asked to complete the satisfaction tool after consultation at a single point of time in a prospective manner.
Results All patients completed the questionnaire. The questionnaire was filled by 120, 116, and 103 patients in Hindi, Marathi, and English, respectively. Both convergent validity and discriminant validity were supported as the correlation coefficient was >0.4 for all items within a scale and <0.7 between different scales. Factor analysis was valid for all except for open-end questions. The internal consistency was >0.9 for all the questions. The mean overall satisfaction score was 88.35 (standard deviation: 19.63). Patients were satisfied in all the aspects of the consultation process, including appointment scheduling, assistant medical staff and faculty, and treating physician. However, some expressed dissatisfaction toward long-waiting times.
Conclusion The translated tool is reliable and valid and effectively measures the satisfaction of patients receiving ambulatory care.

Keywords
- breast cancer
- outpatient
- patient satisfaction
- satisfaction survey

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Introduction

Nowadays, a lot of attention is paid toward the patient's perception of the services provided, especially in oncology. Patient satisfaction measures the gap in the quality of service delivered and patients' expectations.[1] There are various definitions of patient satisfaction.[1–12] It measures the patient's contentment with health-care services.[13] Heath states that a truly satisfied patient can be recognized if he leaves the physician's clinic with a happy feeling.[14] Assessment of satisfaction levels provides a patient-centered dimension of assessing health systems.[15] It is important to assess patient satisfaction with the services at multiple levels as medical care is provided by a team of physicians, nurse, and other ancillary staff. It also forms a vital measure of quality tracking and is usually employed by the hospital administrators as a performance indicator.[16]

While there are numerous methods of evaluating patient satisfaction, satisfaction surveys are widely employed because they are easier to perform. There are numerous validated surveys available to measure patient satisfaction like the European Organization for Research and Treatment of Cancer inpatient and outpatient satisfaction questionnaire (EORTC QLQ-OUTPATSAT35, INPATSAT 32),[17,18] Patient Satisfaction and Quality in Oncological Care,[19] Long form Patient Satisfaction Questionnaire (PSQ-III),[20] and Princess Margaret Hospital Satisfaction with Doctor Questionnaire (PMH-PSQ-MD)[21] are a few of them. They are developed to test the satisfaction of inpatients and also have restricted questions for differential evaluation of various members of the medical team (resident, physician, or nurse). As the needs of developing nations are far different from a developed nation,[22,23] these above questionnaires need to be validated in the Indian setting. Unfortunately, none of these tools were found to be validated in the Indian population till the time of reporting of this study. Hence, we decided to develop an indigenous questionnaire that will be suitable for the Indian population and can be used in an outpatient department (OPD). It was developed in the English language in phase I and pilot tested in 50 patients who were fluent in English and attending the outpatient breast clinic at our institute.[24] This tool was subsequently translated in local languages, that is, Hindi and Marathi. In this study, we intend to perform linguistic validation of the tool in patients with varied linguistic and socioeconomic background as well as test the validity and reliability of this translated questionnaire in a larger cohort of patients.

Materials and Methods

The development process and the initial pilot testing of the patient satisfaction survey (PSS) questionnaire have been published earlier.[24] The results of pilot testing supported convergent validity showing high internal consistency and high reliability. The PSS tool consisted of 28 questions; six questions related to administrative services; one question on waiting time; eight questions on ancillary members of the medical team comprising of resident doctors, nurses, and other staff; and ten questions about the treating consultant. The participants could choose any one of the options on a numerical scale of 1 (very dissatisfied) to 5 (very satisfied) depending upon their experience after OPD consultations. The last three questions were open-ended, and the responses were to be scored as Yes or No. The respondents at the end had to rate their overall satisfaction on the same scale ranging from 1 to 5. Our previous publication describes the details of scoring and conversion of raw scores to final scores that were used for the analysis. The initial tool was developed only in the English language; further, the tool was translated into Hindi and Marathi language each by two independent translators. The draft Hindi and Marathi tools were back-translated by two different independent translators, and a final tool was generated. These final versions of Hindi and Marathi tools along with the English tool were served to the patients as per their preferred language at their first consultation in a prospective manner. Patients from all over India with different socioeconomic backgrounds who were diagnosed with breast cancer and attending outpatient clinics for consultation in our hospital were screened and consequently enrolled. Patients with metastatic disease and poor performance status were excluded from the study.

Patients who had histologically confirmed the diagnosis of breast cancer, planned to receive multimodality cancer-directed therapy (surgery, chemotherapy, and radiation therapy) and who were able to understand either of the three languages were screened for the study and consented. Unfit patients with poor performance status and those unable to read and comprehend the questionnaire were excluded.

To reduce bias, the translated tool was served after the patient had OPD consultation by a clinical research staff not involved in patient care. Patients were asked to fill the tool waiting in the clinic area, and it was anonymous. Three hundred and thirty-nine patients diagnosed with breast cancer consulting in an outpatient clinic in our hospital were enrolled.

Statistical Analysis

The analysis was done using the Statistical Package for the Social Sciences software version 23.0. A pilot study conducted in Tata Memorial Hospital with the PSS questionnaire has shown that ~70% of the patients are satisfied with the health-care services. Assuming that the proportion of patients satisfied with the health services, when assessed by Hindi and Marathi PSS questionnaire, would be $\pm 5\%$ of 70% (between 65% to 75%), a sample size of 340 would be needed to produce a two-sided 95% confidence interval (CI), which was determined by using CIs Formula-Clopper-Pearson method. Data were summarized using the standard measures of central tendency based on the normality distribution of the variables. The item scale and scale–scale correlations were studied for measuring the discriminant and convergent validity. Convergent validity was performed by using the Spearman rank correlation. If individual items within a scale showed moderate or high correlation within their scale (>0.40) convergent validity would be proven. For

discriminant validity, to indicate that the two scales are different in construct, scale to scale correlation coefficient of $\leq$0.70 was required. Discriminant validity for each item was tested by counting the number of times that the item correlated higher with items of other domains than with items of its own domain. Campbell and Fiske suggest that the count should be $<$1½ the potential comparisons.[25] The Kaiser-Meyer-Olkin (KMO),[26] a measure of sampling adequacy and Bartlett's test of Sphericity,[27] which are standard tools for exploratory factor analysis, were used for inferring construct validity. A value of KMO $\geq$0.5 and $p \leq 0.05$ for Bartlett's test is supposed to support construct validity. Similarly, internal consistency and reliability of the questionnaire were assessed by Cronbach's α coefficient. A value of Cronbach's α coefficient $\geq$0.70 supports internal consistency.

Results

All 339 female patients who gave consent for the study responded to the entire questionnaire that showed a high compliance of 100%. The demographic details of the study cohort are shown in ►**Table 1**. The paid and subsidized categories were equally distributed. Majority of the patients were literate 314 (94.6%), homemakers 261 (77.0%), and had good family support 310 (91.4%). Local patients comprised 20% of the entire cohort. The questionnaire was filled in Hindi, Marathi, and English by 120, 116, and 103 patients, respectively.

Table 1 The demographic profile of the patients

Characteristics	Numbers (percentages)
Age	Median 49 years (range: 25–80 years)
Stage (%)	Stage I—38 (11.2)
	Stage II—88 (26.1)
	Stage III—213 (62.7)
Laterality (%)	Left—180 (53.0)
	Right—156 (46.1)
	Bilateral—3 (0.9)
Category (%)	Fully paid—172 (50.7)
	Subsidized—167 (49.3)
Family/social support (%)	Yes—310 (91.4)
	No—29 (8.6)
Education level (%)	Nil—12 (3.5)
	Primary—66 (19.5)
	Secondary—92 (27.1)
	Graduate—151 (44.5)
	Postgraduate—5 (1.5)
	Not mentioned—13 (3.8)
Occupation (%)	Homemaker—261 (77)
	Student—1 (0.3)
	Employed—61 (18)
	Retired—7 (2.1)
	Not mentioned—3 (0.9)
Place of residence (%)	Mumbai—81 (20.3)
	Outside Mumbai—258 (79.7)

Convergent Validity

The interitem correlation for items (1–6) under appointments and secretarial assistance ranged from 0.62 to 0.78; $p < 0.001$; for assisting medical staff and facilities (items: 9–16), the interitem correlation ranged between 0.7 and 0.85; $p \leq 0.001$. For items (17–26) that assessed the satisfaction related to treating physician (consultant), the interitem correlation ranged from 0.67 to 0.86; $p < 0.001$. Since all the items have correlation $>$0.4, convergent validity was supported (►**Table 2**).

Discriminant Validity

►**Table 2** describes the result of discriminant validity in detail. In this analysis, potential correlations are studied between each item of one domain with the items of other domains. The correlation coefficient is recorded for all comparisons. The result of comparisons is recorded as a violation if the correlation coefficient is $>$0.7. If such violations are $<$50%, then it is concluded that the discriminant validity is supported. For items (1–6) under appointment and secretarial assistance, of the 108 potential comparisons, there were no violations. Similarly, for items (9–16) under assisting medical staff and facilities, there was only one violation out of 128 comparisons. For items (17–26) under treating physician (consultant), also there was one only violation out of 140 comparisons. As shown in ►**Table 2**, as all the values for scale-scale correlation are $\leq$0.7, discriminant validity is supported for all the domains.

Table 2 Construct validity and internal consistency of scores for patient satisfaction survey scale

Questions	Cronbach's α	Interitem correlation	Interitem correlation significance value	Scale–scale discriminant validity
Items (1–6) appointment and secretarial assistance	0.93	0.62–0.78	$<$0.001	0.41–0.65
Items (9–16) assisting medical staff and facilities	0.96	0.70–0.85	$<$0.001	0.42–0.70
Items (17–26) treating physician (consultant)	0.97	0.67–0.86	$<$0.001	0.40–0.70

Table 3 Factor analysis and loadings per item using varimax rotation

Scales	Bartlett's sphericity	KMO	Factor loading	Variance explained (%)
Items related to your appointment and secretarial assistance				
Ease of scheduling your appointment	<0.001	0.902	0.702	74.84
Courtesy			0.761	
Efficiency			0.758	
Communication skill			0.779	
Availability of the physician			0.702	
Overall satisfaction			0.788	
Items related to the assisting medical staff and facilities				
Thoroughness about case	<0.001	0.943	0.765	79.20
Courtesy			0.847	
Efficiency			0.815	
Communication skill			0.784	
Clarity in explanation			0.765	
Ability to resolve your queries			0.797	
Privacy of consultation			0.742	
Overall satisfaction			0.821	
Items related to your treating physician (consultant)				
Time spent	<0.001	0.945	0.713	80.01
Willingness to listen			0.821	
Ability to explain			0.823	
Explanation of tests			0.805	
Your involvement			0.741	
Ability to diagnose problems			0.818	
Skill in treating condition			0.798	
Responsiveness to questions			0.817	
Gave comfort and support			0.822	
Overall satisfaction			0.857	

Abbreviation: KMO, Kaiser-Meyer-Olkin.

Factor Analysis

The KMO values as well as Bartlett's test for Sphericity strongly support construct validity for most of the domains, as shown in ►**Table 3**. Thus, after varimax rotation, items 1 to 6 appointment and secretarial assistance account for 74.84% of the variance; assisting medical staff and facilities account for 79.2% of the variance; and treating physician (consultant) accounts for 80.01% of the variance. However, the open-end items have KMO coefficient 0.492; hence, factor analysis for these questions was not valid.

Internal Consistency

For appointment and secretarial assistance domain, the Cronbach's α was calculated as 0.93, Cronbach's α was 0.96 for assisting medical staff and facilities, and 0.97 for treating physician (consultant) domain. The overall reliability for the 25 items was 0.974, as shown in ►**Table 2**.

Patients' Satisfaction

There were a total 246 (72.6% [95% CI: 68–77%]) patients out of 339 patients, who were estimated to be satisfied. The mean overall satisfaction score of the patient was 88.35 with standard deviation (SD) of 19.63. Patients were satisfied in most of the aspect of OPD consultation process including appointment scheduling process with a mean score (SD) of 86.87 (22.78), assistant medical staff and faculty with a mean score (SD) of 88.79 (20.79), and treating physician with a mean score (SD) of 90.19 (19.37); however, some expressed dissatisfaction toward the long-waiting times with a mean score (SD) of 67.48 (33.1), as shown in ►**Tables 4**, **5**, **6**.

Discussion

The main objective of this survey study was to perform linguistic validation of the PSS questionnaire in a larger

Table 4 The mean satisfaction scores of patients with items related to your appointment and secretarial assistance

Items related to your appointment and secretarial assistance	Mean (SD) patients satisfaction score
Ease of scheduling appointment	83.11 (25.45)
Courtesy	85.69 (23.51)
Efficiency	87.09 (23.89)
Communication skill	86.50 (23.09)
Availability of the physician	87.39 (23.19)
Overall satisfaction	86.87 (22.78)

Abbreviation: SD, standard deviation.

Table 5 The mean satisfaction scores of patients with items related to the assisting medical staff and facilities

Items related to the assisting medical staff and facilities	Mean (SD) patients satisfaction score
Waiting time	67.48 (33.01)
Thoroughness about case	88.35 (20.46)
Courtesy	87.68 (20.83)
Efficiency	88.50 (20.99)
Communication skill	87.32 (23.35)
Clarity in explanation	88.57 (21.25)
Ability to resolve your queries	87.68 (22.21)
Privacy of consultation	89.75 (20.71)
Overall satisfaction	88.79 (20.79)

Abbreviation: SD, standard deviation.

cohort of Indian patients compared with the earlier pilot study. In our previous study, in 50 English-speaking patients, the PSS questionnaire supported convergent and discriminant validity and the overall reliability of the PSS was 0.96.[24] In our study, we included women from all over India with different linguistic and socioeconomic backgrounds to represent the true population visiting the daily OPDs. The likelihood of generalizability of the results if supported by the narrow CI (95% CI: 68–77%) of the proportion of satisfied patients as the CI is $<$10% that is acceptable in terms that the true population estimate will fall between these intervals. In this study, the PSS supported convergent and discriminant validity with the reliability of 0.96 and good internal consistency. Furthermore, scores on each domain of the questionnaire correlated significantly with an overall satisfaction score of the patients, suggesting that each question in domain measured some aspect of patient's satisfaction. It also revealed that the items chosen in each domain were related and hence resulted in good internal reliability. Moreover, there was a concurrence between the score of each domain with the overall satisfaction score, implying that all questions impacted patients' overall satisfaction.

Table 6 The mean satisfaction scores of patients with items related to your treating physician

Items related to your treating physician	Mean (SD) patients satisfaction score
Time spent	85.77 (22.47)
Willingness to listen	88.20 (21.86)
Ability to explain	88.72 (22.09)
Explanation of tests	88.86 (20.97)
Your involvement	88.13 (21.26)
Ability to diagnose problems	90.78 (19.56)
Skill in treating a condition	90.86 (19.07)
Responsiveness to questions	88.72 (20.71)
Gave comfort and support	89.68 (20.18)
Overall satisfaction	90.19 (19.37)
Overall satisfaction	88.35 (19.63)

Abbreviation: SD, standard deviation.

The EORTC IN-PATSAT32 is a multidimensional scale specifically designed to assess the satisfaction of care services by patients in oncology setups and was validated in the context of a large multicentric study in 2004. The EORTC INPATSAT 32 that has been validated in different populations has shown strong psychometric properties.[28] The PMH-PSQ-MD is validated for outpatients with Cronbach's α value of 0.97.[29] The most commonly used tool worldwide is EORTC OUTPATSAT35[18] and EORTC INPATSAT32.[17] However, these questionnaires are not validated in the Indian population, and our questionnaire is a novel one in this regard. At the time when the pilot study with PSS was undertaken, the EORTC OUTPATSAT 35 questionnaire was not validated in Indian patients. Hence, the PSS tool was formed to suit the local clinical environment. Moreover, it is now known that the EORTC has revised the OUTPATSAT 35 questionnaire and made a new one EORTC PATSAT 33 core questionnaire and EORTC OUTPAT 7 for the outpatient setting.[18] It comprises of seven questions related to medical professionals, waiting time, and information provided by caregivers. This questionnaire is yet to undergo cross-cultural validation including India.

PSS questionnaire is unique from other tools in various aspects. It has items separately for care provided by resident doctors that no other tools have assessed so far. It has included all the items about a patient's visit in an OPD from the appointment process to decision-making, giving it a holistic value. The items for physicians, nurses, and secretary have been segregated. The majority of the tools are too lengthy (32–60 items), and this restricts its practical use in a busy outpatient clinic. Hence, we developed this questionnaire that is an abbreviated 28 item tool, which will facilitate its use in the clinical practice to evaluate the quality of service.

The present findings support that PSS tool is highly reliable and valid and suitable for use in the Indian population in the outpatient clinic. Patients have certain

expectations from the health-care provider, and their satisfaction or dissatisfaction is an outcome of their experience.[3] Patients' perception of care is also a reflection of the doctor–patient relationship. Psychologists say that satisfied patients tend to follow medical advice with diligence as they trust their physician.[8] Patient satisfaction should be given due importance and efforts must be taken to evaluate and improve it. This PSS tool can be used to assess the satisfaction levels of patients routinely and can guide us to provide patients their unmet needs. It will also be worthwhile to assess the satisfaction levels longitudinally at multiple time points as this will give an opportunity to test–retest the psychometric properties of the PSS questionnaire to study consistency in its performance. This we intend to undertake in the future wherein we would evaluate the satisfaction of the patients at three time points over their treatment course, as we expect that their needs will differ in different phases. Nonetheless, the PSS questionnaire has turned out to be a robust tool which can be considered for routine use and which can also serve as a measure of performance indicator. This tool can be used in other nononcological outpatient clinics as well.

Conclusion

The PSS tool has shown high reliability and validity when tested in the larger cohort of breast cancer patients and can be used in routine clinical practice. The robustness of the tool suggests its potential for wider dissemination across the country in nononcological outpatient clinics as well. Further studies can be considered to evaluate the temporal trends in patient satisfaction over the course of their treatment.

Ethics

This study was approved by the Tata Memorial Centre Ethics Committee on March 22, 2017 and project number 1835 was assigned. Patients were given consent forms in their preferred language and written consent was obtained. The procedures followed were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013.

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None.

Conflict of Interest

None declared.

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Approach to Acute Respiratory Illness in Children with Hematological Malignancy: A Prospective Study Evaluating Utility of CT Scan

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Abstract

Introduction Various pulmonary complications can occur in children with hematological malignancies including both infection and malignant disease infiltration of pulmonary parenchyma.

Objectives To assess the role of CT scan in determining the etiology of acute pulmonary complications in children with hematological malignancies.

Materials and Methods All children < 17 years with newly diagnosed hematological malignancy with respiratory symptoms (Group A) along with children who developed fever with persistent respiratory symptoms as well as worsening chest radiographs during treatment (Group B) and underwent CECT thorax, from February 2019 to July 2020 were enrolled. The final diagnosis was made on the basis of clinical history, laboratory as well as radiological investigations and treatment response.

Results Thirty-seven children with mean age of 7.5 ± 3.5 years and male to female ratio of 1.3:1 who underwent CECT thorax were included in our study. For newly diagnosed cases, i.e., Group A ($n = 8$), the most common cause of respiratory symptoms as identified on CECT thorax was pulmonary tumoral infiltration ($n = 5$) followed by tuberculosis ($n = 3$). However, in Group B ($n = 29$) the cause of persistent respiratory symptoms was identified as infection ($n = 17$) followed by leukemic infiltration ($n = 12$). Thus, chest CT could accurately identify pulmonary tuberculosis, fungal pneumonia, bacterial infection, and pulmonary tumoral infiltrates.

Conclusion CT scan can be used as an adjunctive tool for prompt diagnosis and management of pulmonary complications in children with persistent respiratory symptoms as they are often non-specific.

Keywords
- contrast-enhanced computed tomography
- leukemia
- lymphoma
- lungs
- pediatric

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Introduction

Acute respiratory illness (ARI) in immunocompromised children remains a significant diagnostic challenge for both clinicians and radiologists. Pulmonary infection complicates ~75% of immunocompromised patients during their treatment.[1] Given the innumerable pathogens that can cause infectious complications in immunocompromised children, identifying a specific pathogen can be elusive.

In children developing complications secondary to chemotherapy-induced immune suppression, when combined with certain specific morphological findings and the type and duration of immune suppression, radiological investigations can aid with the decision-making process. Chest radiography is the initial imaging modality of choice for the diagnostic assessment of patients presenting with ARI; however, there is low sensitivity and low specificity regarding the type of specific pathogens.[2] Chest CT has been demonstrated to confer a higher degree of sensitivity and specificity for identifying the underlying cause of pulmonary involvement.

Contrast-enhanced CT chest should be done to evaluate the lungs, mediastinum, and pleural/chest wall abnormalities and identify mediastinal and hilar lymph nodes, as opposed to axial HRCT (high-resolution CT), which is done for pulmonary pathologies only. Volumetric multidetector CT acquisition in most of the modern day scanners can generate reconstructed HRCT images, which obviate the use of traditional axial HRCT acquisition in pediatric patients. Apart from pulmonary infections, non-infectious causes such as malignant pulmonary infiltration, radiation-induced lung injury, pulmonary thromboembolic phenomenon, should also be considered while evaluating acute respiratory illness in this group.

The aim of this study was to assess the role of contrast-enhanced CT scan in determining the etiology of pulmonary complications in children with hematological malignancies presenting with ARI.

Materials and Methods

This was a prospective observational study performed at the Division of Pediatric Hematology Oncology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University from February 2019 to July 2020 (ethical clearance no. Dean/2018/EC/919). Thirty-seven children were included in this study who met our inclusion criteria.

Inclusion Criteria

All children < 17 years with hematological malignancy who were

- Newly diagnosed with respiratory symptoms (group A)
- On chemotherapy and developed fever with persistent respiratory symptoms, i.e., respiratory symptoms present even after 7 to 10 days from start of treatment along with/without worsening chest radiographs (group B)

Exclusion Criteria

- Unwillingness to participate in the study
- Hemodynamically unstable child

Children were investigated and empirical intravenous antibiotics, i.e., piperacillin-tazobactam and amikacin were started as per unit protocol. Investigations such as complete blood count, conventional blood culture, chest X-ray were sent for all children that had either of the two, i.e., fever, cough, or increased respiratory rate for age. Intravenous/oral fluconazole (antifungal) was added after 48 to 72 hours[3] if the child had clinical deterioration despite receiving empirical intravenous antibiotics. As pulmonary infection in immunocompromised children is most likely due to bacterial pathogens,[2] antibiotics was started and resolution of symptoms were expected to occur by 7 to 10 days (arbitrary) with antibiotics, followed by antifungals (as indicated) as per blood culture sensitivity pattern in the pediatric oncology ward. Patients responding to antibiotics in both the groups and having a normal follow-up chest X-ray at 7 to 10 days did not undergo chest CT. In both the groups, if after 7 to 10 days, there was no clinical improvement to empirical antibiotics, a repeat conventional blood culture, chest X-ray, and chest CT was done. The indications of chest CT in our study were persistent respiratory symptoms, irrespective of abnormality on chest X-ray at 7 to 10 days of antibiotics.

Chest CT findings were further corroborated by blood culture, gastric aspirate for Gene Xpert and galactomannan assay (based on availability) in infective cases. As gastric aspirate in children has been found to be equally effective and beneficial in *Mycobacterium tuberculosis* (MTB) detection with non-requirement for specific facilities as compared with bronchoalveolar lavage, it was used in this study for MTB detection.[3] CT-guided tissue biopsy from mediastinal mass was performed in most cases where malignant infiltration was suspected. Children whose parents did not consent for tissue biopsy, it was not done. Pulmonary infiltration was suspected if the clinical condition of the child was consistent with disease infiltration and child had sterile cultures. However, lung biopsy was not performed.

Data were collected with respect to age, gender, duration of symptoms, radiological findings on chest X-ray and chest CT, along with response to treatment. In infective cases, results of blood culture, gastric aspirate for Gene Xpert and galactomannan assay (based on availability) along with results of tissue biopsy in cases where malignant infiltration was suspected were also collected.

CECT Protocol

CT chest was performed using a 128 slice light speed VCT (GE Medical System). Non-ionic contrast agent Iohexol (Omnipaque) of concentration 300 mgI/mL was administered using hand injector (with an optional use of power injector and bolus chase) in a calculated dosage(1–1.5 mL/kg) depending upon the child's weight. In patients with previous history of contrast allergy or high-risk of contrast allergy (previous anaphylactic reactions to food or medication), after injecting the first 1 mL of contrast agent, child was observed for a few seconds for any allergic reactions and again after half

an hour to see any delayed reaction. Scan delay of 25 to 30 seconds was kept following the administration of contrast for optimal enhancement of soft tissue. Images were then reconstructed using different reconstruction algorithm and evaluated in advantage workstation 4.4 and 4.7.

Image Evaluation and Interpretation

All CT scans were evaluated by a radiologist with 7 years of experience. Following definitions were used for characterizing lesions seen on CT scan.[4]

i. Consolidation is defined as homogenous increase in lung parenchymal attenuation with obscuration of airways and vessels.
ii. Ground glass opacities (GGO) are defined when bronchovascular margins are preserved behind hazy area of homogenously increased attenuation.
iii. A nodule around the peripheral pulmonary arterial branches or 3 to 5 mm from the pleura, pulmonary vein or interlobular septa is defined as centrilobular nodule. Appearance of multiple areas of centrilobular nodules with a linear branching pattern was defined as "tree-in-bud" nodules. Nodules were termed as random if they lacked an architectural predominance.
iv. Abnormal widening of the interlobular septa is defined as an interlobular septal thickening.
v. Each parenchymal lesion localized to a particular lobe was evaluated in terms of presence and distribution of abnormality identified on CECT thorax.
vi. Halo sign was defined as ground-glass opacity surrounding a nodule or, a mass or a rounded area of consolidation.

Approach to Diagnosis

Following signs on CT were used to suggest the specific etiology of pulmonary findings.

- Bacterial pneumonia: Patients with segmental or lobar consolidation with/without pleural effusion
- Tuberculosis: Centrilobular nodules with tree in bud pattern, necrotizing mediastinal and hilar lymph nodes, empyema, cavitatory consolidations, military pattern, and cavitatory lesions.
- Fungal infection: Patchy consolidations and halo sign, cavitatory nodules, consolidation with crescent of air.
- Viral pneumonia: bilateral multifocal GGO with patchy consolidations with perihilar distribution along bronchovascular bundles indicative of bronchopneumonia.
- Lymphoma/leukemic infiltrate: mediastinal mass with lung consolidation or randomly distributed nodule with bronchovascular bundle thickening or nodular pleural thickening

All children were followed and a repeat CECT was performed after the completion of treatment in children with tuberculosis and malignant pulmonary infiltration. The final etiological diagnosis was made on the basis of clinical history, laboratory investigations and treatment response was considered as an outcome measure in this study.

Statistical Analysis: SPSS software (Version 22.0. IBM Corp. Armonk, NY, USA) for windows was used for data entry and analysis. All numerical variables are expressed as median with range. For comparison of categorical data chi square test was used. For categorical variables with cell values < 5, Fisher's exact test was used. A p-value < 0.05 was taken as significant.

Ethics: The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1964, as revised in 2013. Ethical clearance from Institute Ethical Committee of Institute of Medical Sciences, Banaras Hindu University, was obtained (Dean/2018/EC/919). Written informed consent was obtained from parents of all children included in our study.

Results

During the study period, a total of 103 children developed ARI and were divided in two separate groups (►**Fig. 1**). The first group (Group A) comprised of newly diagnosed leukemia/lymphoma (59.2% [$n = 61$]). Among them, 29.5% ($n = 18$) had respiratory symptoms at the start of treatment, of which 50% ($n = 9$) improved with empirical antibiotics, 5% ($n = 1$) abandoned treatment, and 44.4% ($n = 8$) underwent CECT thorax. The second group (Group B) consisted of children who developed respiratory symptoms while on different phases of chemotherapy 40.8% ($n = 42$). Among them, 14.3% ($n = 6$) improved with empirical antibiotics, 16.7% ($n = 7$) abandoned treatment, and 69% ($n = 29$) underwent CECT thorax. Our study included a total of 37 children (mean age 7.5 ± 3.5 years; male to female ratio of 1.3:1) who did not show improvement after primary treatment and had persistent respiratory symptoms. Of these 37 children, underlying hematological malignancy included acute lymphoblastic leukemia in 43.2% ($n = 16$), non-Hodgkin lymphoma in 24.3% ($n = 9$), acute myeloid leukemia in 21.6% ($n = 8$), and Hodgkin's lymphoma in 10.8% ($n = 4$) (►**Table 1**).

In the group A ($n = 8$), causes of persistent respiratory symptoms as identified on CECT chest were pulmonary metastatic infiltration in 62.5% ($n = 5$) cases followed by tuberculosis in 37.5% ($n = 3$), whereas in group B ($n = 29$), diagnosis included infection in 58.6% ($n = 17$) children followed by pulmonary metastatic infiltration in 41.3% ($n = 12$). Among the infections, CECT findings were consistent with pulmonary tuberculosis 23.5% ($n = 4$), fungal infection 35.3% ($n = 6$), and bacterial infection 41.2% ($n = 7$).

Among children who underwent chest CT in both groups, 24.3% children ($n = 9$) despite having a normal chest X-ray on day 7, underwent chest CT to elucidate the cause of respiratory distress. Chest CT was able to detect pulmonary changes, i.e., tubercular ($n = 2$) in group A and disease infiltration ($n = 3$), followed by pneumonia, i.e., fungal in ($n = 3$) and bacterial ($n = 1$) in group B.

Pulmonary Tuberculosis

CECT suggested pulmonary tuberculosis in seven children who demonstrated centrilobular nodules with tree in bud appearance ($n = 6$) most frequently (►**Fig. 2A**), followed by

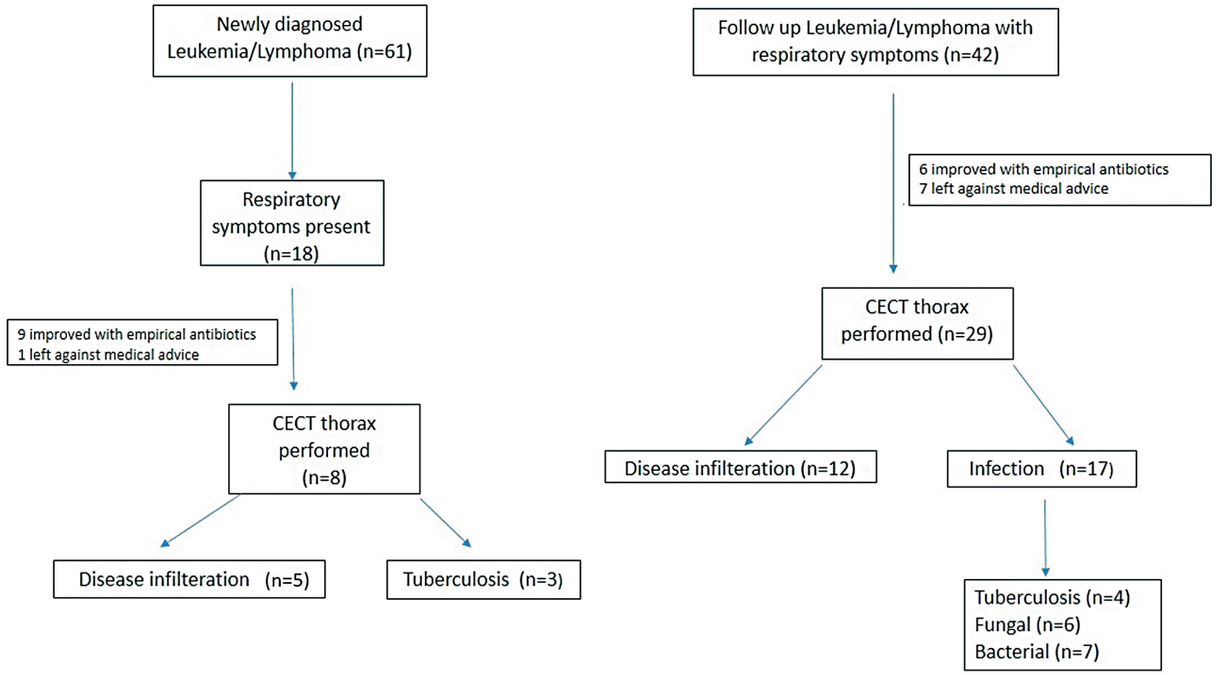

Fig. 1 Flow diagram depicting patient enrolment.

Table 1 Baseline characteristics of study population

Characteristics	
Age	7.5 ± 3.5 years
M:F ratio	1.3:1
Underlying pathology: *n* (%)	
ALL	16 (43.2%)
AML	8 (21.6%)
NHL	9 (24.3%)
HL	4 (10.8%)
Presenting symptoms: *n* (%)	
Fever	31 (83.7%)
Cough	17 (45.9%)
Rapid breathing	12 (32.4%)
Chest pain	1 (0.02%)
Etiological cause: *n* (%)	
Bacterial	7 (18.9%)
Fungal	6 (16.2%)
Tuberculosis	7 (18.9%)
Leukemic infiltration/disease	17 (46%)

segmental/subsegmental consolidation ($n = 4$), and military tuberculosis with random nodules in one child. Other findings were pleural effusion ($n = 3$), GGOs ($n = 1$), and necrotic mediastinal lymph nodes ($n = 3$). Gene Xpert (gastric aspirate) was sent for all these children that was positive in three children (Group A [$n = 1$]; group B [$n = 2$]). Antitubercular treatment (ATT) was started in all these seven children, irrespective of Gene Xpert results. Five children improved following ATT, and two children died due to relapse of underlying malignancy (►**Table 2**).

Fungal Infection

Children with CT features of fungal infection ($n = 6$) revealed segmental/sub segmental consolidation ($n = 4$), GGO ($n = 3$), halo sign ($n = 3$), reverse halo sign ($n = 1$), multiple cavitatory lesions ($n = 1$) and pleural effusion ($n = 3$) (►**Fig. 2B**, **2C**). Fluconazole (empirical antifungal) was started in all children ($n = 37$) if there was no improvement in fever after adding antibiotics for 48 hours. Of the six children with CT features of fungal disease, galactomannan was positive in two children and *Candida* was isolated from blood in two children. Among these six children, in five children, antifungals were escalated, i.e., amphotericin B ($n = 4$) and voriconazole ($n = 1$). All six children responded to antifungals.

In bacterial pneumonia ($n = 7$), findings included lobar/sublobar consolidation ($n = 4$), segmental/sub-segmental consolidations ($n = 3$), pleural effusion ($n = 5$) and homogenously enhancing (non-necrotic) mediastinal lymph nodes ($n = 5$) (►**Fig. 2D**). In these children, antibiotics were escalated based on blood culture. If blood culture did not yield any organism, the antibiotics were escalated according to blood culture sensitivity pattern in the pediatric oncology ward. The most common organisms isolated were bacteria, i.e., MRSA ($n = 2$), *E. coli* ($n = 1$) and Co NS ($n = 1$) followed by *Candida* ($n = 2$).

Pulmonary Metastatic Infiltrates

In cases of leukemic infiltrates ($n = 7$), CT findings included bronchovascular thickening ($n = 4$), GGO ($n = 4$), random nodules ($n = 5$), halo sign ($n = 2$), pleural thickening with

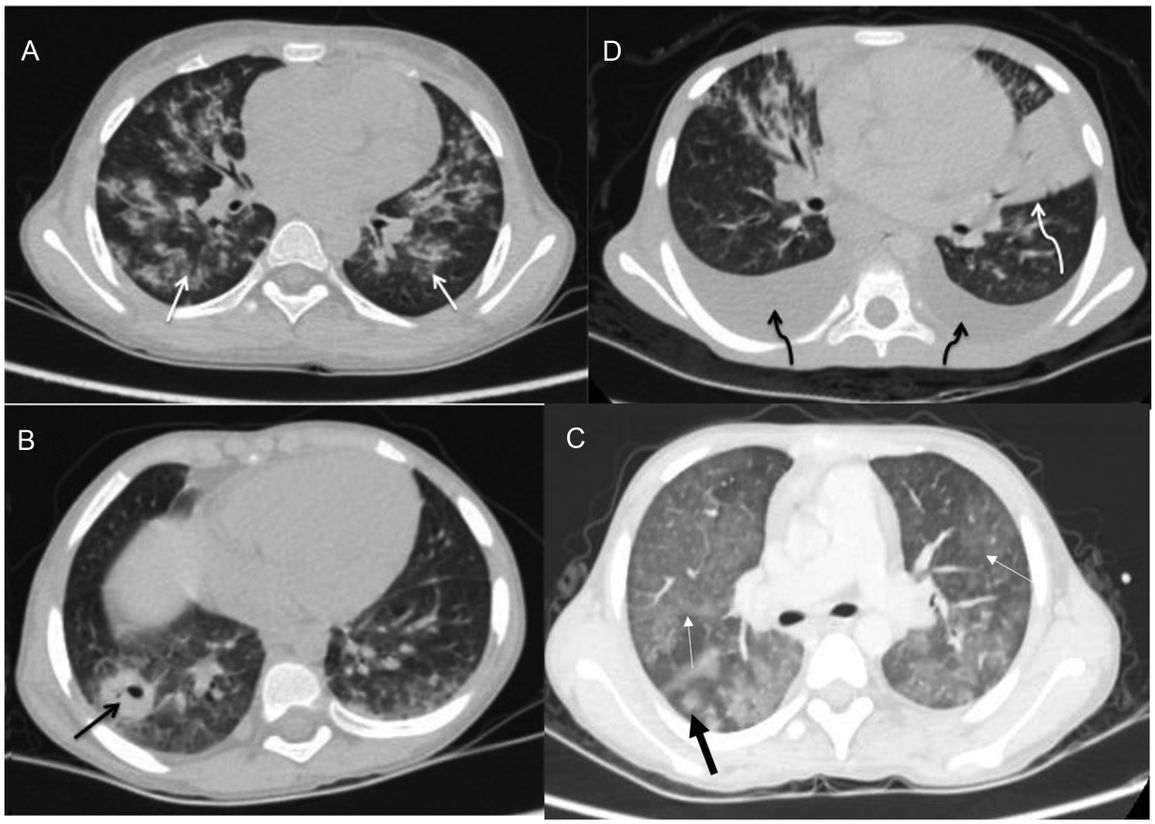

Fig. 2 Axial CECT images of four different patients showing (**A**) bilateral pulmonary infiltrates in form of centrilobular nodules (white arrows) with adjacent ground glass opacities representing tubercular involvement (**B**) bilateral pleural effusion (black curved arrow) and lobar consolidation in left lingular segments (white curved arrow) in bacterial infection and (**C**) cavitatory lesion in the right lower lobe (black arrow) suggestive of fungal infection. (**D**) Bilateral ground glass opacities (white arrows) with halo sign (thick black arrow) in fungal infection.

effusion ($n = 2$), subsegmental consolidations ($n = 4$), discrete mediastinal nodes ($n = 6$), and mediastinal mass ($n = 1$). In cases of lymphoma with pulmonary infiltrates ($n = 10$), CT findings included segmental/sub-segmental consolidations ($n = 7$), pleural effusion with pleural thickening ($n = 4$), mediastinal mass ($n = 4$), discrete mediastinal nodes ($n = 6$), GGO ($n = 2$), and halo sign ($n = 2$). Patients with mediastinal mass ($n = 6$) underwent CT-guided biopsy that yielded the diagnosis. Hyperleukocytosis was seen in two children with relapsed ALL and one child with refractory NHL (►**Table 3**). Based on chest CT findings along with tissue diagnosis, in all these children ($n = 17$) empirical antibiotic/antifungal were stopped and chemotherapy was planned according to tissue biopsy report.

Discussion

The results of our study prove that CECT of chest done at 7 to 10 days of onset of persistent respiratory symptoms can efficiently detect the pulmonary involvement by infective/tumoral infiltrates, even with the normal chest radiographs. Further, CT scan can provide clues toward underlying etiology, narrow down the differential consideration, and help initiate additional diagnostic measures.

Chest radiography remains the initial imaging modality of choice for the evaluation of immunocompromised patients presenting with acute respiratory symptoms. However, radiographs can be normal in up to 10% of patients with lung pathology in immunocompromised patients.[2] Our experience also showed that even with normal lung radiographs, CT could detect the findings in nine patients (34%). The American College of Radiology (ACR) appropriateness criteria for imaging of chest in immunocompromised patients (both adult and pediatric) recommend CT with contrast as the next imaging modality with normal, equivocal, or non-specific chest radiographs or with those demonstrating multiple, diffuse, or confluent opacities. However, separate criteria do not exist for pediatric patients, especially regarding the time to obtain CT scan. Our study suggests that CT with contrast should be done if the child is not responding to empirical antibiotic therapy at 7 to 10 days of persistent respiratory symptoms.

Children with bacterial pneumonia ($n = 7$) had lobar/sublobar consolidations, along with pleural effusion ($n = 5$) on chest CT as has been also reported by Copley et al. Caution should be exercised when diagnosing bacterial infection as CT findings can overlap with various non-infective causes such as pulmonary hemorrhage and acute eosinophilic pneumonia in children.[5] Also, CT findings may overlap with atypical pneumonia including viral infections but the presence of ground glass opacification with consolidation, peribronchial thickening and lobular instead of

Table 2 CECT findings of children who had respiratory distress due to infectious etiology

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations		CECT findings	Treatment	Follow-up
				Chest X-ray (day 7)				
1	7/M	ALL with pulmonary tuberculosis	Fever cough Rapid breathing for 20 days	Patchy opacity in right upper lobe, B/L CP angle bluting	Pleural R/M-high ADA lymphocytosis (91%)	Patchy consolidation along with ground glass opacities, centrilobular nodules and bilateral pleural effusion was observed	Empirical antibiotics On the basis of CECT and pleural tap R/M suggesting TB, ATT was advised for 6 months	Clinical improvement observed following ATT
2	9/M	AML with fungal pneumonia	Cervical lymphadenopathy for 15 days Fever and cough for 5 days	Normal	Galactomannan assay- positive	Focal ground glass opacities with surrounding consolidation (reverse halo sign) and focal patchy opacity were observed	Empirical antibiotics Amphotercin B administered for 14 days.	Fever subsided and child clinically improved
3	12/M	ALL with fungal pneumonia /septic pulmonary embolism	Fever (during induction phase of chemotherapy)	Focal patchy opacities and left sided loculated effusion	Blood C/S was positive for MRSA	Randomly distributed cavitary and non-cavitary nodule with left sided empyema and peripheral patchy consolidation with surrounding GGO were observed	Empirical antibiotics along with Amphotericin B.	Clinical response after Vancomycin administration
4	3/M	ALL with pulmonary tuberculosis	Cough and neck swelling for 15 days fever for 2 days	Opacity in right middle lobe and infiltrative pattern	Blood culture-sterile Gene Xpert-Negative	Multiple bilateral centrilobular nodule with tree in bud appearance, focal GGO and right middle lobe atelectasis was observed	Empirical antibiotics Anti-tubercular drug was advised for 6 months	Clinical improvement observed after ATT intake
5*	4/M	ALL with pulmonary tuberculosis	on/off fever, Rapid breathing and cervical lymphadenopathy	Multiple reticular opacities	Blood C/S- sterile Gene Xpert-Negative	Multiple patchy consolidation in bilateral upper lobe with multiple ground glass opacities, centrilobular nodules with tree in bud appearance	ATT was advised for 6 months	Clinical improvement observed after ATT intake
6	2/F	ALL with pulmonary tuberculosis	Fever and cough for 20 days History of significant weight loss	Inhomogenous opacity in Right upper zone	Gene X-pert-negative	Sublobar consolidation in right upper lobe, pleural effusion and mediastinal lymph nodes	Empirical antibiotics ATT was advised for 6 months	Clinical improvement observed after ATT intake.
7*	3/F	ALL with pulmonary tuberculosis	On/off fever for 22 days and cough for 5 days	ight lung infiltrates	Blood C/S - sterile Gene X-pert-positive.	Diffuse ground glass opacities and patchy consolidation in bilateral upper and lower lobe, centrilobular nodule showing tree in bud appearance in B/L lower lobes and mediastinal lymph node was observed	Empirical antibiotics ATT advised	Child died due to progressive disease
8	6/M	NHL with Bronchopneumonia	On/off fever for 1 month	Normal	Blood culture sterile	Lobar consolidation with centrilobular ground glass opacities and sub-centrimetric mediastinal lymph nodes	Empirical antibiotics	Fever improved following meropenem and vancomycin administration
9	1/F		On/off fever for 15 days	Normal			Empirical antibiotics	

(*Continued*)

Table 2 (*Continued*)

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations		CECT findings	Treatment	Follow-up
		AML with fungal pneumonia			Blood c/s- sterile Gene X-pert-negative Galactomannan assay- Not done	Focal diffuse GGO and centrilobular nodule and mild pleural effusion s/o infective etiology		Child improved clinically after amphotericin B administration
10	4/M	NHL with bronchopneumonia	Fever and cough for 15 days	Bilateral inhomogenous opacities	Blood c/s sterile Gene X-pert-negative.	B/L lobar consolidation with minimal pleural effusion was noted s/o infective cause	Empirical antibiotics	Clinical improvement after Teicoplanin and meropenem administration
11	12/M	ALL with fungal pneumonia	Fever for 12 days	Inhomogenous opacity in right mid zone	Blood c/s –candida Galactomannan assay- Not done	Randomly distributed multiple nodules with surrounding GGO and patchy consolidation in right middle lobe, subcentrimetric mediastinal lymph node and minimal pleural effusion noted	Empirical antibiotics Amphotericin-B administered following CECT findings and culture report	Clinical improvement after amphotericin B administration
12	4/M	ALL with Septic pulmonary embolism Vs fungal infection	Fever for 15 days	Normal	Blood C/S sterile Gene X-pert-negative Galactomannan assay positive	Multiple cavitary lesion with surrounding consolidation in B/L lung field with mediastinal lymph node	Empirical antibiotics with Fluconazole	Child improved after day 4 of fluconazole administration.
13	13/M	ALL with fungal pneumonia	Child fever for 20 days and cough for 15 days.	Bilateral inhomogenous opacities	Blood culture – candida Galactomannan assay not done	Segmental consolidation with surrounding GGO in left upper lobe, and few centrilobular nodule with tree in bud appearance, and minimal pleural effusion	Empirical antibiotics with amphotericin B was administered for 2 weeks	Clinical improvement after amphotericin B administration
14*	7/M	ALL with fungal pneumonia	Fever for 10 days and poor oral intake for 1 month	Normal	Blood culture sterile Gene X-pert-positive	Multiple random nodules with surrounding GGO, mild interstitial thickening and mediastinal lymph node	Empirical antibiotics with fluconazole. ATT advised following CT findings and positive Gene Xpert	Child improved following ATT administration.
15	5/F	AML with fungal pneumonia	Cough and rapid breathing for 4 days	Focal opacity	Blood C/S sterile Gene X-pert-negative Galactomannan positive	Patchy consolidation with surrounding GGO, focal and diffuse GGO and randomly distributed nodule was observed	Empirical antibiotics with fluconazole	Child responded to voriconazole
16	6/M	AML with bronchopneumonia	Fever and cough for 12 days	Consolidation, CP angle blunting	Blood c/s–positive for coagulase negative staphylococcus	Lobar consolidation with pleural effusion and mediastinal lymph node was observed	Empirical antibiotics with fluconazole vancomycin was advised as per blood culture sensitivity	Clinical improvement after Vancomycin administration
17	16/F	AML with pulmonary tuberculosis.	Fever, cough for 25 days and rapid breathing for 10 days	Normal	Blood culture sterile Gene X-pert negative	Centrilobular nodule with tree in bud appearance and pleural effusion	Empirical antibiotics with fluconazole ATT was advised based on CECT findings and no	.Clinically improvement following ATT intake for 6 months

Table 2 (*Continued*)

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations		CECT findings	Treatment	Follow-up
							response to antibiotics as well as antifungals	
18	12/F	AML with bronchopneumonia	Fever and rapid breathing for 4 days	Inhomogenous opacities	Blood culture – MRSA**	Segmental consolidation with pleural effusion, few centrilobular nodule and subcentrimetric mediastinal lymph node	Empirical antibiotics with fluconazole Vancomycin was advised as per blood culture sensitivity	Clinical improvement after vancomycin administration
19	8/F	ALL with bronchopneumonia	Fever and rapid breathing for 10 days	Consolidations	Blood culture - *E. coli*.	B/L segmental consolidation with peri bronchovascular nodule and few subcentrimetric mediastinal lymph node	Empirical antibiotics Imipenem was advised as per blood culture sensitivity	Clinical improvement after Imipenem administration
20	9/F	AML	Fever and cough for 3 days	Consolidations	Blood c/s sterile Gene X-pert - negative	B/L lobar consolidation with pleural effusion and mediastinal lymph node.	Broad spectrum antibiotics was started.	Responded to the treatment.

*Before starting chemotherapy, ** MRSA, methicillin-resistant *Staphylococcus aureus*.

segmental distribution[4] favor viral pneumonia which was not seen among any child in this study. Also, the absence of cavitatory lesion, necrotic mediastinal lymph nodes and predominant tree-in-bud nodules pointed toward bacterial etiology.

The presence of centrilobular nodule with tree in bud appearance, segmental/sub-segmental consolidation (especially in upper lobes), have been described to be associated with pulmonary tuberculosis in immunocompromised host,[5,6] as was also seen in this study. Similar CT findings can also be seen in *Pneumocystis jiroveci*,[7] invasive pulmonary aspergillosis,[7] mucormycosis,[8,9] and candidiasis.[8,9] However, nodules or areas of consolidation with a surrounding halo of GGO representing pulmonary hemorrhage are cardinal features when considering a possibility of fungal pneumonia in neutropenic children.[10] Sometimes, areas of cavitation representing infarction also develop in the neutrophil recovery phase,[11] that are more frequently observed in *Candida* than *Aspergillus* infection. In our study, one of six children had multiple cavitatory lesions that improved following fluconazole administration that favors the possible candida infection in this child.

The role of chest radiographs in detecting non-infectious complications such as tumor recurrence and pulmonary metastasis in children with history of malignancy, is limited. In this study, seven children who had disease infiltration (confirmed by CECT findings as well as clinical condition) showed inhomogeneous opacities on chest radiographs. The presence of pulmonary tumoral infiltration on CT scan is usually suggested by presence of a coexisting mediastinal mass (lymphoma) and lung consolidation or randomly distributed nodule with bronchovascular bundle thickening (leukemia), reflecting predilection of leukemic infiltrates for perilymphatic pulmonary interstitium or nodular pleural thickening[12,13]

Thus, we would like to emphasize that chest radiography still remains the imaging modality of choice for the diagnostic assessment of immunocompromised children presenting with acute respiratory illness.[14] It cannot only detect infectious complications such as pleural effusion, empyema, and pneumothorax[14,15] but serial chest radiographs along with pattern and distribution of abnormality can also aid in formulating a differential diagnosis.[14,15] However, they lack sensitivity to detect subtle abnormalities in symptomatic immunocompromised children. Also, chest radiographs are non-specific with regard to specific pathogen.[1] On the contrary, chest CT is more sensitive than chest radiography for detecting subtle pulmonary parenchymal abnormalities due to its superior spatial resolution and cross-sectional display of findings.[14] In a study by Heussel et al, CT could aid in diagnosing pneumonia in 60% of febrile neutropenic patient with normal chest radiograph at least 5 days before abnormalities were visible on chest radiographs.[16] The results of our study emphasize that utilizing a chest radiograph as an initial modality and incorporation of CECT as a second-line modality is a cost-effective approach that can be utilized especially in low-income countries. Moreover, CT can obviate the need for specialized biochemical testing

Table 3 CECT findings of children that had malignant disease infiltration

S no.	Age (y)/ Sex	Diagnosis	Clinical presentation	Investigations		CECT findings
					Chest X-ray	
1	8/F	Relapsed ALL	On/off fever, neck swelling, cough and rapid breathing	Hyperleukocytosis	Normal	Multiple diffusely spread patchy ground glass opacities (GGO) with mild interstitial thickening in bilateral lungs and moderate pleural effusion and enlarged mediastinal lymph node.
2	13/M	Relapsed ALL	Fever and difficulty in breathing	Blood C/S - Sterile Gene X-pert - negative	Normal	Subpleural patchy opacities with interstitial thickening, and subcentrimetric random nodules
3	6/F	Relapsed ALL	On/off fever and lymphadenopathy	Hyperleukocytosis	Normal	Multiple randomly distributed nodule with surrounding GGO, nodular thickening of interlobular fissure and enlarged mediastinal lymph node
4	10/M	Relapsed ALL	On/off fever and cough	Blood C/S - sterile	Widened mediastinum, Inhomogenous opacities	Multiple mediastinal lymph node with subsegmental patchy consolidation, random nodules and focal GGO
5	11/M	Relapsed ALL	On/off fever and rapid breathing	Blood C/S - Sterile	Mediastinal widening	Conglomerated mediastinal lymph nodes with adjacent subsegmental consolidation and pericardial effusion, randomly distributed multiple soft tissue density nodule, mild pleural thickening and bony erosion of sixth rib.
6*	2/F	NHL	Fever and lymphadenopathy	Blood C/S - Sterile	Right upper lobe opacity. Widened mediastinum	Near complete thrombosis of SVC, proximal right subclavian and B/L brachiocephalic vein. Randomly distributed nodule with few showing surrounding GGO, right upper lobe segmental consolidation and bilateral pleural effusion with mild pleural thickening. Few subcentrimetric mediastinal lymph nodes.
7	11/M	Relapsed AML	Fever and cough	Blood C/S - Sterile Gene X-pert - negative	Inhomognoeus opacity	Focal patchy consolidation, multiple diffuse patchy GGO with mild interstitial thickening and subcentrimetric mediastinal lymph nodes.
8*	13/M	NHL	Fever chest pain and rapid breathing		Lung opacity, CP angle blunting	Anterior and superior mediastinal mass with right upper lobe consolidation and moderate pleural effusion.
9*	9/M	HL	Fever, neck swelling for 7 months	Blood C/S - Sterile Gene X-pert - Negative.	Inhomogneous opacity	Patchy consolidation, bilateral nodular pleural thickening and mediastinal lymph nodes
10	5/M	Refractory NHL	Fever		Inhomogneous opacity	Focal subsegmental consolidation, Soft tissue density random nodule and hilar lymph nodes.
11*	8/M	HL	Fever, rapid breathing and lymphadenopathy		Consolidation with inhomognoeus opacity	Subsegmental consolidation, centrilobular nodule with surrounding mild GGO with mediastinal lymph node
12	4/F	Refractory NHL	Rapid breathing		Bronchopneumonia, bilateral CP angle blunting	Segmental consolidation, bilateral nodular pleural thickening with pleural effusion and mediastinal lymph nodes
13	6/F	Refractory HL	Fever, rapid breathing and lymphadenopathy	.	Mediastinal widening	Large mildly enhancing mediastinal mass with necrosis, nodular thickening of pleura with pleural effusion

Table 3 (*Continued*)

S no.	Age (y)/ Sex	Diagnosis	Clinical presentation	Investigations		CECT findings
					Chest X-ray	
14	6/F	Relapsed NHL	On/off fever, cough and rapid breathing		Mediastinal widening	Mediastinal enhancing mass occupying superior and anterior mediastinum, pleural thickening and mediastinal lymph nodes
15	8/F	Refractory NHL	Fever and rapid breathing.	Hyperleukocytosis	Bilateral inhomogenous opacities	Segmental consolidation, B/L diffuse focal GGO with interstitial thickening and calcified enlarged mediastinal lymph nodes
16	7/M	RefractoryNHL	Fever, cough and rapid breathing	Blood C/S - Sterile Gene X-pert - negative.	Mediastinal widening.	Anterior mediastinal enhancing mass with bilateral minimal pleural and pericardial effusion. Patchy ground glass opacities present
17*	7/F	HL	Neck swelling for 6 months	Blood C/S - Sterile Gene X-pert - Negative	Inhomogenous opacities	Middle lobe segmental consolidation, halo sign and cervical non-necrotic lymph nodes

*Before starting chemotherapy.

which can eventually decrease the overall cost incurred to the patients.

The major limitation in this study was our small cohort size and lack of detailed microbiological/histopathological assessment through lung biopsy. In the majority of cases, our diagnosis was based on response to antibiotics and clinical follow-up. Also, we did not screen for viral infections due to a high cost of PCR based test to detect the same. The strength of this study was, however, its prospective nature. Therefore, we suggest that there is a need for multicentric prospective studies that can evaluate the role of CT scan in diagnosing etiology of persistent respiratory symptoms in pediatric immunocompromised patients in a resource limited setting.

Conclusion

In conclusion, chest CT can be a useful adjunctive tool when the etiology for ARI is not clear and resources are limited. Chest CT has the ability to identify the presence of pulmonary disease with high sensitivity, along with vital diagnostic information about the pattern of involvement as well as the most likely etiological pathogen.

Data, Materials and/or Code Availability

Data are available with the corresponding author and can be shared on reasonable request.

Ethics Approval

The study was approved by the institutional ethics committee of Institute of medical Sciences, Banaras Hindu University.

Funding

None.

Conflict of Interest

None declared.

Consent

Written informed consent was obtained from all the patients included in this study.

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Role of Antifungal Prophylaxis in Invasive Fungal Infection in Children with Acute Lymphoblastic Leukemia—A Retrospective Cross-Sectional Study

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Abstract

Introduction Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Its outcome in India is not as good as that in the western world. One of the important reasons for lesser survival rates is opportunistic infections, including invasive fungal infections (IFIs). Antifungal prophylaxis (AFP) in ALL children is routinely not followed. However, owing to its incidence in high-risk ALL, this study is focused on the use of AFP in those children.

Objectives This retrospective study investigated the role of AFP in newly diagnosed children with high-risk ALL on intensive blocks of therapy on regimens B and C of the United Kingdom Acute Lymphoblastic Leukemia 2003 protocol.

Materials and Methods The study was conducted in a tertiary care center from 1st December 2013 to 31st December 2019 and included children with ALL from 1 to 18 years of age. Routine AFP with voriconazole was commenced for high-risk ALL children from 1st July 2017 onward in our center. We analyzed data of all IFIs in children before and after AFP with National Cancer Institute high-risk status who had been started on regimen B induction and regimen B or C consolidation and intensification phases.

Results A total of 55 children with high-risk ALL were included in the study. The median age was 4 years, with the majority being between the age of 1 and 10 years (38 out of 55; 65%) and predominantly male (36 out of 55; 69%). Total incidence of IFI in our cohort was 51% (28 out of 55). A significant number of children (16 out of 22 [70%]) who were not on prophylaxis developed IFI versus children (12 out of 33 [28%]) on prophylaxis ($p = 0.008$). The most common organisms isolated were *Candida parapsilosis* and *Candida tropicalis.* Children not receiving AFP were found to be 4.7 times (95% confidence interval: 1.44–15.13) more likely to get IFI than the ones receiving AFP. The presence of concurrent bacterial infection increases the risk of IFI ($p = 0.04$).

Conclusion The incidence of IFI was high in high-risk ALL children who were not on AFP. The introduction of routine AFP reduced the incidence of IFI.

Keywords

- Acute lymphoblastic leukemia
- fungal infection
- childhood cancer

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy worldwide, accounting for more than 25% of all pediatric cancers.[1] Pediatric ALL is often cited as one of the true success stories of modern medicine.[2] The United Kingdom Acute Lymphoblastic Leukemia (UKALL) 2003 trial[3,4] results have shown an overall outcome of 90% in the United Kingdom.[3] Its event-free survival rate at 3 years in India has been observed, ranging from 41to 85% across the country.[5,6]

Children undergoing the treatment for cancers are at an increased risk of developing invasive fungal infections (IFIs). IFIs pose a significant challenge to the management of ALL as it results in morbidity, mortality, and interruption of treatment. Incidence of IFI was found to be high in children with acute myeloid leukemia (AML) (up to 29%), allogeneic hematopoietic stem cell transplantation (HSCT), and relapsed ALL.[7] The overall case fatality rate is about 20 to 70%, with the most inferior outcome noted with disseminated disease. *Candida* species was the most common organism isolated, followed by *Aspergillus*. Recently, Zygomycetes, *Fusarium spp*., and *Sedoporium spp.* are being increasingly observed in IFI cases.[8,9] The fungal microflora present in our set-up, primarily consisted of *Candida parapsilosis* and *Candida tropicalis*, both of which are fluconazole resistant. Also, we wanted to target molds which remain the most common etiology for IFIs in immunocompromised patients, that is, here, ALL children. Because of these two reasons, voriconazole was chosen as antifungal prophylaxis (AFP) of choice and the antifungal policy was gradually adjusted in our medical center.

Incidence of IFI is comparatively less common during the treatment for newly diagnosed ALL than in AML/relapsed ALL/HSCT cases, and it varies depending on the protocol, regimen followed, and risk factors involved. However, there are no standard guidelines for commencing AFP in children receiving the treatment for ALL. The analysis of infection-related mortality in the UKALL 2003 protocol[10] showed that 20% of patients had a fungal infection (predominantly *Aspergillus*), and it was common during the induction phase of the treatment. It is the second most common cause of infection-related mortality in ALL children. Hence, we investigated the role of AFP in children with ALL to improve the quality of life and reduce treatment-related morbidity and mortality.

Objectives

This study was to investigate the role of AFP in newly diagnosed ALL children who had National Cancer Institute (NCI) high-risk status during the intensive phases of regimens B and C, as per UKALL 2003 protocol.

Methodology

Study Population

It was a retrospective study. All children aged consecutively between the age of 1 and 18 years diagnosed with ALL who had NCI[11] high-risk status (initial white blood cells [WBC] count $\geq$50,000/mm^3 or age $\geq$10 years or T cell type) between 1st December 2013 and 31st December 2019 admitted and treated at our tertiary care center, Kasturba Medical College and Hospital, Mangalore, were included. All the details of children with the type of leukemia (B or T cell), age at diagnosis, date of initiation of treatment, regimen, post-induction medical residual disease status, details about febrile neutropenia episodes, event dates (relapse and death) during the induction, consolidation, interim maintenance or escalating Capizzi, and delayed intensification blocks were obtained using structured proforma through review of medical records. All these pieces of information were obtained after due permission from the Medical Records Section of the hospital. Children on regimen A, aged less than 1 year or more than 18 years, relapse/recurrent cases, and IFIs in the maintenance phase of treatment were all excluded from our study.

Invasive Fungal Infection Prophylaxis

In our unit, AFP was started as per routine practice on 1st July 2017 for those children receiving treatment on regimens B and C of the UKALL 2003 protocol. The prophylaxis was based on the observation of presumed increased incidence of IFI in our cohort of children with ALL. Hence, the study population was divided into two groups, the first group included the children diagnosed before 1st July 2017 and not on AFP and the second group included children diagnosed after 1st July 2017 and on AFP. The antifungal prophylactic agent used was oral voriconazole (dose ranging between 6 to 10 mg/kg/dose) twice daily, and for those who cannot take the drug orally or due to financial constraints, these children received intravenous (IV) conventional amphotericin B (1 mg/kg/d) on alternate days. While receiving amphotericin B, creatinine and potassium levels were monitored twice weekly. Due to the culture pattern in our set-up being fluconazole resistant as well to target molds, voriconazole was chosen as our AFP of choice and the antifungal policy was gradually adjusted. Itraconazole (5 mg/kg/d in two divided doses) and fluconazole (12 mg/kg/dose once-daily dosing) were used as AFP before the introduction of voriconazole in 2017. Unfortunately, therapeutic drug monitoring for voriconazole was not performed on our patients due to the nonavailability of the facility.

Treatment Regimen for Underlying Leukemia

ALL was diagnosed based on bone marrow examination showing blast cells $\geq$20% and confirmed through flow cytometry.[12] All the children with ALL were treated on the uniform protocol mentioned in UKALL 2003 as outlined in ►**Fig. 1**.

Treatment for Invasive Fungal Infection

For all children who developed fever, before the initiation of broad-spectrum antibiotics, tests such as blood culture and complete blood count were performed along with urine culture performed in children <5 years and girls of all ages. As per the guidelines, we started amphotericin B (1 mg/kg/d, conventional drug given through IV) in children

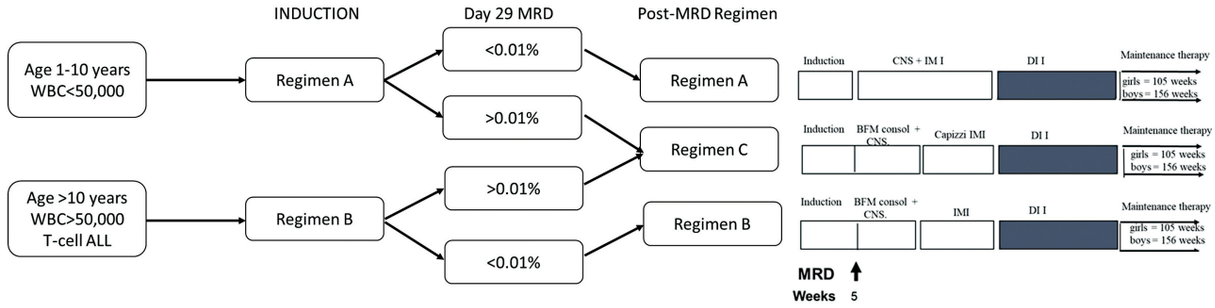

Fig. 1 UKALL 03 treatment regimens. BFM, Berlin–Franklin–Munster consolidation; IM, interim maintenance; DI, delayed intensification; MRD, minimal residual disease.

with persistent fever spikes and neutropenia ($<500/mm^3$) lasting more than 96 hours after starting antibiotics with negative bacterial cultures. If suspicion of IFI was raised, based on prolonged fever and negative cultures, chest X-ray and abdominal ultrasonography were performed in all children. Serum galactomannan levels were analyzed using Platelia Aspergillus Ag enzyme-linked immunosorbent assay kit, and cerebrospinal fluid analysis and culture, computed tomography (CT) chest/sinus, echocardiography, and other imaging studies were performed on a case-to-case basis. IFI was classified according to the European Organization of Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) guidelines.[13]

Sample Size and Outcome Measures

This was a time-bound study analyzing all the ALL diagnosed children admitted during the study period and including only those satisfying the inclusion criteria. The primary outcome of the study was to identify and classify fungal infections and to assess the role of AFP in preventing them. The secondary outcome measure was to identify the relevant risk factors contributing to the fungal infection.

Ethics

The study was approved by the Institute's Ethics Committee (IEC KMC MLR 02-2021/71), and all the patients consented to the collection and analysis of the data. Kasturba Medical College Hospital, Mangalore, is a tertiary-level teaching hospital that has a dedicated Division of Pediatric Oncology under the Department of Pediatrics. Written informed consent was waived off due to the retrospective nature of the study. No harm was done to the study participants, and all the ethical principles under the Declaration of Helsinki were met.

Definitions

Febrile Neutropenia

A single spike of fever >38°C or 100°F with an absolute neutrophil count lower than $500/mm^3$, according to National Institute for Health and Clinical Excellence guidance.[14,15]

Invasive Fungal Infections

EORTC/MSG[13] has standardized the pathological characteristics of proven/probable/possible fungal infection based on host factors, clinical criteria, and mycological criteria.[9] They are as follows:

- Possible IFI—the absence of mycological evidence but the presence of both clinical and host factors.
- Probable IFI—the presence of all criteria: imaging studies showing features suggestive of fungal infection and mycological evidence of fungal elements from sputum, bronchoalveolar lavage, sinus aspirate using cytology/direct microscopy/culture, or detection of antigen/cell wall constituents (such as beta-galactomannan and beta-glucan).
- Proven IFI—histopathological/cytopathologic/microscopic evidence from normally sterile sites showing the fungal organism with evidence of tissue destruction or blood culture growth of a fungal organism.

Statistical Analysis

The data were coded in an excel sheet and fed into IBM Statistical Package for the Social Sciences version 25.0, Armonk, NY, United States for analysis. Frequency and percentage were used to express categorical variables, and continuous variables were expressed with mean and standard deviation. The groups were compared using one-way analysis of variance test to state their significance. The relationship between AFP and invasive fungal disease was tested using binary logistic regression. The associations of IFI with risk factors were analyzed using the chi-square test. p-Value < 0.05 was considered statistically significant in a two-tailed test.

Results

Study Population, Patient Characteristics, and Overall Invasive Fungal Infection

A total of 55 out of 80 NCI high-risk ALL children fulfilled the inclusion criteria (►**Fig. 2**). For the rest of the children, either information was inadequate or they were transferred to other centers for management soon after the diagnosis. Among 55 children, 41 children had a high WBC count of $\geq 50,000/mm^3$, 12 children had T cell ALL, and 2 children were aged above 10-year-old with a WBC count of $<50,000/mm^3$.

Children were almost equally distributed among regimens B and C following induction (26 and 29, respectively). In our cohort, the total incidence of IFI was 51% (28/55). Out of the 55 children, 33 (60%) of them were on AFP, and among them, only 12 (28%) had a fungal infection (►**Table 1**). Out of

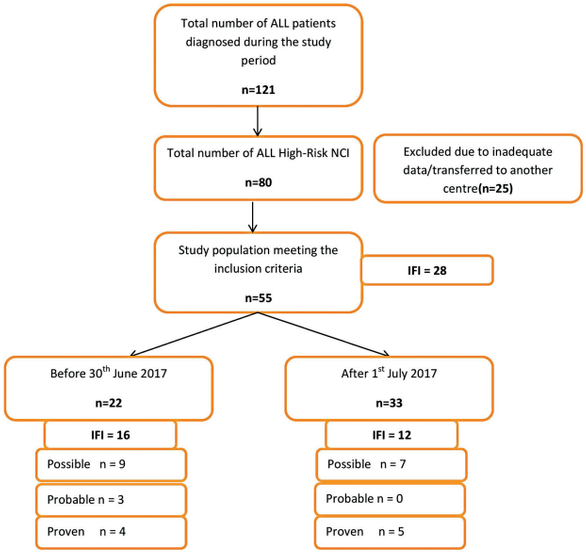

Fig. 2 Flow diagram depicting the study design.

22 children (40%) who were not on AFP, 16 of them developed a fungal infection (70%; p-Value = 0.008).

The characteristics of 28 children with IFIs are summarized in ►**Table 2**. Children between the age of 1 and 10 years ($p = 0.012$) on regimen C and boys were predominantly affected. IFI was noted more commonly in these phases of treatment: induction in 50% (14 out of 28) of patients followed by consolidation in 25% (7 out of 28) of patients and delayed intensification in 25% (7 out of 28) of patients. As per the EORTC/MSG guidelines, on the classification of IFIs, possible infection was seen in 57% (16 out of 28) of the children, followed by proven infection in 32% (9 out of 28) of the children and probable infection in 11% (3 out of 28) of the children.

All children, irrespective of their IFI classification, underwent a chest X-ray and ultrasonography (100%). Echocardiography was performed in 15 patients (27%) out of 55 with IFI, and all were found to be normal. In addition, imaging studies such as CT scan for chest and sinuses; MRI brain based on medical history and examination was performed. A total of eight patients were screened by these techniques, and it was found that two patients had fungal pneumonia, two patients had fungal frontal sinusitis and mastoiditis, and three patients had fungal granulomas in the brain.

All the children diagnosed with probable IFI had an estimation of serum galactomannan, which was >0.5 IU/mL (normal <0.5 IU/mL), indicating *Aspergillus* infection. In children with proven infection, *Candida species* ($n = 11$) were the most common organisms isolated. Among them, *C. parapsilosis and C. tropicalis* (44%) were the predominant fungal species isolated.

Possible Invasive Fungal Infection

Among 57% of the children (16/28) with a possible infection, most had a fungal disease in their induction phase of chemotherapy, and 50% (8 out of 16) developed a fungal infection on prophylaxis. Ultrasonography performed on the abdomen picked up the liver and splenic granuloma, suggesting candidiasis in two children. One had a sinus infection out of the two screened, and two out of three had fungal pneumonia (67%).

Probable Invasive Fungal Infection

Probable infections were more common in 67% (two out of three) of the patients during the delayed intensification phase of treatment, and 67% of them developed a fungal infection on prophylaxis. The three children with fungal brain granuloma presented with seizures/altered sensorium/focal neurological deficit.

Proven Invasive Fungal Infection

Thirty-three per cent of children with proven infection predominantly developed the fungal disease during the induction phase of chemotherapy. However, there was not much difference in the other phases where (5 out of 9) 56% of the children were on prophylaxis. *C. parapsilosis and C. tropicalis* were the predominant fungi isolated.

Table 1 Characteristics of the study population

Total number of patients diagnosed with high-risk ALL during the study period		55
Age	1–10 y	38 (69%)
	≥10 y	17 (31%)
Sex	Male	36 (65%)
	Female	19 (35%)
UKALL 03 regimen	B	26 (53%)
	C	29 (47%)
No. of children on AFP		33 (60%)
No. of children with fungal infection on AFP		12 (33%)
No. of children without AFP		22 (40%)
No. of children with fungal infection not on AFP		16 (73%)

Abbreviations: ALL, acute lymphoblastic leukemia; AFP, antifungal prophylaxis; UKALL, United Kingdom Acute Lymphoblastic Leukemia.

Table 2 Characteristics of children with invasive fungal infection

Total number of children with fungal infection		28 (51%)		*p*-Value
Age	1–10 y	19 (68%)		*0.012*
	>10 y	9 (32%)		
Sex	Male	15 (54%)		0.706
	Female	13 (46%)		
UKALL 03 regimen	B	10 (36%)		0.136
	C	18 (64%)		
Central line	Present	7 (25%)		*0.012*
	Absent	21 (75%)		
Type	Chemoport	5 (71%)		
	Femoral	2 (29%)		
Phase	Induction	14 (50%)		
	Consolidation	7 (25%)		
	Delayed intensification	7 (25%)		
IFI	Possible	16 (57%)		
	Probable	3 (11%)		
	Proven	9 (32%)		
Investigations	Chest X-ray	28		
	Blood culture	28		
	Candida Albicans	2 (22%)		
	Candida parapsilosis	4 (44%)		
	Candida krusei	1 (12%)		
	Candida Tropicalis	4 (44%)		
	Galactomannan level (Aspergillus)	3/3		
	Imaging	USG abdomen	2	
		CT sinuses	2	
		CT/MRI head	3	
		CT chest	2	
		2D Echo	15 (54%)	

Abbreviations: 2D, two dimensional; CT, computed tomography; IFI, invasive fungal infection; MRI, magnetic resonance imaging; UKALL, United Kingdom Acute Lymphoblastic Leukemia; USG, ultrasonography.

Invasive Fungal Infection and its Risk Factors

According to our study, the presence of an associated bacterial infection increases the risk of IFI, but the sample size was minimal to calculate the odd's ratio ($p = 0.04$). Children had a concurrent bacterial infection, and the causative organisms were *Klebsiella pneumonia* in two children with associated *Enterococcus* in one, *Pseudomonas aeruginosa* in another, and the last child with *Escherichia coli*. There was no significant association between IFI with age ($p = 0.083$), gender ($p = 0.054$), in-situ central line ($p = 0.70$), and regimen ($p = 0.68$; ►**Table 3**).

Table 3 Risk analysis of invasive fungal infection with its risk factors

Variable	Odd's ratio with 95% confidence interval	*p*-Value
Gender	0.33 (0.1–1.1)	0.054
Central line	0.79 (0.24–2.6)	0.70
Associated bacterial infection	–	0.04
Age	1.8 (0.6–5.6)	0.083
Final regimen	1.25 (0.43–3.61)	0.68

Antifungal Prophylaxis and Invasive Fungal Infection

The most common antifungal prophylactic agent administered was voriconazole in 26 children (79%) at 6 mg/kg/dose twice daily, followed by itraconazole in 4 children (12%). One child was on fluconazole prophylaxis, and another one was on an alternate day dosage of amphotericin B.

Out of the two groups, 33 children (60%) were on AFP, 22 (40%) were not on prophylaxis, and no significant differences in age, gender, treatment regimen, presence of central line, and or associated bacterial infection between the two groups were found. However, we found a statistically significant difference in IFI (11 out of 33 vs. 16 out of 22; $p = 0.008$), signifying incidence of fungal infection was lesser in children on AFP (►**Supplementary Table S1**). Our study established the relationship between AFP and IFI using binary logistic regression analysis. According to our study, children off AFP were discovered to be 4.7 times (95% confidence interval: 1.44–15.13, Nagelkerke R^2 0.166, Wald 6.589, $p = 0.007$) more likely to get IFI than children on AFP.

Discussion

Our present study showed that the overall incidence of fungal infection was 51% in high-risk ALL cases. Other Indian studies have shown a wide range of IFI prevalence from 6.6 to 74.6% in ALL children, but they have not shown the incidence in high-risk children. Studies worldwide have shown a high incidence rate of IFI in ALL children, more specifically in the high-risk group.[16,17] An 8-year study in Indian children has shown a 6.6% incidence of IFI and a 44% mortality rate in ALL children.[18] In our study, the induction phase of chemotherapy accounted for the maximum number of cases of invasive fungal disease like other previously published[19,20]

There are multiple risk factors associated with the emergence of a fungal infection in a child.[21] From our study, associated bacterial infection was identified as a risk factor. Age, central venous access, or gender did not increase the chance of fungal infection. The other likely reasons for increased prevalence in our center are the use of dexamethasone during induction and an environment where the increased humidity helps spores of molds to grow and stay for a longer duration.[22] The incidence and the outcome of IFI in ALL children in low- and middle-income countries are shown in ►**Table 4**. According to a study conducted in Australia, the prevalence of fungal infection in developed countries was only around 9.7%.[23]

IFIs were more common in children from 1 to 10 years in regimen C, but a statistically significant correlation between age with IFI was not found in our study ($p = 0.083$). Previous studies have shown that an increase in age increases the risk of IFI.[21,24,25]

All the children with possible infection were either diagnosed clinically or based on imaging findings suggestive of fungal infection. All children with probable infections had documented serum galactomannan levels. Serum galactomannan is a very useful biomarker as most cultures turn up sterile, and invasive tissue diagnosis is not always feasible in this population. It has a sensitivity of about 60 to 80% and excellent specificity of 80 to 95%.[26] Among the species isolated in our cultures, *Candida* species that are not *Candida albicans* (45%) especially *C. parapsilosis* are found to be predominant compared to *C. albicans,* as reported in other studies as well.[20,22,24,25]

The antifungal agent commonly used for primary prophylaxis in our study was voriconazole (75%). All the children tolerated the drug well, and no adverse reactions were noted. Dorthea et al, in their prospective multicentric study predominantly involving children with ALL, found voriconazole prophylaxis to reduce the incidence of IFI, and only one breakthrough fungemia and manageable adverse effects were noted. It had established the safety and tolerability of voriconazole in children[27] but not in all studies.[28] In their pediatric AFP guideline for 2014, Science et al found the moderate quality of evidence in starting AFP in ALL patients.[8] The other few antifungal agents such as amphotericin B, fluconazole, and echinocandins have been studied; however, not enough evidence is available to suggest routine use of these drugs. A study on the use of fluconazole prophylaxis in acute leukemia in children also indicated a reduction in IFI incidence. Still, it did not establish the safety data of fluconazole.[8] The randomized controlled trial performed to compare the efficacy of voriconazole and low dose amphotericin B in pediatric ALL showed better results with voriconazole in efficacy and safety profile.[29] International guidelines state that voriconazole is the recommended antifungal for high-risk ALL children. It is administered at oral doses of 9 mg/kg/d twice daily (BD) (maximum dose 350 mg) for age 2 to 14 years or <50 kg, 200 mg BD for age >15 years or > 50 kg; IV doses of 8 mg/kg/d BD (day 1: 9 mg/kg) for age 2 to 14 years or < 50 kg and 4 mg/kg BD (day 1: 6 mg/kg) for age >15 years or >50 kg with regular therapeutic drug monitoring (trough 1–3 µg/mL). Liposomal amphotericin-B thrice weekly or echinocandin are other alternatives. In our center, it is a practice to withhold antifungal azoles one day before vincristine injection as it worsens the vincristine toxicity,[30] and restart it 24 to 48 hours later. This might also be a reason for an increased incidence of breakthroughs. Previous studies have reported 27% IFI in pediatric oncology patients (9% in ALL) while on caspofungin prophylaxis,[31] 3.1% of HSCT transplant children developed IFI on micafungin prophylaxis,[32] and 6.7% of AML children had breakthrough IFI on voriconazole prophylaxis,[33] but not in all.[28]

The incidence of fungal infection in children on AFP was only 28% compared to 70% in the control group in our study. AFP drastically reduced the rate of IFI in high-risk ALL children, and we found a 65% reduction in incidence according to our study. Though enough evidence is not available to recommend routine use of AFP in ALL children, the incidence of IFI is high in children belonging to a high-risk group. As shown by our study and previous studies also, the burden of fungal infection is high in Asian countries. However, the exact incidence in India is not available.[34,35] The latest 2020 clinical practice guidelines by Lehrnbecher

Table 4 Incidence and outcome of IFI in children with ALL in low- and middle-income countries

Author (Ref)	ALL-HR (Y/N)	IFI incidence in ALL	Time period	Cases (*N*)	Mortality	AFP (A/P)	Type of study	Analysis
Kumar et al[37]	N	14/17 (74.6%)	2013–2014	59	4/7(57%) in the induction phase	A	Prospective study—New Delhi	Prevalence of IFI is very high in children with persistent febrile neutropenia who are not on AFP.
Tüfekçi et al[38]	Y	7/17 (41%)	2001–2013	174	NR	A	Retrospective study—Turkey	Higher prevalence of IFI with persistent febrile neutropenia in HR-ALL children.
Evim et al[39]	Y	84/238 (35.2%) with 18 (21%) in HR blocks	2010–2015	238/289	34%	P-26/87 developed on IFI—fluconazole followed by Itraconazole	Retrospective study—Turkey	Increased IFI in high-risk ALL children even on AFP and higher mortality rate.
Kaya et al[19]	N	10/106 (10.2%)	1998–2007	106/154	5%	P	Retrospective study—Turkey	AFP with fluconazole may be reducing the incidence and mortality of IFI.
Supatharawanich et al[40]	N	12/150 (8%)	2009–2019	150/241	8.3%	P-4/12 had IFI on AFP (itraconazole and posaconazole)	Retrospective study—Thailand	AFP reduces IFI in relapsed leukemia but not in ALL children.
Yi et al[41]	N	65/214 (30.7%)	2014–2017	214	NR	A	Retrospective study—PR China	The occurrence of IFI in children with ALL relates to the time of hospitalization and the level of neutrophils.
Zhang et al[42]	Y	63/155 (40.6%)	2017–2018	155	NR	P-45% IFI—No AFP vs. 37% on AFP (posaconazole and fluconazole)	Retrospective study—PR China	Incidence of IFI with AFP was comparable between the two groups (on AFP vs. off AFP).
Das et al[18]	N	46/55 (83%)	2006–2013	692	44%	A	Retrospective study—India	IFI most common cause of treated related mortality in pediatric ALL.
Bal et al[43]	N	24/125	2005–2013	125	13.3%	A	Retrospective study—Turkey	Younger age, prolonged neutropenia, and induction phase chemotherapy were considered risk factors for IFI.

Abbreviations: ALL, acute lymphoblastic leukemia; AFP, antifungal prophylaxis; HR, high risk; UKALL, United Kingdom Acute Lymphoblastic Leukemia; IFI, invasive fungal infection.

et al state that consider administering systemic AFP to children and adolescents with newly diagnosed and relapsed ALL at high risk for IFI. However, they state low quality of evidence and weak recommendation due to the absence of comprehensive IFI incidence data in low-risk ALL children therefore warranting further protocol-specific recommendation and are strictly against the use of routine IFP in low-risk ALL children.[36]

Limitations

It was a retrospective study and, therefore, subject to certain limitations inherent in its design. For example, the use of preexisting case records makes it difficult to obtain information on potential confounding variables. In addition, it had a relatively small sample size.

Conclusion

This study showed that the incidence of IFI can be remarkably high among children with high-risk ALL during intensive phases of therapy, and the use of AFP reduces the incidence of IFI in these children. From these findings, therefore, the routine use of AFP during the intensive phase of chemotherapy in high-risk pediatric ALL children may be considered.

Declarations

Ethics statement

Ethical Approval (Including Committee and Record Number)

Permission granted by the Institutional Ethics committee of Kasturba Medical college hospital Mangaluru on (IEC KMC MLR 02-2021/71)

Informed Consent

Consent has been obtained initially at the time of commencement of treatment to collect the data on characteristics of acute lymphoblastic leukemia, treatment regimens, and febrile neutropenia episodes.

Author Contribution

N.S. collected and analyzed the data and drafted the manuscript, and H.P.L. conceived the idea and reviewed and edited the manuscript.

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None.

Conflict of Interest

None declared.

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Outcomes and Management of Head and Neck Cancer at a South Indian Cancer Centre: A Retrospective Study

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Abstract

Introduction Head and neck cancers are one of the most common cancers in the Indian subcontinent. The trends of these cancers worldwide have drastically changed over the past 15 years. In spite of all the new technology and timely diagnosis, the treatment of these cancers is still a challenge. These cancers still continue to be a significant cause of morbidity and mortality worldwide.

Objectives To identify different patterns of care received by patients with primary head and neck cancer in a single center and analyze the outcomes of the different patterns of care received by these patients in terms of overall survival and disease-free survival.

Materials and Methods We included 707 patients with primary head and neck cancer registered and treated in our institution from January 2015 to December 2017. The demographic details of the patient, treatment received, and outcomes of treatment were collected retrospectively from our hospital's medical registry. Descriptive analysis was performed by calculating mean and standard deviation for quantitative variables, whereas frequency and proportion were calculated for categorical variables. The mean/median overall survival and recurrence-free survival were compared across various explanatory parameters using log rank–test. A p-value < 0.05 was considered statistically significant.

Results A total of 707 patients were included in the final analysis. The median age of presentation was 60 years. In total, 50% of patients presented with stage IV disease at diagnosis and 78% had a history of smoking or other tobacco use. Oral cavity was the most common primary site. Concurrent chemotherapy with radiation therapy was the most common modality of treatment used in 49% of patients: RT was the common modality of treatment in 21% patients. Fourteen percent patients were treated by only surgery. All patients who underwent treatment were included for survival analysis,

Keywords
- head and neck cancer
- survival
- epidemiology
- patterns of care
- outcome
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- chemotherapy

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which showed that the median overall survival time was 42 months (34–49 months). The median duration of disease free-survival time was 37 months (30–43 months).
Conclusion In our study, most patients presented with locally advanced disease. Multimodality treatment yielded better results. Based on our study, in early-stage cancer, where single modality treatment was used, adjuvant therapy should be tailored based on nomogram.

Introduction

Head and neck cancers (HNCs) are a heterogenous group of cancers that arise from the mucosa of the aerodigestive tract. According to the GLOBOCAN 2018 data, 2,05,325 new cases of HNC are diagnosed in a year and 1,22,834 deaths are associated with HNC in India. Cancers of the lip and oral cavity are the second most common cancers following breast cancer. HNC constitutes 10.4% of the cancer burden and they account for 16.1% of cases in males and 4.8% of the cases in females.[1] Tobacco exposure and alcohol dependence are the two main causes of HNCs.[2] Over the past 15 years, the trends have drastically changed with increased incidence of human papilloma virus causing HNCs.[3,4] The majority of HNCs are diagnosed at late stages.[5] Inspite of changes in technology, the diagnosis and management of these tumors are still a challenge. The aim of this study was to describe the modalities of treatment and outcomes in patients with head and neck cancer.

Materials and Methods

This study was a retrospective observational study.

Inclusion Criteria

All newly diagnosed primary head and neck cancer belonging to these sites–oral cavity, oropharynx, hypopharynx, nasopharynx, and larynx between January 2015 and December 2017 were included in the analysis. Cases with primary head and cancer treated during the study period and who developed recurrence or progression during follow-up were recorded. In the cases showing advanced stage of the diseases, treatment received in form of palliative radiotherapy, palliative chemotherapy was also included.

Exclusion Criteria

Those patients who had treatment elsewhere were excluded from the study.

The demographic details of the study population, tumor characteristics, stage (according to American Joint committee on cancer 7th edition), and treatment received were collected from the hospital's medical registry records. All patients were discussed in the institutional Tumor Board meeting (Departments involved were Radiation oncology, Medical Oncology Surgical Oncology, Palliative Care, Pathology and Radiology) and the treatment was decided. Patients treated during the study period and developed recurrence or progression during follow-up were recorded. Primary outcome of the treatment was assessed after 2 months following the completion of treatment with history, clinical examination, imaging (CT scan neck with contrast) and was defined in terms of complete response (CR), partial response (PR), residual disease or static disease. This was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0. The overall outcome of treatment is defined in terms of overall survival (OS) and disease-free survival (DFS). Overall survival is defined as the time from the date of diagnosis of the disease to the date of death of the patient due to any cause. Disease-free survival is defined as the time from the date of completion of treatment to the date of detection of recurrence. The follow-up strategy was for the first year, every 3 months, for the second year every 6 months, and for the third year every 12 months. These follow-ups included assessment of medical history, physical examination (complete head and neck exam; mirror and fiberoptic examination as clinically indicated), imaging (CT scan neck/MRI) done 8 weeks after completion of treatment and then yearly if the patient is symptomatic, and chest X-ray.

Statistical Methods

Sample size was around 400 patients calculated using formula $n = \mathrm{t2} \times p(1-p)/\mathrm{m2}$

Descriptive analysis was performed by evaluating mean and standard deviation for quantitative variables, whereas frequency and proportion were evaluated for categorical variables. Key outcomes included overall survival and disease-free survival. The key explanatory parameters considered for the analysis were the demographic characteristics of the patient such as age, past history of co-morbidities, disease characteristics, and treatment-related parameters. If the data were not available on any particular explanatory parameter they were considered as missing values and were excluded from the analysis while assessing the association of that factor with disease-free survival. The number of proportion of the missing values for each parameter was explicitly mentioned in the descriptive analysis. For survival analysis cases, data lost to follow-up or missing data were censored. Differences between groups in the median overall survival and disease-free survival according to possible explanatory parameters were assessed with log-rank test, and presented with Kaplan–Meier survival plots. A p-value < 0.05 was considered statistically significant. The IBM SPSS version 22 software was used for statistical analysis (IBM Corp.Released 2013. IBM SPSS statistics for windows, Version 22. Armonk, NY:IBM Corp).

Ethics

All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013.The informed consent for this study was waived by the institutional ethics committee, G. Kuppuswamy Naidu Memorial Hospital, Coimbatore, Tamil Nadu as this is a retrospective study. The code for this study was (ECR209/INS/TN2013/RR-19 .dated 28 December 2019).

Results

We included a total of 707 subjects. During the study period of 3 years, the incidence of primary HNC was around 250 per year (35%).

Patient Characteristics

The age of diagnosis ranged from 27 year to 92 years with a median age being 60 years. There was a 1-year-old child diagnosed with rhabdomyosarcoma of the posterior tongue. The disease was more common in men than women (77% versus 22%) with a ratio of 3:1. Over 90% had an ECOG performance status 1 (►**Table 1**).

Approximately 62% of the subjects did not have any associated comorbidities. The most frequent co-morbidities observed were hypertension (21%), diabetes (18.8%), coronary artery disease (6.7%), and asthma (1.56%). Positive serology for significant viral infections at diagnosis included HIV in (four patients), HCV in (two patients) and HBV in (one patient). Among patients with HIV, the most common site of HNC was found to be the oral cavity and oropharynx. A history of smoking or other tobacco use was found in 78% of patients and history of increased alcohol intake was documented in 50%.

Table 1 Details of demographic and clinical parameters

Parameters	Percentage
Age group	
Up to 50	20.79% (147)
51 to 70	59.83% (423)
> 70	19.38% (137)
Smoking/tobacco history	
Yes	77.51% (548)
Alcohol history	
Yes	49.50% (350)
Site	
Oral cavity	40.45% (286)
Oropharynx	23.62% (167)
Hypopharynx	19.94% (141)
Larynx	11.46% (81)
Others	4.52% (32)
Stage grouping	
I	12.73% (90)
II	13.72% (97)
III	18.81% (133)
IVA	50.50% (357)
IVB	4.24% (30)

Tumor Characteristics

The primary tumor site were oral cavity (40%), oropharynx (24%), and hypopharynx (20%). Tongue (40%) was one of the most common subsite in the oral cavity followed by buccal mucosa (32%). In oropharyngeal tumors, the most common site were third posterior part of tongue (45%) and tonsil (19%). Pyriform fossa (73%) was the common sub-site within the hypopharynx, while cancers involving the vocal cords (70%) was the most common subsite within the larynx. Maxillary sinus was the most common PNS involved in six patients with only one patient presenting with ethmoid sinus carcinoma. In this study, 36% of patients presented with T2 disease at the time of diagnosis and cervical lymph nodes involvement was present in 63% of patients.

At the time of diagnosis, metastatic disease was present in 1.4% of patients. Stage IV disease was documented in 50% of patients at diagnosis.

Squamous cell carcinoma was the most common histological type occurring in 87% of patients. The other histological types included verrucous carcinoma (15 patients), adenoid cystic carcinoma (five patients), nasopharyngeal-carcinoma (three patients), and mucoepidermoid-carcinoma (two patients). Rarer histological types included lymphoepithelial carcinoma (one patient), myoepithelial carcinoma (one patient), schwannoma of the pyriform fossa (one patient), and rhabdomyosarcoma of the posterior tongue (one patient). Around 38% of squamous cell carcinomas were graded as moderately differentiated.

Treatment Planned

All 707 patients were discussed in the institutional multidisciplinary tumor board and their treatment was planned. In case of patients with localized, early-stage disease, single modality of treatment in the form of surgery or radiotherapy was suggested. For patients with locally advanced diseases, the treatment was suggested depending on the site, stage, and performance status of the patient. In patients having locally advanced disease, multimodality treatment was used in the form of concurrent chemoradiation (CRT) or surgery, followed by adjuvant treatment in case of operable diseases. In case of metastatic disease at the time of diagnosis palliative treatment in the form of chemotherapy or radiotherapy was suggested.

In our study population, the majority of them had locally advanced disease; so, chemoradiation (CRT) was suggested for 339 patients (48%), only RT alone for 151 patients (21%), and only surgery alone was suggested for 100 patients (14%). Surgery followed by adjuvant treatment was recommended for 74 patients (10%) and neoadjuvant chemotherapy followed by radical local treatment was suggested for 13 patients (2%) (►**Table 2**). Palliative chemotherapy was suggested for five

Table 2 Descriptive analysis of treatment planned in the study population ($N = 707$)

Treatment planned	Frequency	Percentages
RT + CT	339	47.95
RT	151	21.36
Surgery	100	14.14
Surgery→ Adjuvant RT ± CT	74	10.47
NACT→ RT ± CT	13	1.84
Others	30	4.24

patients and palliative RT for bone metastasis was recommended for one patient. In view of advanced disease and poor health palliative care was suggested for 11 patients.

Patterns of Care Received

The type of surgery depended on the site of disease. Most oral cavity cancers were treated with surgery with or without adjuvant treatment. Wide excision and neck dissection were performed in 86% of patients. Extensive surgeries such as laryngectomy, mandibulectomy, and maxillectomy were performed in 20 patients. No postoperative complications were documented in 95% of those patients having surgery. A few complications observed included flap infection (one patient), flap vein thrombosis (one patient) and sepsis in (one patient) (►**Table 3**).

Forty nine percent (198) of patients received concurrent chemoradiation and 21% patients (85) received only RT. A radical dose of 66 Gy was administered in 33 fractions. The conventional dosage schedule was used in 85% of patients, and six patients (1.6%) were treated with a hypo fractionated schedule. Intensity-modulated radiotherapy (IMRT) technique was performed in 99% of patients. The mean RT duration was 6.2 weeks with interruptions occurring in 16% of patients. Most interruptions to radiation therapy occurred during the 5th or 6th week of treatment. The most common reasons for interruption were neutropenia (19%) and sepsis (8%). Death during treatment occurred in five patients (7.9%). During RT, grade II skin reactions were documented in 47% of patients, and grade II mucositis was documented in 70% of patients.

Table 3 Descriptive analysis of pattern of care received in the study population ($N = 405$)

Treatment planned	Frequency	Percentages
RT + CT	198	49
RT	85	21
Surgery	58	14
Surgery→ Adjuvant RT ± CT	48	12
NACT→ RT ± CT	4	1
Others	12	3

Concurrent chemoradiation in 339 patients and neoadjuvant chemotherapy in 13 patients was recommended. Cisplatin (40 mg/m^2) was administered in 222 patients (81%) as weekly concurrent chemotherapy and weekly carboplatin was administered (AUC 2) in 17 patients. Cisplatin (75–100 mg/m^2) given every 3 weeks was used in eight patients. Neoadjuvant chemotherapy was indicated for T4b and N3 nodal disease, TPF regimen was used in seven patients. Interruptions during chemotherapy were found in 45% of subjects. The most common reason for interruption was due to neutropenia in 51.1% of patients. Around three patients developed 5–fluorouracil-induced cardiac complication and one patient developed hypersensitivity to platinum. The most common acute complication of chemotherapy was found to be mouth ulcers occurring in 61.65% of the patients followed by neutropenia in 19% of patients. Palliative chemotherapy was suggested in five patients. The palliative chemotherapy regimen was cisplatin +5-flurouracil and cisplatin and paclitaxel.

Outcomes of Treatment

Among the 707 patients included in the study 405 patients (57%) completed their planned treatment, 244 patients (34.5%) declined treatment, 46 patients (6.5%) did not complete treatment and palliative care was provided to 12 patients (2%). Some of the documented reasons for defaulting in patients included financial constraints or decision to continue treatment at government hospitals (28.6%), followed by neutropenia in 19% of patients. Patients died, i.e., 7.9% (5) during treatment due to various reasons-sepsis (2 patients) febrile neutropenia (2 patients), cardiogenic shock (1 patient). The primary response was assessed 2 months after completion of treatment in 405 patients with clinical examination and imaging including computed tomography. Sixty-nine percent had a complete response to treatment; 22% of patients had residual disease, 6% were lost to follow-up, and 3% had progressive disease. During the course of follow-up. recurrent disease was seen in 15% of patients and 1.5% of patients developed second primary tumor. The majority of recurrences were local (76%) and distant recurrence was documented in 11 patients (24%) including lung in five patients, bone in three patients, pleura in two patients, and mediastinal lymph nodes in one patient. The median follow-up period for this study was 27 months (1 month–54 months).

Survival Analysis

Survival analysis included 463 of the 707 patients who underwent any anticancer treatment. The median overall survival was 42 months (95% CI 34.186–49.814) and the median disease-free survival time was 37 months (95% CI 30.349–43.651). The inter-quartile range was calculated to be of 8.45. Survival was shorter in patients aged > 70 years (OS:28 months, DFS: 27 months) than those aged < 50 years (OS: 45 months, DFS: 43 months).

The median overall survival time according to varying patient age groups was found to be 45 months in 50 years, 42 months in 51 to 70 years, and 28 months in > 70 years. The

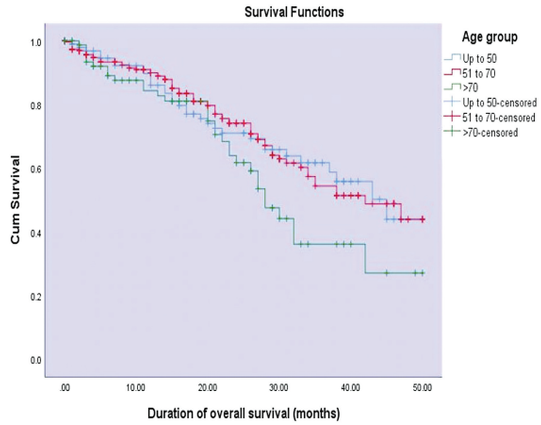

Fig. 1 Kaplan–Meier curves of duration of overall survival (months) across various age groups (p-value = 0.100).

difference in the duration of overall survival distribution and age group groups was discovered to be statistically not significant (►**Fig. 1**).

The median overall survival at the time of diagnosis was found to be 42 months in patients who had stage I and II disease, 45 months in stage III disease, and 37 months in stage IV disease. Similarly, the median DFS was evaluated to be 42 months in early stage I and II disease, 30 months in stage III disease, and 35 months in stage IV disease. Cancers of the hypopharynx and larynx had a median survival of 45 months, followed by 43 months for oral cavity, 33 months for nasopharynx, and unknown primary tumor with neck as the secondary site: 31 months for oropharynx and 28 months for malignancies involving paranasal sinus, ear and nasal cavity (►**Fig. 2**). Similarly, hypopharynx and larynx had median DFS of 42 months followed by 38 months in the oral cavity, 33 months in the nasopharynx, and unknown primary tumor; and 26 months in the oropharynx. Patients treated with CRT had a median survival period of 38 months. Treatment with CRT was associated with a DFS of 31 months compared with other combined modalities, which had a DFS of 33 months.

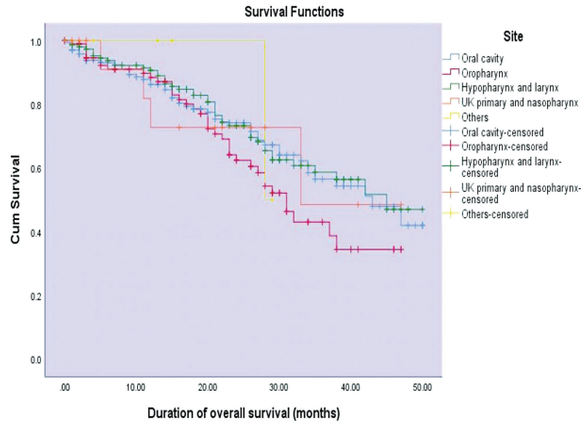

Fig. 2 Kaplan–Meier curves of duration of overall survival (months) across various sites of head and neck (p-value = 0.100).

Discussion

Our institution data on patients diagnosed with head and neck cancer between January 2015 to December 2017 showed that the disease was more common among men with a median age of diagnosis of 60 years. Around 54.7% of patients presented with a stage IV disease at the time of diagnosis. Association with history of smoking or any kind of tobacco use was found in 77.5% of patients in the study. The strong association between tobacco and several HNC has been well established by Wynder et al and several other studies in the literature.[6,7]

A report from south Indian population shows that the trend is emerging showing that there is a definite increase in the number of patients presenting with tongue cancers.[8]

Oral cavity was the most common site involved followed by oropharynx and hypopharynx. Concurrent chemoradiation was the most common modality of treatment used. All patients who underwent treatment were included for survival analysis which showed that median overall survival was 42 months and the median DFS was 37 months. Decreased survival was found in patients more than 70 years of age, with cancers of the oropharynx and having stage IV disease.

This study was a retrospective observational study in which data were collected from a hospital-based cancer registry. Cancer registries are good sources of information on the demographics, tumor characteristics, and stage at diagnosis.[9] Benefit of any treatment in oncology can be defined in two ways-the patient either live longer (OS) or live better (q uality of life). OS is a universally accepted measure of benefit and is the most commonly used measure.[10] Because we wanted to compare the outcomes of the different patterns of treatment in our institute, overall survival was considered as the primary end point. Disease-free survival is a surrogate end point and is most commonly used to assess the benefit of adjuvant treatment.

However, with improvements in modern radiation techniques, the intent of treatment in HNC has been more inclined toward cure with functional preservation. This could explain why CRT was the major modality of treatment preferred for locally advanced HNC in our study population. More than 50% of the study population presented with stage IV disease at the time of diagnosis. Similar presentations were found in the retrospective study performed by Roy et al.[11] The outcomes and epidemiology of HNC were evaluated from a cancer registry, and it was found that 49% of the study population had stage IV disease at the time of presentation.[12] This can be attributed to illiteracy and lack of awareness among the general population regarding the disease. In developing countries such as India, the majority of the people presented with advanced disease at the time of diagnosis. Therefore, HNC in developing countries contribute to a significant mortality and morbidity.[13]

In our study, the primary response was assessed 2 months after completion of treatment in 405 patients. It showed that 69.3% of patients had a complete response to treatment;22.2% had residual disease, 2.7% had a progressive disease, and 5.6% were lost to follow-up. Steinbichler et al in Austria performed a study on persistent disease following

first line treatment in HNC. Out of the 741 patients studied, 76% had complete response to treatment, 24% had persistent or residual disease.[14]

Out of the 707 patients, survival analysis was performed for 463 patients who underwent treatment at our center. The median overall survival was evaluated to be 42 months and the median disease-free survival time was evaluated to be 37 months. The median overall survival and disease-free survival were found to be decreased in patients of age $>$ 70 years (OS-28 months, DFS-27 months) when compared with those $<$ 50 years (OS-45 months, DFS-43 months). However, this difference was not found to be statistically significant.

Both median OS and DFS were found to be decreased in cancers of oropharynx when compared with cancers of the oral cavity, hypopharynx, and larynx. In our study, laryngeal cancers are found to have better survival when compared with other sites. These results were in accordance with study by Cadoni et al and Kambiz et al, where the median survival time was higher for laryngeal cancers and reduced survival was associated with increasing age of diagnosis and advanced tumor stage.[15,16] In both of these studies, the 4-year overall survival for all HNC sites was around 60%. Cancers involving nasal cavities, paranasal sinuses, and ears had very poor survival rate. HPV positivity was more commonly found in oropharyngeal cancers among non-smokers.[17,18] HPV 16 positivity was associated with an increased risk of HNC, especially oropharyngeal cancers.[19] Future studies should include HPV data to observe its impact on the multimodality treatment.

In our center, single modality of treatment was recommended for early-stage localized diseases. Multimodality of treatment including surgery, chemotherapy, and radiation therapy had a slightly better survival than CRT. However, this difference was not statistically significant.

Accelerated radiation and hypofractionation are effective methods of increasing therapeutic benefits of radiation. A meta-analysis on the role of chemotherapy in HNC (MACH-NC) showed that hypofractionated RT with concurrent chemotherapy was the best modality.[20]

Latest update of (MACH-NC) is that overall survival was not increased by addition of induction or adjuvant chemotherapy. Efficacy of induction chemotherapy decreases with poorer performance status.

It has been shown that hypofractionated RT can achieve similar tumor response to conventional fractionated RT in HNC although with some increased toxicity.[21]

·Similarly, randomized RTOG trials showed hyperfractionated RT had better local control and overall survival compared with conventional fractionation in HNC.[22,23]

The strength of the study was the number of patients, data being collected from a hospital-based cancer registry, treatment of all patients being decided by a multidisciplinary team of medical professionals.

Limitations

The maximum duration of follow-up observed in our study was only 50 months and the last patient recruited was in December 2017. Due to limitations in time and resources, a 3-year or 5-year survival analysis could not be performed. This would have given us more scientific and meaningful conclusions on the outcomes of HNC.

In this study, we have not assessed the HPV status. Recently, we started testing HPV status for all oropharyngeal cancers for its future potential implications. We are also planning for clinical trials including dose escalation strategies in locally advanced head and neck cancer particularly in non-responders.

Conclusion

In our study, most patients presented with locally advanced disease. Multimodality treatment yields better results. Based on our study in early-stage cancer where single modality treatment was used, adjuvant therapy should be tailored based on nomogram.

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None.

Conflict of Interest
None declared.

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Granulocyte Transfusion Therapy: Institutional Experience of Benefit in Cancer Patients with Prolonged Neutropenic Sepsis—A Retrospective Study

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Abstract

Introduction Patients undergoing intensive chemotherapy for hematological malignancy and stem cell transplantation are at increased risk of neutropenia.

Neutropenia is among the frequent side effects of intensive treatments, and when absolute neutrophil count (ANC) falls $< 500/\mu L$, the risk of microbial and fungal infection increases significantly.

As neutropenia is the main cause of these infections, transfusion of granulocyte immediately as a replacement is a life-saving therapeutic option to support these patients by restoring neutrophil counts and aiding in the resolution of infection.

Objective The present study is a retrospective single institutional analysis of granulocyte transfusion therapy in children and young adults with cancer who received treatment with GT during prolonged and profound life threatening neutropenia.

Materials and Methods This study was a retrospective analysis of 66 granulocyte transfusions in 36 patients of hematological and solid malignancy with severe and prolonged neutropenia in the department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences Indore, between September 2019 and March 2022.

Donors were either patients' relatives or voluntary donors without comorbidities.

All granulocyte concentrates were collected by centrifugation leukapheresis and irradiated with 2500 centigray and immediately transfused in full, to the patient over 60 ot 120 minutes with appropriate premedication.

Results A total of 36 patients (M:F, 19:17) with a median age of 16 years (2–43) received 66 granulocyte transfusions. The diagnosis of patients included acute myelogenous leukemia ($n = 17$), B cell acute lymphoblastic leukemia ($n = 10$), non-Hodgkin lymphoma ($n = 3$), Ewing's sarcoma ($n = 2$), neuroblastoma ($n = 1$), malignant melanoma ($n = 1$), aplastic anemia ($n = 1$), osteosarcoma ($n = 1$). All had severe neutropenia with absolute neutrophil count $< 0.5 \times 10^9/L$. The median duration of

Keywords
- cancer
- granulocyte transfusion
- neutropenia

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severe neutropenia was 16 days. Patients received a median cell dose of granulocytes 2.9×10^{10}/L. A favorable response was seen in 28 (78%) patients, whereas an unfavorable response was seen in 8 patients (23%).

Conclusion A granulocyte therapy was effective in many critically sick patients with prolonged and profound neutropenia. Granulocyte transfusions may be more beneficial in selected patients where it provides more time to overcome refractory infections with broad-spectrum antibiotics. Granulocyte transfusion are at best a "bridge" that gives time to marrow recovery. The challenges to using GT are clinical, finding patients who may get benefitted, and logistical, selection of donors and harvest technique. Randomized trials with large numbers of patients are required to prepare guidelines for granulocyte use.

Introduction

Patients received aggressive chemotherapy for hematological malignancy and stem cell transplantation are at higher risk of neutropenia.

Bacteria, viruses, and fungi are the main complication-producing agents in most patients with profound and prolonged treatment related to neutropenia despite newer antimicrobials and antifungals.

Neutropenia is among the common side effects of intensive treatments, and when absolute neutrophil count (ANC) falls < 500/µL (Grade IV neutropenia), the risk of microbial and fungal infection increases significantly.

As of now, bacterial and fungal infections such as *Aspergillus* and *Fusarium* in patients with neutropenia have increased and eventually morbidity and mortality rates.[1]

Improvement in the overall general and intensified care in oncology units with the use of newer and effective broad-spectrum antimicrobial and antifungal drugs resulted in significantly better survival.

Irrational prescription of higher antimicrobial and antifungal without checking the sensitivity has led to the development of resistance to these drugs across India and due to this, dreaded infections do not respond as needed.[2]

As neutropenia is the main cause of these infections, transfusion of granulocyte immediately as a replacement is a life-saving therapeutic option to support these patients by restoring neutrophil counts and aiding in the resolution of infection.

Granulocyte transfusion (GT) therapy was conceptualized in the 1960s, and many studies have shown that it is a useful supportive therapy in the case of neutropenia.[3–6]

Granulocytes transfusion used for prophylactic therapy with antimicrobials in patients who received intensive chemotherapy and developed severe neutropenia.[5,7–9]

The present study was a retrospective single institutional analysis of granulocyte transfusion therapy in children and young adults with cancer who received treatment with GT during prolonged and profound life-threatening neutropenia.

Materials and Methods

This study was a retrospective analysis of all patients who received granulocyte transfusions between September 2019 and March 2022 in the Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences Indore, India.

Granulocyte transfusion (GT) therapy was prescribed in all patients with (1) absolute neutrophil count (ANC) < 500 cells/µL, (2) evidence of bacterial or fungal infection (i.e., clinical presentation, positive cultures, biopsy, or radiological evidence), and (3) lack of response to the recently introduced antimicrobials for 48 hours.

After granulocyte transfusions, we monitored ANC until recovery to > 500/µL. No fever in more than 48 hours, symptomatic relief, and negative cultures with radiological absence of infection were considered as a response. A tandem GT was given to nonresponders.

Donors were either patients' relatives or voluntary donors without comorbidities and blood group incompatibility with the patient. After informed consent, screened donors received subcutaneous colony-stimulating growth factor (G-CSF) 10 µg/kg with injection dexamethasone 8 mg and were taken for granulocyte harvest after 10 to 12 hours via peripheral vascular access by centrifugation leukapheresis using the Fresenius COM TEC system. All harvest volume was irradiation with 2500 centigray and transfused to the patient over 60 to 120 minutes after appropriate premedication.

Statistical Analysis

The data were collected in an Excel sheet and statistical analysis was performed using SPSS, version 23.0. Considering the nature of the study, no formal sample size was employed. Categorical variables are presented as numbers and percentages, whereas continuous variables are expressed as median and range.

Ethics

This study was conducted in accordance with the ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practices, and the applicable legislation on non-interventional studies. The study protocol was approved by the institutional ethics committee (IEC no. SAIMS/IEC/2022/11). Informed consent was waivered due to the retrospective nature of the study.

Table 1 Clinical characteristics of patients received granulocyte transfusion therapy

Characteristics of patients	
Number of patients	36
Age (y), median. ange	16 (2–43)
Sex	
Male	19 (53%)
Female	17 (47%)
Underlying disease, *n*	
Acute myelogenous leukemia	17
B-cell acute lymphoblastic leukemia	10
Non-Hodgkin lymphoma	3
Ewing's sarcoma	2
Neuroblastoma	1
Aplastic anemia	1
Malignant melanoma	1
Osteosarcoma	1
Severe neutropenia (ANC $< 0.5 \times 10^9$/μL), *n*	36/36
Duration of neutropenia, days, median (range)	16 (7–24)
G-CSF treatment used before granulocyte therapy	36/36
Systemic treatment with antimicrobial before granulocyte, *n*	36/36
Systemic treatment with antifungal before granulocyte, *n*	36/36
Granulocyte cell dose received, median (range), *n*	2.9×10^{10}/L (2.0×10^{10}/L–4.8×10^{10}/L)
Days to neutrophil recovery, median (range) *n*	9 (3–19)
Adverse effect	1/66

Results

A total of 36 patients (M:F, 19:17) with a median age of 16 years (2–43) received 66 granulocyte transfusions. The disease-wise distribution were acute myelogenous leukemia ($n = 17$), B cell acute lymphoblastic leukemia ($n = 10$), non-Hodgkin lymphoma ($n = 3$), Ewing's sarcoma ($n = 2$), neuroblastoma ($n = 1$), malignant melanoma ($n = 1$), aplastic anemia ($n = 1$), osteosarcoma ($n = 1$). All had severe neutropenia with absolute neutrophil count $< 0.5 \times 10^9$/L. The median duration of severe neutropenia was 16 days (7–24 days). Granulocyte transfusion therapy was prescribed in patients because of persistent neutropenic fever with pneumonia ($n = 18$), soft tissue infections ($n = 8$), neutropenic enterocolitis ($n = 7$), and deterioration in condition despite granulocyte colony-stimulating factor (G-CSF), broad-spectrum antimicrobial therapy and antifungal therapy. GT was given until ANC $> 0.5 \times 10^9$/L. Patients received a median cell dose of granulocytes 2.9×10^{10}/L (range 2.0×10^{10}/L–4.8×10^{10}/L). A favorable response was seen in 28 (78%) patients in terms of early recovery from neutropenia and resolution of infections. The median time to neutrophil count recovery was 9 days (3–19 days), whereas 8 patients (23%) showed poor response, who succumbed to infections. GT were tolerated by all patients except for transfusion-associated acute lung injury (TRALI) in one patient who succumbed despite all intensive care in the hospital. The clinical characteristics of patients who received granulocyte transfusion therapy are shown in ►**Table 1**.

In all 36 patients, post chemotherapy neutropenia was developed, including one post autologous stem cell transplantation. Microbiologically documented infections were seen in 35 patients (97%). Nine patients developed invasive fungal infections and 29 bacterial infections. The infection profile and culture positivity are shown in ►**Table 2**.

All patients received ongoing antimicrobial and systemic antifungal therapy before and during GT treatment. All 66 donors tolerated apheresis well with no adverse effects.

Table 2 Infection profile/cultures in patients

Infection agent	Number of positive cultures
Acinetobacter	1
Klebsiella	17
Pseudomonas	7
Escherichia coli	1
MRSA	3
Candida, mucormycosis	9
Total	38

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3 Granulocyte donor characteristics

Donor characteristic	Number	Median
Number of donors	66	
Donor pre leukapheresis WBC counts, median (range)		3.17×10^{10}/L (2.19×10^{10}/L–4.49×10^{10}/L)
Adverse effects in donor	0/66	

Abbreviation: WBC, white blood cell.

Median pre leukapheresis WBC counts were 3.17×10^{10}/L (2.19×10^{10}/L– 4.49×10^{10} /L). Granulocyte donor characteristics are shown in ►**Table 3**.

Discussion

Transfusion of granulocytes is an efficacious therapy to fight severe life-threatening bacterial and fungal infections in patients with neutropenia.

Donor injection of colony-stimulating growth factor (G-CSF) with dexamethasone mobilizes granulocytes into the peripheral blood from the marrow, increasing the granulocyte count in 2 to 12 hours.[10] Collection of up to 5 to 10×10^{10}/L granulocytes in one session became possible.[11–13]

Large granulocyte doses raise ANC in patients with neutropenia.[14]

After G-CSF administration, increased neutrophils accumulate at the location of inflammation or infection and help in getting rid of infection.[15]

Lee et al[16] reported G-CSF with dexamethasone was better as compared with dexamethasone alone in mobilizing granulocyte from the bone marrow to peripheral blood to increase harvest volume.

Drewnian et al[17] described that due to upregulation of Toll-like receptors after G-CSF and dexamethasone, donor cells secrete IL-8, which helps in controlling microbial infections.

Progressive infection in neutropenic patients not responding to antimicrobial and antifungal within 48 hours, granulocyte transfusions have been recommended to raise ANC promptly to faster recovery. The therapeutic dose of granulocyte and its efficacy is still controversial. Next, 2–3×10^{10}/kg is the minimum granulocyte dose needed to increase ANC and transfusions are given until the absolute neutrophil counts become more than 500/μL and/or until the resolution of infection.[18,19]

The Resolving Infection in Neutropenia with Granulocytes (RING) trial[20] concluded that patients who received granulocytes dose $> 0.6 \times 10^9$/kg reported improved survival at 42 days as compared with patients who received a dose $< 0.6 \times 10^9$/kg. The median granulocyte dose received by our patients was 2.9×10^{10}/kg equivalent to the above studies.

Nikolajeva et al[21] reported a decrease infection-associated death in patients who received a median cell count of 1.5 to 3.0×10^8 granulocytes/kg.

Garg et al[22] reported that an increase in the total leucocyte count 6 hours after a high dose of 10×10^8/kg of GT did not affect the survival at 30 days.

Grigull et al[7] and Seidel et al[23] reported that granulocyte transfusion is feasible and safe in controlling the treatment of refractory bacterial infection and decreasing mortality.

Atay et al[24] analyzed 35 pediatric patients who had 111 granulocyte transfusions in view of the increased risk of neutropenia, reported 82.4% infection-related survival of 82.4% and overall survival (OS) of 77% at day 30.

Garg et al[22] and Zhou et al[25] showed that granulocyte therapy is useful in managing severe infections due to neutropenia in patients with hematological disorders or undergoing hematopoietic stem cell transplantation (HSCT) along with more benefits in patients having respiratory system infections (80%) in comparison to bloodstream infection group (58.3%) and skin or mucous infection group (20%).

In accordance with other studies, our study showed that 28/36 (78%) patients responded to granulocyte transfusions, recovered from life-threatening infections; however, 15/28 (54%) patients died on account of the progression of their disease. Also, 8/36 (22%) of our patients showed a transient response but eventually died; only one death was due to a post GT pulmonary event.

Lee et al reported benefits of GT in gram-negative bacterial and resistant infections as compared with infections with gram-positive organisms. The difference in response is possibly due to an early uptake with persistent retention of neutrophils at gram-negative infection sites, whereas there is no increase in neutrophil uptake at gram positive infection sites.[16]

The common etiology for sepsis was gram-negative organisms at our institute.

The effectiveness of granulocyte transfusions is determined by their starting time. Early transfusion during sepsis increases the chances of survival by preventing the onset of multiorgan damage. Sachs et al showed a 92.6% overall response to early GT and a better toxicity profile. Uppuluri et al[2] reported early administration of granulocyte within 48 hours of a septic episode resulting in significant improvement in the overall survival (41% to 54%).

Garg et al[22] reported that GT within 7 days of neutropenic sepsis leads to significantly higher overall survival in patients ($p = 0.01$).

The modest survival in our study is probably due to a delay in starting GT, difficulty in finding donors, and lesser affordability.

Tandem granulocyte transfusions in neutropenic patients are effective. Seidel et al[23] reported repeated transfusion of granulocytes for 5 days with a minimum of 3×10^8/kg neutrophils/concentrate, stabilized ANC, reduced the neutropenic duration, and increased infection control.

In our study, all 8 patients who had received a single transfusion of granulocytes died.

Price et al[14] and Adkins et al[26] reported GT was well tolerated and the incidence of serious adverse events in recipients was uncommon. Chills and rigor were frequent side effects in recipients of granulocytes.

Other reported adverse events of GT are transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-associated dyspnea, hypotension, post-transfusion purpura, transfusion-transmitted infection, and risk of alloimmunization. At our center, all granulocyte collections were irradiated before transfusion to decrease the chance of alloimmunization.

Conclusion

A granulocyte therapy was effective in many critically sick patients with prolonged and profound neutropenia. Granulocyte transfusions may be more beneficial in selected patients where it provides more time to overcome refractory infections to broad-spectrum antibiotics. Granulocyte transfusion are at best a "bridge" that gives time to marrow recovery. The challenges to using GT are clinical, finding patients who may get benefitted, and logistical; selection of donors and harvest technique. Randomized trials with large numbers of patients are required to prepare guidelines for granulocyte use.

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None.

Conflict of Interest
None declared.

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Gestational Choriocarcinoma Manifesting as Spontaneous Hemothorax in Third Trimester of Pregnancy: A Case Report

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Abstract

Gestational trophoblastic neoplasia (GTN) is an aggressive malignancy arising from the trophoblastic tissue. It is rarely seen in association with advanced intrauterine pregnancy. Most common manifestations are due to bleeding caused by the rich vascularity of trophoblastic tissue. We describe here a case of a 28-year-old female patient who presented to us at 32 weeks of pregnancy with sudden onset dyspnea and hemodynamic instability. On evaluation, imaging techniques revealed a gross left hemothorax requiring intercostal tube insertion for stabilization. Emergency thoracotomy and hemothorax drainage were performed wherein a tumor mass in the lower lobe of left lung was identified and resected. Histopathological examination confirmed the diagnosis of choriocarcinoma. Beta HCG levels were found to be elevated. Final diagnosis of a FIGO stage IV high-risk gestational choriocarcinoma was made. Following this, six cycles of multi-agent EMA-CO chemotherapy was administered to the patient. Patient had an excellent response to treatment with documented serial fall in β HCG levels and she continues to be in remission after 6 months of follow-up. In conclusion, in the circumstance of any pregnant women presenting with abnormal bleeding symptoms such as hemothorax, choriocarcinoma as a cause should be considered for early diagnosis and effective management.

Keywords
- gestational choriocarcinoma
- hemothorax
- pregnancy

Introduction

Gestational trophoblastic neoplasia (GTN) represents a spectrum of proliferative abnormalities of trophoblasts associated with pregnancy.[1] Choriocarcinoma is a highly aggressive form of gestational trophoblastic disease presenting with early distant metastasis due to high metastatic potential.[2] Although molar pregnancies are most commonly associated with choriocarcinoma, 25% of cases follow previous abortions, while 22.5% arise in normal pregnancy, and 2.5% are subsequent to ectopic pregnancy. All cases are associated with elevated β human chorionic gonadotrophin (HCG) levels.[3]

While choriocarcinoma generally presents with gynecological manifestations such as vaginal bleeding, as many as

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one-third of the patients can manifest with only non-gynecological symptoms due to metastases to various sites.[4] Favored sites of metastases are lungs (80%), followed by vagina (30%), brain (10%), and liver (10%).[2] Abnormal bleeding at these locations could be the primary presentation due to the rich vascularity of lesions at these sites.[5] Pulmonary metastatic choriocarcinoma mainly presents with hemoptysis, dyspnea, pleuritic pain, and cough[6]; pleural effusion or non-traumatic hemothorax being rare manifestations.[7] Metastatic gestational choriocarcinoma presenting in a normal intrauterine pregnancy is exceptionally rare and is assigned a higher World Health Organization (WHO) score with historically high maternal and fetal mortality.[8] Herein, we report a rare case of spontaneous hemothorax in the third trimester of pregnancy leading to a diagnosis of choriocarcinoma.

Case Presentation

A 28-year-old housewife presented at 32 weeks of gestation to the institution with 2-day history of progressive dyspnea and reduced fetal movements. She was triaged as G2P1L1 with a 3-year-old female child and present spontaneous conception. Her first and second trimesters were uneventful. She developed mild breathlessness and discomfort 2 days ago, which subsided on their own, however, were aggravated on the morning of day of admission. She had no significant medical or family history.

Patient was irritable and tachypneic with signs of tachycardia and hypoxia. Clinical examination was significant for reduced breath sounds in the left hemithorax. A chest X-ray showed a massive pleural effusion in the left lung. A subsequent CT scan of the thorax revealed gross left hemothorax with internal organized hyperdense content causing a contralateral shift of mediastinum and compression of the left lung. A few focal small hyperdense organized hematomas were also observed along the left diaphragmatic pleura. Another small hypodense lesion with peripheral eccentric nodular enhancement in collapsed left lower lobe was suspected of being a capillary hemangioma (►**Fig. 1A**). An intercostal drainage tube was placed to decompress the left hemithorax. She had severe anemia requiring multiple blood transfusions. The obstetric ultrasonogram showed a single intrauterine fetal demise (IUD) of 33 weeks 4 days gestation with a normal placenta.

An emergency thoracotomy and hemothorax drainage with clot removal were performed. A mass in the lower lobe of the left lung (►**Fig. 1B**) and another vascular mass in the apex of chest wall were identified. Wedge resection of the former site and sclerotherapy of the latter site were performed. The patient also underwent a lower segment cesarean section and a 2.2 kg preterm IUD fetus was delivered. The placental examination did not reveal any abnormality. The histopathological examination of the lung mass was suggestive of a poorly differentiated malignant tumor compatible with choriocarcinoma (►**Fig. 1C**). These tumor cells showed positive immunohistochemical (IHC) staining for PANCK (pan cytokeratin) and β HCG suggestive of choriocarcinoma (►**Fig. 1D**). Serum β HCG level was reported to be 25,600 mIU/mL and α fetoprotein level was found to be 5.3 ng/mL clinching the diagnosis of metastatic gestational choriocarcinoma.

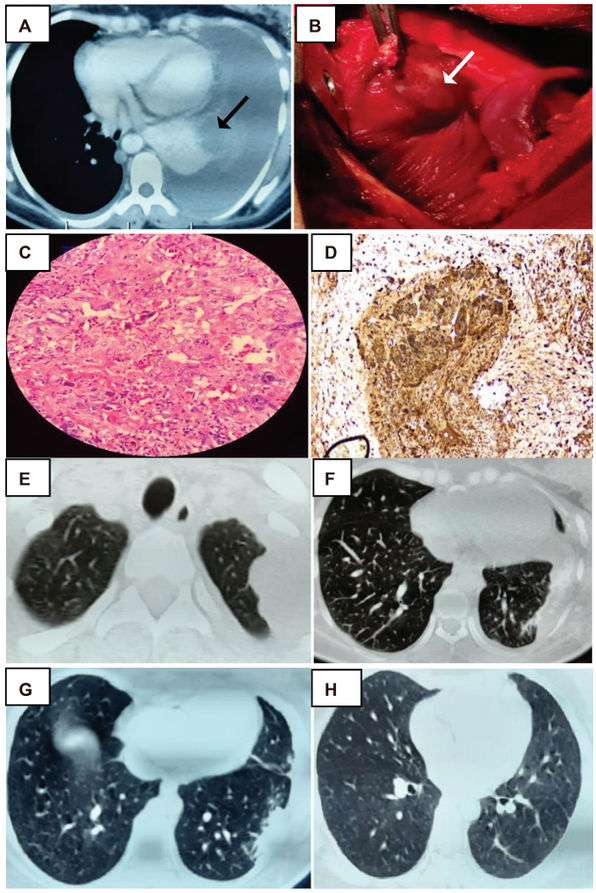

Fig. 1 CT thorax showing hemothorax, lesion in left lower lobe (black arrow). (**A**). Intraoperative lung mass (white arrow). (**B**) Syncitiotrophoblast surrounded by cytotrophoblast in biopsy and IHC positive for β HCG;. (**C and D**) Post-surgery CT thorax - residual lesions in the left upper and lower lobe. (**E and F**) CT thorax post treatment with soft calcified nodule over left upper lobe and normal lower lobe (**G and H**).

Follow-up CT imaging of the thorax showed residual pleural-based lesions in apical segment of the left upper and lower lobes of the lungs (►**Figs. 1E** and **1F**). An observation of left pleural minimal-organized hemothorax was also noted. CT scans of the abdomen and pelvis confirmed a bulky uterus with enhancing submucosal vasculature suggestive of post cesarean changes. MRI scan of the brain did not reveal any metastases.

A diagnosis of stage IV high-risk choriocarcinoma based on the International Federation of Gynecology and Obstetrics (FIGO) system was made. The WHO score was declared as 10 [antecedent pregnancy (2), HCG (2), site (4), number of metastases (1), size (1)]. The patient was started on chemotherapy that consisted of six cycles of intravenous EMA-CO protocol (etoposide 100 mg/m^2, methotrexate 100 mg/m^2 bolus, and 200 mg/m^2 infusion over 12 hours and actinomycin D 0.5 mg on first day; etoposide 100 mg/m^2, actinomycin D 0.5 mg on the second day with four doses of 15 mg folinic

Table 1 Chronological trend of β HCG levels (mIU/mL)

Date	Beta HCG (mIU/mL)
17/03/2021	25,600
31/03/2021	91,900
29/04/2021	1335
21/05/2021	23.66
25/06/2021	0.730
21/09/2021	0.187
19/10/2021	<0.100
09/11/2021	<0.100
16/02/2022	<0.100

acid rescue every 12 hours from 24 hours after beginning of methotrexate; cyclophosphamide 600 mg/m^2 and vincristine 1 mg/m^2 on the eighth day and intrathecal methotrexate 12.5 mg) delivered every three weekly for all cycles.

There was remarkable response to chemotherapy in the form of shrinkage of metastatic foci and dramatic decline of serum β HCG to below-detectable levels. Post-therapy CT scan revealed a small nodule over the upper lobe of left lung with soft calcification (►**Fig. 1G** and **1H**). The patient is currently on follow-up after 6 months and doing well with normal serum β HCG values (►**Table 1**).

Discussion

In the developed world, the incidence of gestational choriocarcinoma is estimated to be ~1 in 40,000 pregnancies; being much lower (1 in 160,000 pregnancies) in the setting of a viable gestation.[9] In Asia, Africa, and Latin America, this ratio is reported to be 1 per 500 to 1,000 pregnancies.[10] Malignant potential of the disease is also reported to be higher in Southeast Asia, which is 10 to 15% compared with 2 to 4% in the West.[11]

In our patient, spontaneous hemothorax occurred simultaneously with a third trimester intrauterine pregnancy presenting a diagnostic dilemma. This diagnosis is exceptionally rare and has a poor maternal and fetal prognosis. Worldwide literature review of cases by Steigrad et al could identify a total of 36 cases of gestational choriocarcinoma coexisting with a normal intrauterine pregnancy in the 20th century. Both mother and fetus survived in only 25% of the cases.[8] Our patient was initially suspected to have a vascular cause for the hemothorax such as capillary hemangioma and underwent thoracotomy. Hemothorax may be a result of vascular invasion by trophoblastic emboli causing pulmonary infarction or due to direct involvement of pleura.[7] In this case, hemothorax may be attributed to the rupture of the metastatic lung nodule as well as bleeding from the pleural-based lesion.

Trophoblastic tumors are usually perfused by fragile vessels. Trophoblastic cells have the innate capacity to invade and erode the capillary vessel wall leading to hemorrhage.[12] Conversion of normal trophoblast cells in the current gestation, transformation of residual trophoblast tissue from a previous pregnancy or conversion of one of the products of conception in a multiple fetal pregnancy are some of the theories postulated to explain choriocarcinoma in an ongoing viable pregnancy.[4] Also, the placental examination and pelvic imaging in our patient did not reveal any primary focus of choriocarcinoma. The lack of primary focus may be explained by persistence of metastatic foci despite spontaneous regression of the primary tumor; resurrection and malignant change of trophoblastic cells present in the extrauterine vessels under stimulation of endocrine factors during the current pregnancy; and intra-placental choriocarcinomas having more minute microscopic foci without overt macroscopic presentation that are not picked up on pathological examination.[4] Regrettably, the diagnosis of choriocarcinoma as the cause of hemothorax was established only after thoracotomy and histopathological examination of the metastatic tissue, which prompted the measurement of serum β HCG levels leading to a considerable delay in initiation of chemotherapy from the presentation.

Successful outcome of a pregnancy in gestational choriocarcinoma presenting after 24 weeks of pregnancy have been documented in a few case reports.[4,5,13,14] While most cases of hemothorax associated with choriocarcinoma have been in the setting of prior history of abortion or amenorrhea[15–20]; very few instances of spontaneous hemothorax with advanced intrauterine pregnancy have been reported. Sudduth described an occurrence of bilateral hemothoraces due to choriocarcinoma in a woman presenting at 32 weeks of amenorrhea wherein a healthy male infant was delivered.[14] Our patient unfortunately had an intrauterine fetal demise at presentation. Massive bleeding within the pleural cavity and delayed presentation could be one of the reasons for fetal demise. This emphasizes the importance of considering choriocarcinoma as a possibility in any pregnant woman presenting with the rare scenario of spontaneous hemothorax for establishing early diagnosis and initiation of appropriate therapy for a better maternal and fetal outcome.

Despite presenting with metastasis, choriocarcinoma is a highly chemotherapy sensitive tumor. The stage and risk score of the disease at the time of diagnosis determine the chemotherapy regimen used. The FIGO staging system identifies four stages based on the extent of the disease, whereas the WHO prognostic scoring system gives a numerical score on the basis of the patient and tumor characteristics.[21] Our patient was high risk in view of antecedent pregnancy and pleural metastasis.

Low-risk groups with FIGO stage I or stage II and III with a WHO risk score below 7 are treated with single-agent chemotherapy regimen (methotrexate or actinomycin D) to obtain maximum remission rates with less toxicity.[22] However, high-risk patients (FIGO stage IV or stage II and III with a WHO risk score over 6) require first-line multiagent chemotherapy regime in view of risk of resistance to single-agent chemotherapy. The combination of the drugs etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA-CO) is the regimen of choice.[23]

Complete remission rate in low-risk groups is nearly 80% after single-agent chemotherapy with an overall survival rate of almost 100% with multi-agent therapy and recurrence rates are less than 5%. While 85% of stage II and 75% of stage III patients attain full remission after front-line multi-agent chemotherapy, overall cure rates reach 95 to 100% after secondary therapy. In stage IV groups, up to 80% of patients are ultimately cured with intensive multi-agent therapy and radiation or surgical adjuvant therapy when needed. Depending on the initial stage, recurrence rates vary between 8 and 10%.[24] Chemotherapy is continued until HCG values have normalized followed by at least two to three courses of consolidation chemotherapy for the purpose of eradicating all viable tumors.[21]

Patients failing the EMA-CO regimen are mostly salvaged with paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or with EP/EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D). For women failing EP/EMA or TE/TP, options include high-dose chemotherapy (HDC) regimens with autologous peripheral stem cell support and immunotherapy.[21] A recent retrospective analysis reported remission rates of 41% with HDC and peripheral stem cell support. An HCG level $>$ 12 IU/L before or after HDC, stages II–IV, and presence of metastases were all associated with adverse survival outcomes. However, HDC was associated with significant toxicity with a procedure mortality in 3 out of 32 patients.[25]

GTN tissue constitutively and strongly expresses programmed cell death ligand 1 (PD-L1).[26] The significant advances in immunotherapy in recent years has led to the use of immune checkpoint inhibitors in GTN. The PD-1 (programmed cell death 1) inhibitor drug pembrolizumab has demonstrated efficacy in a few cases of unresectable, chemo-resistant GTN.[27,28] The PD-L1 inhibitor avelumab has also shown efficacy in GTN, inducing complete serological response in $\sim$53% of patients who had previously received single-agent methotrexate or actinomycin-D. One patient subsequently had a normal pregnancy as well.[29] Anti-PD-1/anti-PD-L1 treatment is generally tolerated well with minimal toxicity as reported in majority of patients. It presents a much less toxic alternative to HDC with autologous stem cell transplantation.[28]

All patients require post-treatment surveillance through checking for β HCG levels for detection of recurrences. After HCG value is normalized, serial determinations of HCG levels are continued at 2-week intervals during the first 3 months of remission and then at monthly intervals for at least 12 months.[30]

Conclusion

Spontaneous hemothorax is a life-threatening emergency. It can be one of the rare presentations of metastatic gestational choriocarcinoma in the setting of a current pregnancy. Our case emphasizes the need for a strong clinical suspicion in any pregnant woman presenting with abnormal bleeding symptoms such as hemothorax despite the absence of a detectable primary focus of choriocarcinoma. This is to ensure early diagnosis and management of this chemosensitive tumor.

Declaration of Patient Consent

Informed consent of the patient was acquired.

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Conflict of Interest

None declared.

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Relapsed Plasmablastic Lymphoma in an HIV-Infected Patient—Experience of High-Dose Chemotherapy with Autologous Stem Cell Rescue: A Case Report with Review of Literature

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Abstract

Plasmablastic lymphoma (PBL) is a subtype of non-Hodgkin lymphoma with dismal outcome despite multidrug chemotherapy regimen leading to high rates of disease recurrence. High-dose chemotherapy with autologous stem cell rescue (HDCT/ASCR) is an effective salvage therapy in patients with chemo-sensitive human immunodeficiency virus (HIV)-associated non-Hodgkin lymphoma. We report a case of 38 years old male with relapsed PBL associated with underlying HIV infection, who underwent HDCT/ASCR. He presented with low-grade fever and abdominal discomfort. He was evaluated with fluorodeoxyglucose positron emission tomography scan followed by omental biopsy that confirmed disease relapse. He received second-line therapy containing bortezomib and daratumumab and achieved remission (CR2). Subsequently, he underwent HDCT/ASCR. He has been clinically asymptomatic in good general condition having disease-free survival of 18 months after HDCT/ASCR. Our objective of presenting this case report is its complexity from presentation, diagnosis, and treatment. We take this opportunity to review the epidemiology and clinicopathological characteristics of PBL, as well as discuss the advancements in therapeutic options of this challenging disease.

Keywords

- plasmablastic lymphoma
- HIV infection
- combined antiretroviral therapy
- autologous stem cell transplant

Introduction

Plasmablastic lymphoma (PBL) is a variant of non-Hodgkin lymphoma with an aggressive biology. The management of this disease poses both diagnostic and therapeutic challenges in view of distinctive morphology, immunohistochemistry profile, and atypical clinical presentation along with the lack of standard treatment in the upfront and relapse settings. This leads to high rates of disease relapse and subsequent high mortality.[1] The prognosis remains poor due to early relapse and resistance to conventional cytotoxic agents from cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)-like regimen. There have been case reports where prolonged remission has been achieved with multiple myeloma-like

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treatment.[2] Retrospective analysis from large phase 2 trials, single-center experiences, and case reports have shown the benefit of high-dose chemotherapy with autologous stem cell rescue (HDCT/ASCR) in human immunodeficiency virus (HIV)-positive patients with relapsed non-Hodgkin lymphoma.[3] The prognosis of PBL in relapse setting is poor and there may be benefit of early HDCT/ASCR in the course of disease especially in high-risk subtypes. To achieve better outcome, we need to explore the role of HDCT/ASCR after achieving first remission (CR1) and in relapse setting in the case of HIV-positive patients with PBL.

Case Report

Our patient was diagnosed with HIV infection in 2012, followed by disseminated tuberculosis 2 years later that had presented as bilateral psoas muscle abscess. He was referred to us in 2016 with acute abdominal discomfort and oliguria. Computed tomographic (CT) scan revealed enlarged retroperitoneal lymph nodes causing bilateral ureteric compression (stage II). There was no history of B symptoms. Besides elevated lactate dehydrogenase (LDH) (750U/L), other blood investigations including complete blood count and renal function tests were normal. CT-guided biopsy of retroperitoneal lymph node was performed. With a strong suspicion of lymphoma, he was given intravenous dexamethasone after bone marrow biopsy. Following this, patient had symptomatic relief in abdominal discomfort and had resolution of oliguria within 8 hours. Histopathological examination reported PBL that also showed CD38+ and CD138+ and CD20- on immunohistochemistry. Epstein–Barr encoding region (EBER) in situ hybridization was not done. Cerebrospinal fluid (CSF) cytology for malignant cells was negative and bone marrow cytology testing was not involved. He received chemotherapy with B-EPOCH (bortezomib 1.3 mg/m^2 intravenous push weekly, oral prednisolone 60 mg/m^2 twice a day on days 1–5, etoposide 50 mg/m^2, vincristine 0.4 mg/m^2, and doxorubicin 10 mg/m^2 as continuous infusion on days 1–4, with cyclophosphamide 750 mg/m^2 on day 5) under pegylated G-CSF prophylaxis with intrathecal methotrexate. Fluorodeoxyglucose positron emission tomography (FDG PET/CT) scan after six cycles showed complete metabolic response. He continued antiretroviral (efavirenz, emtricitabine, tenofovir) and antitubercular therapy (levofloxacin, ethionamide, ethambutol). Follow-up FDG PET/CT scans were done annually for the following 2 years as our institutional practice to know the disease status that did not show any recurrence of disease.

In March 2019 (Disease Free Interval of 27 months), patient presented with low-grade fever and abdominal discomfort. Ultrasound of abdomen showed moderate ascites. Ascitic fluid analysis did not show atypical cells and Gene Xpert analysis for tuberculosis was negative. Real-time Ebstein–Barr virus by polymerase chain reaction of blood was negative. He had to undergo four sessions of large volume paracentesis over the next 2 weeks. Clinically, patient was in good performance status. There was no lymphadenopathy and he had doughy abdomen on palpation.

FDG PET/CT scan in March 2019 showed diffuse omental FDG uptake (SUVmax 4.2) with no evidence of nodal involvement (stage IIE) (►**Fig. 1**). Laparoscopic omental biopsy was done in April 2019.

Histopathological findings of hematoxylin and eosin stain (►**Fig. 2A**) showed sheets of large atypical lymphoid cells with plasmacytic differentiation with abundant cytoplasm, paranuclear hof, and large nuclei with an immunoblastic appearance. IHC was positive for CD38 (►**Fig. 2B**), CD138 (►**Fig. 2C**), and negative for LCA, CD79a, CD20, CD3, pancytokeratin, and calretinin. EBER in situ hybridization was not done. With this, diagnosis of relapsed PBL was established.

After the confirmation of relapse, he received salvage chemotherapy with three cycles of 3 weekly ifosfamide, etoposide, and carboplatin along with weekly bortezomib, daratumumab, and dexamethasone (Vdd) for 9 weeks from May 2019 to July 2019. He tolerated this therapy well without any adverse events. There was clinical improvement with softening of abdomen and resolution of ascitic fluid on ultrasound examination after 3 weeks of starting chemotherapy.

FDG PET/CT scan 6 weeks after three cycles showed complete metabolic response (►**Fig. 1**). There was a detailed discussion with patient and his immediate family members about long-term outcome, high risk of disease relapse, limited available treatment options, and the risks and benefits associated with HDCT/ASCR. He was also explained risk of transplant-related mortality and exacerbation of preexisting HIV infection and tuberculosis.

Baseline HIV viral load was negligible. CD4 count was 467cells/μL and TB Gold test was negative. Hematopoietic stem cells were mobilized with G-CSF 10 μg/kg body weight from days 1 to 5 with injection plerixafor 0.24 mg/kg body weight on days 4 and 5. Two days of peripheral blood stem cell apheresis yielded CD34 cell count of 3.87×10^6 cells/kg body weight.

He was continued on combined antiretroviral therapy (cART) with abacavir, dolutegravir, and lamivudine combination once daily and this was continued as per the advice of infectious disease specialist. He was started on prophylactic ciprofloxacin, acyclovir, and fluconazole. He received myeloablative conditioning with lomustine, cytarabine, cyclophosphamide, etoposide regimen followed by stem cell infusion in November 2019. He required six units of irradiated packed RBC and three units of irradiated platelet concentrates during posttransplant hematopoietic recovery. Apart from grade 1 oral Mucositis, no other chemotherapy-related toxicities or adverse events were observed. He was engrafted on day +11 (granulocyte) and day +15 (platelet) and was subsequently discharged on day +18. HIV viral load (<20 copies/mL) and TB Gold test (negative) were rechecked prior to discharge.

Patient has been on monthly follow-up with clinical examination and imaging. He is asymptomatic and has gained weight. His hemogram, liver, renal function tests, serum LDH in December 2020 are normal. PET CT scan in December 2020 (►**Fig. 1**) showed no evidence of disease, translating into disease-free survival (DFS) of 13 months after the transplant.

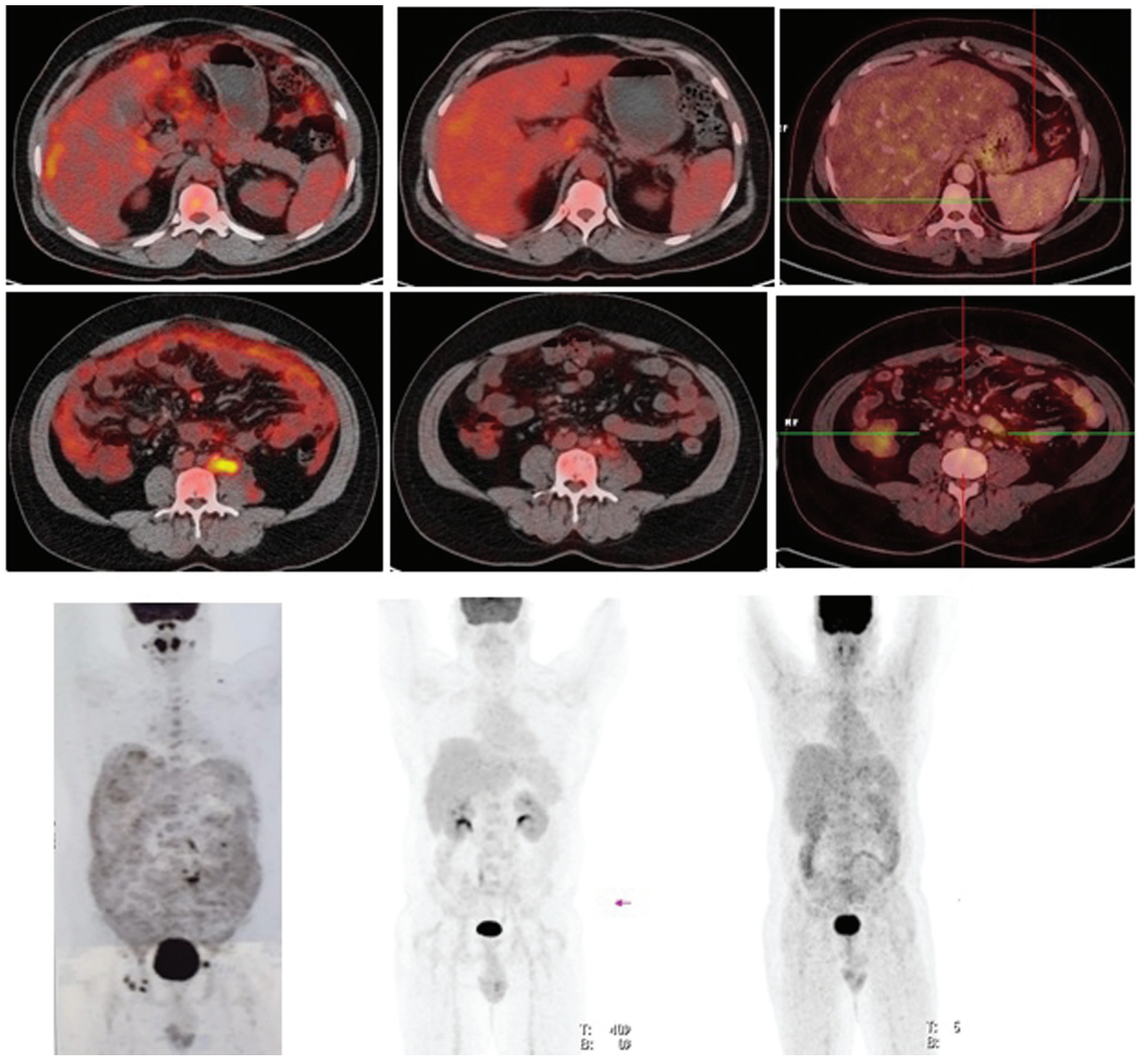

Fig. 1 Fluorodeoxyglucose positron emission tomography fused images in March 2019 (left)—at the time of relapse, October 2019 (center)—after salvage chemotherapy and December 2020—13 months after transplant. Maximum intensity projection images in March 2019 (left)—at the time of relapse, October 2019 (center)—after salvage chemotherapy and December 2020—13 months after transplant.

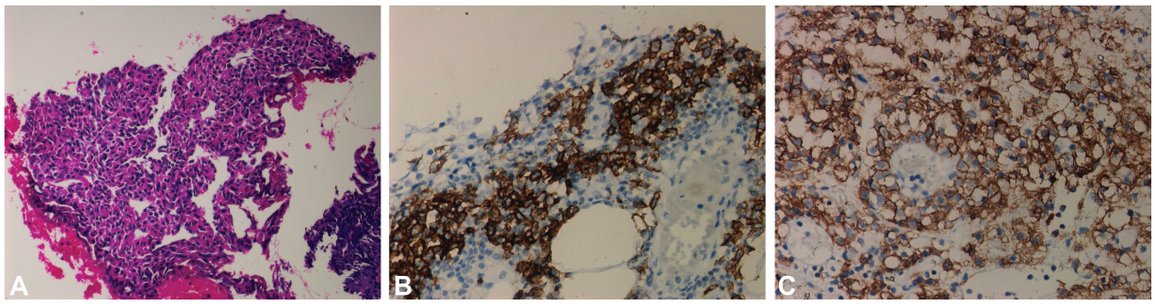

Fig. 2 (**A**) Low power view showing sheets of plasmacytoid cells in omental fat. (**B**) Plasma cells showing strong membranous positivity with CD38. (**C**) Plasma cells showing strong membranous positivity with CD138.

Discussion

PBL was first shown to have an association with HIV and EBV coinfection and was recognized as an aggressive subset of lymphoma by the World Health Organization.[1,4] However, its association with HIV-negative individuals, such as those having undergone past organ transplantation and allogeneic hematopoietic stem cell transplant and in few of them who are immunocompetent, has been described.[5]

Delecluse et al first described series of PBL cases in 1997, where features such as presence of HIV infection and presentation in oral cavity were associated with aggressive tumor biology and conferred poor response to conventional chemotherapy, leading to dismal outcome.[6] These tumors have a predilection to extramedullary sites, of which oral cavity has been predominant, followed by other sites like gastrointestinal tract, lung, sinus, testicles, and bone.[7] Our patient had retroperitoneal lymphadenopathy causing bilateral ureteric obstruction at the time of first presentation, while at relapse there was involvement of peritoneum and omentum presenting with refractory ascites.

PBL cells have immunoblastic morphology and display plasmacytic differentiation on immunophenotyping, with strong expression of biomarkers such as CD38, CD138, MUM1, BLIMP1, XBP1, MYC and variable expression of biomarkers such as CD45, CD79a, EMA, and CD30. There is generally no expression of B cell markers such as CD20 and PAX5. Autoimmune diseases, chronic inflammation, previous history of treatment for malignancies like lymphoma and acute leukemia, and elderly age have been reported as risk factors in HIV-negative patients for PBL by Lysa group.[8]

The diagnosis of PBL can be challenging, and depends upon history, clinical presentation, immunoblastic morphology, and the characteristic immunophenotypic pattern of CD20 negativity with positive markers of postgerminal center B-cells and plasma cells, such as CD138/syndecan with exclusion of other closely resembling conditions. The outcome of patients with PBL without active treatment is grim with a median overall survival (OS) of 3 and 4 months for HIV-positive and HIV-negative patients, respectively.[9] In contrast, PBL patients who are HIV positive and achieve complete remission after chemotherapy have a better outcome.[10]

The use of CHOP is considered inadequate therapy. Current guidelines recommend more intensive regimens like infusional etoposide, vincristine and doxorubicin with bolus cyclophosphamide and prednisone (EPOCH), cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC), or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyper-CVAD).[11–13] Few studies have identified a survival benefit of using EPOCH over CHOP in patients with HIV-associated lymphomas.[14]

Our patient was treated with six cycles of bortezomib and EPOCH with intrathecal methotrexate prophylaxis and achieved complete remission (CR1). Intrathecal prophylaxis is mandatory in the treatment of PBL, as it has high risk of central nervous system progression either during the treatment or at the time of relapse.[15] Two cases of spontaneous remission of PBL with antiretroviral therapy[16] and one patient with *MYC* rearrangement have been reported.[17] Nearly 30% of PBL express CD30 marker and therefore a response was seen to brentuximab vedotin in patients with CD30-expressing relapsed PBL.[18]

CD38 is a transmembrane receptor highly expressed on the surface of plasma cells and plasmablasts. Therefore, daratumumab (human IgG1k anti-CD38 monoclonal antibody) could be a possible part of treatment protocol.[19,20] As some cases of PBL including EBV-positive and EBV-negative exhibit high expression of PD-1 and PD-L1, these patients may benefit from checkpoint inhibitors.[21]

HIV-associated PBL patients often have *MYC* translocation, and as bromodomain extraterminal (BET) inhibitor (JQ1) can induce cell cycle arrest by the inhibition of *MYC* transcription in preclinical studies, this will make BET inhibitors as a promising agent in these patients.[22]

Agents like tocilizumab (interleukin-6 [IL-6] receptor antagonist) and siltuximab (monoclonal antibody against IL-6) have shown clinical response, probably by starving IL-6, or by inducing apoptosis in the PBL-1 cell line.[23] Plasmablastic cell lines (PBL-1) can be targeted by inhibiting the PI3K/Akt/mTOR pathway as this is one of the major IL-6 signaling pathways occurring downstream of IL6–6R/GP130/JAK.[21] Other future possible therapies specific to EBV-directed agents are arginine butyrate, ganciclovir, and autologous EBV-specific CAR T cells with anti-CD30 properties.[24,25]

Autologous stem cell transplantation has been performed in few case reports, in first remission (CR1) and also in relapse setting, under the cover of cART. The experience with HDCT/ASCT in the relapsed setting is rather limited, although some suggest that persistent complete remission can be achieved in chemotherapy-sensitive disease using conditioning regimes like carmustine, etoposide, cytarabine, and melphalan.[26] An Italian study (Italian Cooperative Group on AIDS and Tumors) on five patients of seropositive PBL resulted in complete remission and prolonged OS after HDCT/ASCR.[27] Case report from Moffitt cancer center in four non-HIV PBL patients who underwent autologous HSCT of which three patients were in CR and one patient was in PR. The patient who was in PR had DFS of 14 months, other 3 patients who had CR had DFS 2, 18, and 38.5 months, respectively.[28] Our patient achieved complete remission (CR2) with salvage therapy and underwent HDCT/ASCR.

AlloHSCT for PBL patients with HIV infection has several challenges, such as curative aspect of HIV status, drug interactions between antiretroviral drugs and transplant related medications, risk of opportunistic infection, high incidence of concomitant infections like viral hepatitis, effect of HIV on quantitative and qualitative function of T cell, bone marrow microenvironment, and cytokine milieu.[29] In 2009, Hamdani and Devine reported a case of PBL in CR2 with AlloHSCT using reduced intensity conditioning regimen from a matched unrelated donor.[30]

Patient has completed 19 months DFS from time of autologous stem cell rescue, leading an active life and is under close observation.

To the best of our knowledge, this is the first case report from India of an HIV-positive patient with PBL who underwent successful HDCT/ASCR under the cover of antiretroviral therapy.

Conclusion

Bortezomib containing regimen is effective in both newly diagnosed and relapsed PBL. HDCT/ASCR is a feasible option

with better DFS in patients with chemo-sensitive HIV-associated non-Hodgkin lymphoma disease. In HIV-infected patients, cART should be initiated or optimized under the supervision of an infectious disease specialist with experience in the potential interactions between anticancer agents and cART. We suggest continuing cART during the entire treatment of PBL including HDCT/ASCR.

Ethics

The ethics committee approval for publication (ECC/ONCO/June/28, dated: 28/06/2021) was obtained from Jaslok Hospital and Research Centre institutional ethics committee.

Conflict of Interest

None declared.

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Refractory Primary Mediastinal B-Cell Lymphoma: A Case Report of Conventional Chemotherapies, Immune Checkpoint Inhibitors, Polatuzumab Vedotin, Transplantation, and Post-Transplant Large Granular Lymphocytosis

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Abstract

We report a case of stage IV primary mediastinal B-cell lymphoma in a 27-year-old young woman, who was refractory and chemoresistant to frontline conventional rituximab-based intensive chemotherapy and subsequent lines of conventional and immune checkpoint inhibitor-based therapies. She was successfully treated using a polatuzumab-based regimen and consolidated with an allogeneic haploidentical hematopoietic stem cell transplantation. She developed post-transplant large granular lymphocytosis that was managed conservatively. She is now relapse-free, 600 days post-transplant. The management of this patient provided several teaching points in the use of different modalities of immunotherapies in a hard-to-treat cancer and its related conditions.

Keywords

- primary mediastinal B-cell Lymphoma
- relapsed refractory disease
- chemoresistance
- polatuzumab vedotin
- haploidentical transplantation

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a relatively rare subtype of non-Hodgkin lymphoma (NHL) mainly occurring in adolescents and young adults.[1] The malignant cells express B-cell markers CD19, CD20, CD22, CD79a.[2] Optimal first-line treatment options vary based on center experience and include da-EPOCH-R, CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone-rituximab) and R-V/MACOP-B (rituximab, etoposide or methotrexate, doxorubicin,

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cyclophosphamide, vincristine, prednisone, bleomycin) followed by radiotherapy (RT) in selected cases.[1,3]

Although it has a more favorable outcome to initial therapy than diffuse large B-cell lymphoma (DLBCL), 10 to 30% of PMBCL patients have primary refractory or relapsed (R/R) disease. The outcomes of the latter condition are poor.[4] Relapse generally occurs in the initial 12 months, is more likely to be widespread, and can involve the central nervous system (CNS). Once relapsed or progressive disease, the median overall survival is ~16 months.[5] RT alone can be curative in patients with limited disease and RT-naïve patients.[6] Second-line treatment regimens are similar to those used in DLBCL and include rituximab, ifosfamide, carboplatin, and etoposide, rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP), and others, including autologous hematopoietic cell transplantation (HCT).[7] For patients undergoing autologous HCT for chemotherapy-sensitive disease, outcomes are more favorable and comparable to relapsed DLBCL. Incomplete response to initial therapy, an advanced Ann Arbor stage at disease progression, and failure to achieve a partial remission or better to second-line therapy are scenarios associated with inferior event-free and overall survival following transplant.[8] As there is no single standard of care, institutions choose treatment regimens that are appropriate for their setting based on available and emerging peer-reviewed evidence. We share our experience with the management of a young woman diagnosed with PMBCL and the lessons we learnt as we managed the relapsed and refractory course of her disease.

Case Presentation

A 27-year-old woman presented with gradually progressive breathing difficulty and chest pain in January 2017. On evaluation elsewhere with CT chest, she was diagnosed with a bulky mediastinal mass ($11.5 \times 12 \times 9$ cm) and a whole-body positron emission tomography-computed tomography (PET-CT) scan revealed mediastinal mass with additional multiple extra nodal sites of disease (hypermetabolic lesions in adrenals, kidneys, both ovaries). A guided core biopsy was suspicious of NHL and immunohistochemistry revealed tumor cells to be positive for CD20, PAX 5, CD23, and CD30 and diagnosis was consistent with PMBCL. She received her initial therapy with six cycles of dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab (da-EPOCH-R) as well as CNS prophylaxis with intrathecal methotrexate. Post-chemotherapy, PET-CT revealed a persistent mediastinal low-grade metabolic lesion (standardized uptake value [SUV]: 2.6) and a biopsy revealed necrotic tissue. She was consolidated with involved field radiotherapy and followed up. After an initial asymptomatic period of 6 months, she complained of pain in abdomen. PET-CT scan showed a new lesion in the left retrosternal space, duodenojejunal flexure, and proximal jejunum with minimal increase in the metabolic activity of the anterior mediastinal soft tissue mass. Biopsies were repeated from both sites and confirmed B-cell NHL. She was then referred to our center.

After a review of biopsies (►**Fig. 1**) to confirm PMBCL and imaging, she received first-line salvage chemoimmunotherapy with R-DHAP for three cycles. PET-CT scan thereafter was suggestive of residual disease (metabolically active retrosternal mass, Deauville score 4). She then received a second-line salvage chemoimmunotherapy with three (28 day) cycles of pembrolizumab (200 mg intravenously, day 1), rituximab (375 mg/m^2, day 1), bortezomib (1.3mg/m^2, days 1, 8, 15), and vinorelbine (25mg/m^2, days 1 and 8) combination in a 21-day cycle. This was started after special permission from the institutional lymphoma multidisciplinary team discussion based on emerging evidence in R/R PMBCL and the refractory nature of disease.

The usage and approval of checkpoint inhibitors (pembrolizumab) in PMBCL are biomarker agnostic. The determination of programmed death receptor-1 or programmed death receptor ligand-1 status is not mandatory and was not done in this patient. Following this regimen, however, PET-CT scan suggested progressive disease with new lesions in the transverse colon. She was lost to follow-up for 3 to 4 months when she apparently received some form of alternative therapy (dendritic-cell immunotherapy × 6

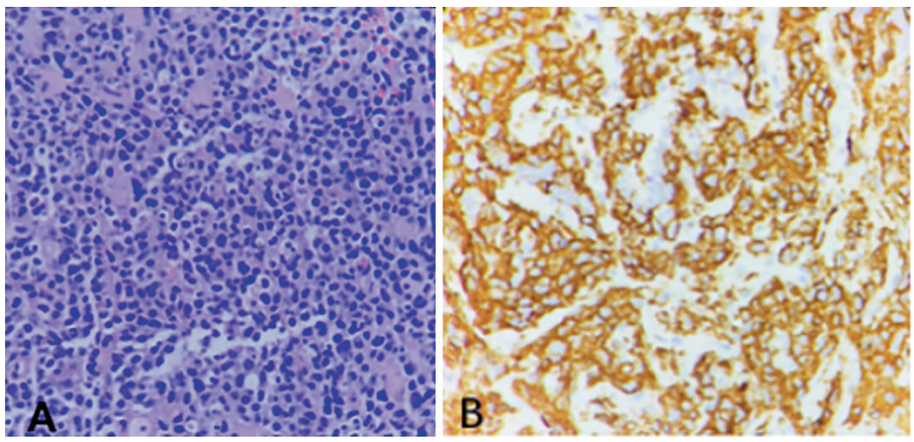

Fig. 1 (A) Hematoxylin and eosin (200X) showing large atypical lymphoid cells with mitosis and apoptosis in diffuse sheets; (B) immunohistochemistry: CD79a; 400x of the lymph node showing strong positivity.

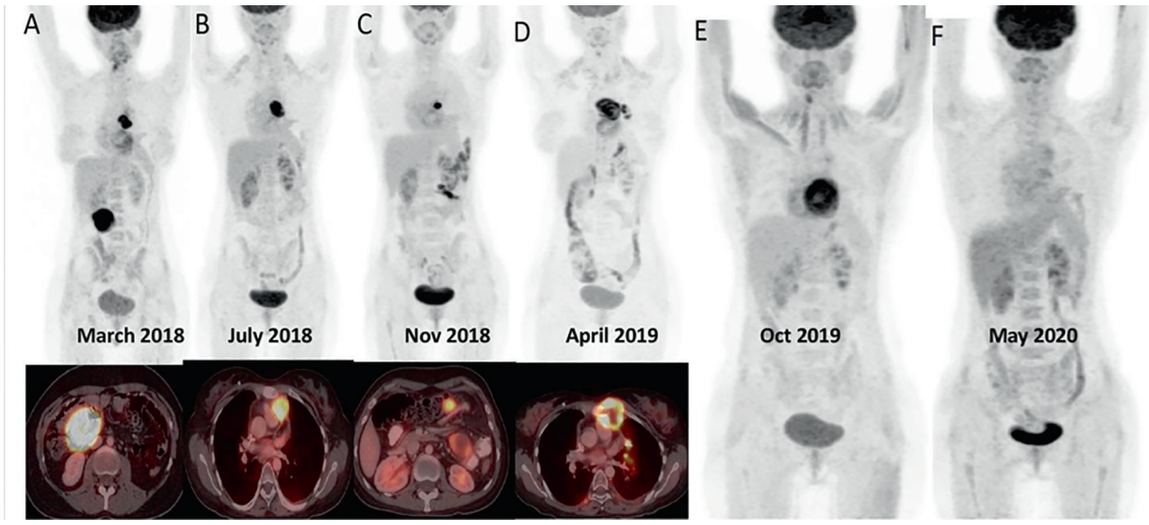

Fig. 2 Comparative positron emission tomography images from relapse diagnosis till post-transplant complete response status. (**A**) At relapse; (**B**) post- dexamethasone, high-dose cytarabine, and cisplatin (1st salvage); (**C**) post-pembrolizumab-based therapy; (**D**) pre-polatuzumab; (**E**) post-six cycles polatuzumab-based therapy; (**F**) post-transplant.

cycles), details of which were not furnished to our team. She had progressive disease with the alternative therapy as well. With limited options, she was then administered four cycles of metronomic chemotherapy using oral cyclophosphamide (300mg/m^2/week), lenalidomide (10mg/day, days 1–14), and dexamethasone (20 mg twice weekly) in a 28-day cycle with palliative intent. Thereafter, the PET-CT scan was suggestive of progressive disease (size and avidity) in the sternal lesion, development of new nodules in upper lobe of left lung and pleura, with resolution of jejunal and transverse colon lesions (►**Fig. 2**).

As she was refractory to three lines of therapy, she was now eligible for a polatuzumab vedotin compassionate access program from Roche pharmaceuticals in India. Accordingly, she received six cycles of polatuzumab-rituximab and bendamustine (Pola-BR) after which she was in a complete metabolic response (CR). As she was in a CR, she was keen on pursuing a curative therapy and was offered the option of an allogeneic HCT as consolidation, to which she agreed. Two more cycles of bendamustine and rituximab were used to bridge until she was ready for transplant. Her pre-HCT workup was unremarkable, and a pre-HCT PET-CT scan was again in a metabolic CR (with a metabolically inert lytic lesion in the manubrium of sternum with anterior mediastinal mass). She underwent a haploidentical matched (6/10 HLA match) related donor (mother) allogeneic peripheral blood HCT after reduced intensity conditioning (RIC) regimen with fludarabine-treosulfan. She received fludarabine (30 mg/m^2/day for 5 days: 240 mg) from day 6 to day 2 and inj. treosulfan (10 g/m^2/day: total 48 g) from day 6 to day 4, FT10 regimen. Graft-versus-host disease (GVHD) prophylaxis used was post-transplant cyclophosphamide-mycophenolate mofetil and tacrolimus. Her post-HCT period was uneventful except Grade 4 nausea and vomiting along with mucositis and a left Internal Jugular vein thrombus. On day 42, she had transient cytomegalovirus (CMV) viremia that was managed with oral valganciclovir. On day 60, PET-CT was in complete metabolic response (inert anterior mediastinal mass). Her post-engraftment day 28 and day 215 chimerism confirmed 100% donor cells.

►**Supplementary Fig. S1** shows the sequential lines of treatment received by the patient. On regular follow-up, she was diagnosed with a T-cell-large granular lymphocytosis (T-LGL, ►**Supplementary Fig. S2**) by day 165, on workup for persistent pancytopenia with lymphocytosis. On flow cytometry (►**Supplementary Fig. S3**), the gated abnormal T-cells were positive for sCD3, CD2, CD5, CD7, CD8, CD16, CD57 TCR α/ β. There was an oligoclonal band on TCR-G gene rearrangement polymerase chain reaction (►**Supplementary Fig. S4**). Her immunosuppression was tapered. However, pancytopenia persisted, and she was started on low-dose methylprednisolone with cyclophosphamide for T-LGL from day 210. On her last follow-up, she had completed 600 days (>1 year) of HCT without any evidence of GVHD or relapse. Her blood counts have now improved, and she is on tapering doses of steroids and cyclophosphamide.

Discussion

PMBCL is a rare and unique subtype of B-cell NHL. PMBCLs harbor numerous molecular alterations and surface antigen immunophenotypic features. These may be amenable to targeting with novel therapies including checkpoint inhibitor immunotherapy, as shown in ►**Table 1**. Underrepresentation of PMBCL in large-B-cell lymphoma clinical trials precludes a clear interpretation of the effects of novel immunotherapies and targeted therapies tested in these studies to PMBCL as a disease entity. Studies exclusively looking at R/R PMBCL are scanty and unlikely in the future. With the advent of chimeric-antigen receptor-T (CAR-T) cell therapy, response rates in R/R large B-cell lymphoma are

Table 1 Novel therapies for relapsed/refractory PMBCL[4]

Agent	Mechanism	Comments
Pembrolizumab	Check point inhibitor	High response rate, manageable safety (KEYNOTE 013 AND KEYNOTE 170)
Ruxolitinib	JAK 2 inhibitor	Phase 1 study, efficacy to be determined
SB518	JAK2/FLT3 inhibitor	Phase 1 study, efficacy to be determined
Brentuximab vedotin	ADC targeting CD30 antigen	Phase 2 study, low response rate

Abbreviation: PMBCL, primary mediastinal B cell lymphoma.

encouraging with an overall response rate of 83% and CR rate of 58%; R/R PMBCL patients are underrepresented.[9] In an NCI (National Cancer Institute, USA) study evaluating the role of CAR-T therapy in R/R B-cell lymphoma, of the four patients with R/R PMBCL, two (50%) had CR and one (25%) had stable disease.[4]

Our patient received an accepted upfront therapy for PMBCL that was followed by an early relapse. She thereafter received sequential lines of therapy that included conventional chemotherapy, immune checkpoint inhibitor-based treatment, and immunomodulatory therapy. However, she continued to have persistent/refractory disease. Polatuzumab vedotin (Pola) is an antibody drug conjugate comprising of an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin, a microtubule-disrupting cytotoxin. Polatuzumab vedotin, in its first phase 1 study in NHL patients, showed an objective response in 14 of 25 patients as monotherapy and 7 of 9 patients in combination with rituximab. Fifty-eight percent of the patients experienced grade 3 to 4 adverse effects when the drug was administered at a higher dose (2.4 mg/kg).[10] Subsequently, in the phase 2 study, Pola at dose of 2.4 mg/kg in combination with rituximab showed an objective response and CR of 54 and 21% patients, respectively. Grade 3 to 4 adverse events occurred in 77% of patients, most common being neutropenia.[11] Although Pola-BR was found to achieve a CR of 40% in R/R-DLBCL in a large phase 2 study, it had only one patient with PMBCL.[12] In recent preclinical studies, Pola alone and in combination with obinutuzumab was found to be cytotoxic to PMBCL cells.[13] Our patient achieved PR following three cycles of Pola-BR and a CR on completion of six cycles of Pola-BR.

Allogeneic HCT is an accepted consolidation strategy in salvage therapy of refractory or relapsed aggressive B-cell lymphomas and haploidentical HCT has demonstrated efficacy in such situations.[14,15] As she had no matched donors in her family or accessed donor registries, consolidation was achieved using a RIC haploidentical allogeneic HCT, which was largely uneventful. She developed T-LGL around day 165 post-HCT, which manifested as persistent cytopenia and lymphocytosis. T-LGL leukemia is a heterogeneous disorder characterized by persistent peripheral blood lymphocytosis and falls under the mature T and NK cell neoplasm in the World Health Organization (WHO) classification of hematolymphoid neoplasm (ICD-O code: 9831/3).[2] This complication is observed following allogeneic HCT in 0.5 to 18.4% of patients. The development of LGL has been associated with and attributed to various conditions such as immune system reconstitution, CMV viremia, and GVHD.[16] Our patient had transient CMV viremia post-HCT. First-line treatment is usually with steroids that leads to normalization of counts in 65% of patients. Thirty-four percent of those treated required $\geq$2 lines of treatment.[17] Our patient did not qualify the diagnostic criteria for T-LGL leukemia as diagnosis and treatment was initiated before "6 months of persistent lymphocytosis" due to persistent cytopenias. Hence, she was labeled as T-LGL. Epstein–Barr virus status was not checked in our patient at T-LGL diagnosis. Our patient had improvement in cytopenia following second-line treatment with immunosuppressive therapy for T-LGL using cyclophosphamide and continued steroids. On last-follow-up, nearly 600 days post-HCT, she maintains CR and is on tapering doses of immunosuppressive therapy of T-LGL.

The strengths of our approach to the case scenario were the appropriate and timely use of a novel agent after careful review of its role from initial studies. The patient, in CR, thereafter, received consolidation therapy in the form of allogeneic HCT considering the refractory nature of the disease and her young age. Limitation in our report was the use of combination of checkpoint inhibitor-based immunotherapy with chemotherapy, based on limited evidence from monotherapy studies using pembrolizumab.[18] An additional limitation in our report is that the cause of T-LGL was not exhaustively evaluated. Detailed evaluation of differential diagnoses would ideally include a workup to rule out viral infections and auto-immune conditions as well.

Conclusions

The treatment of this patient provided many learning opportunities to our team, in the complex management of R/R PMBCL. One, it illustrates that not all PMBCL respond well to upfront intensive therapy and early relapse remains a major challenge in improving outcomes. Two, the advent of novel therapies has provided treating physicians with opportunities to persist with treatment to achieve a response and a potential cure, in selected patients. Three, polatuzumab vedotin is an active agent in aggressive R/R B-cell lymphomas. Four, in young and fit patients, allogeneic HCT, including haploidentical donor HCT, is a feasible consolidation strategy in R/R disease who respond to salvage therapy. Five, T-LGL is a recognized side effect of HCT, and its management needs a nuanced approach. Six, the human side of this experience is the patient herself who persevered with the team, endured multiple lines of therapy, continues regular follow-up for her care and taught us the same.

Authors' Contribution

VSR conceived and led the idea for the case report. VSR, RP, and RN wrote the manuscript, contributed to the design, and edited the manuscript. LZ, SSV, DKM, and JD contributed to pathology, laboratory hematology, and imaging inputs, respectively, pictures and edited the manuscript. VSR, RN, RP, JK, SB, AN, and MC examined and treated the patient, and edited the manuscript.

Availability of Data and Material (data transparency)

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of Patient Consent

Informed consent was taken from the patient.

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None.

Conflict of Interest

VSR reports advisory fees (institutional) and nonfinancial Institutional support from PFIZER, institutional grants and nonfinancial support from INTAS Pharmaceuticals, institutional grants from NATCO Pharmaceuticals, institutional grants from ROCHE, institutional grants from BMS, institutional grants and nonfinancial support from CIPLA Pharmaceuticals, institutional grants from EMCURE, personal fees (institutional) from ASTRA ZENECA, nonfinancial institutional support from Dr. REDDY's Laboratories, outside the submitted work. RN has received research grants, advisory board fees as well as Speaker fee from Cipla, Freisenius Kabi, Johnson and Johnson, Mylan, Novartis, and Dr. Reddy's Laboratory, outside the submitted work. MC reports advisory fees (institutional) and nonfinancial Institutional support from PFIZER, institutional grants and nonfinancial support from INTAS Pharmaceuticals, and institutional grants from NATCO Pharmaceuticals, outside the submitted work. Other authors declare no relevant conflicts of interest with respect to the submitted work.

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Post COVID-19 Thrombocytosis in a Child with B-cell Acute Lymphoblastic Leukemia

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We report a pediatric B cell ALL case who developed thrombocytosis on chemotherapy with a high titer of SAR-CoV-2 IgG antibody.

Patients with COVID-19 infections present with abnormalities in the coagulation system, including elevated D-dimer and fibrinogen, and usually have mild thrombocytopenia. There are a few reports of thrombocytosis due to COVID-19 infection in children.[1] We report a child with high-risk B cell acute lymphoblastic leukemia (ALL) in the consolidation phase of chemotherapy presenting with thrombocytosis.

The SARS-CoV-2 infection causes a wide range of clinical symptoms. It causes inflammation which in severe cases, progresses to cytokine storm, with frequent involvement of the hemostatic system.[2] SARS-CoV-2 infects the human body by binding with the angiotensin-converting enzyme-2 (ACE-2) receptor and can directly enhance platelet activation.[3] It leads to abnormal coagulation findings, e.g., elevated d-dimer and fibrinogen and mild thrombocytopenia.[1] The majority (58–95%) of COVID-19 patients may have mild thrombocytopenia, with the severe disease having a lower platelet count than non-severe disease by 23000–31000/µL.[4] Thrombocytosis due to COVID-19 infection has been reported and increased thrombopoietin levels after pulmonary inflammation is considered one of the possible mechanisms.

In our case, a 6 year old girl, a case of B cell ALL on the consolidation phase was found to have thrombocytosis (absolute platelet count [APC] – 11,47,000/µL) with a normal peripheral smear. The child was asymptomatic with a normal systemic examination. The child had documented severe thrombocytopenia during induction chemotherapy and had received multiple platelet transfusions. Post-induction bone marrow evaluation showed negative minimal residual disease (MRD) and normal platelet counts. The child had not received steroids post-induction chemotherapy. On further evaluation, COVID antibodies were positive (78.00 AU/mL). The child did not suffer from an overt COVID infection in the past or have received a COVID vaccination yet. Inflammatory markers were within normal limits (total leukocyte count-4100, C-reactive protein, 0.06 mg/dL, procalcitonin-0.05 ng/mL, serum fibrinogen-2.1 g/L, D-dimer-412 µg/L). Infective workups were negative and the iron studies were within normal range. The child was managed conservatively and serial monitoring of platelet counts with ongoing chemotherapy was done, which showed a decreasing trend over a period of time and platelet counts returned to normal range after 4 weeks. There are several mechanisms that contribute to thrombocytopenia-direct infection of the megakaryocytes and platelets in the bone marrow, peripheral destruction of platelets, decreased production of endothelial damaged induced platelet activation that leads to its removal from circulation.[5] Thrombocytosis in COVID-19 infection can occur secondary to thrombocytopenia as a part of homeostatic compensation to platelet consumption due to inflammatory response by COVID-19 infection; however, the exact cause is yet to be defined. COVID-19 infection is a state of cytokine excess and can reactively enhance the production of thrombopoietin (TPO), which in turn leads to secondary thrombocytosis.[5] Thrombocytosis in cancer patients can occur as a reactive phenomenon with the disease in remission and a regenerating marrow but such high levels of platelets are unusual in the initial phase of therapy. Thrombocytosis can also occur due to endothelial injury that stimulates the von Willebrand factor (vWF) release. It binds with platelet membrane glycoprotein Ib (GPIb) vWF and leads to increased platelet production.[5]

Our case highlights thrombocytosis post-COVID infection in a child on cytotoxic therapy. Post COVID thrombocytosis needs

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attention in children with cancer (a prothrombotic state) due to the additional risk of thrombotic events.

Availability of Data and Materials
Available.

Ethics Approval and Consent to Participate
Ethics approval was obtained from the parents.

Consent for Publication
Consent for publication was obtained from the parents.

Conflict of Interest
None declared.

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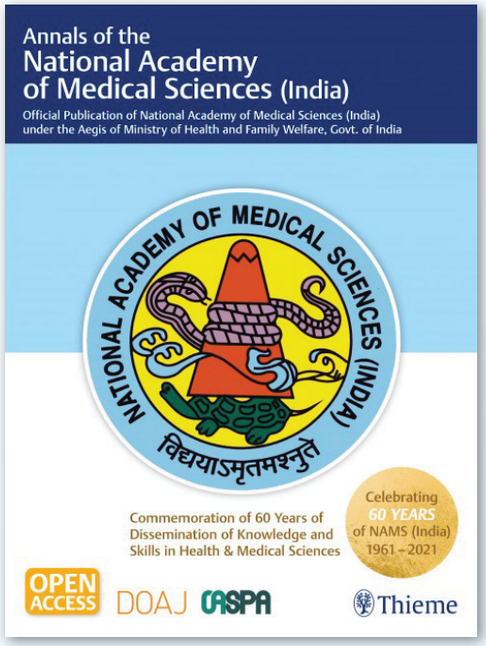

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