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Review Article

Indian Council of Medical Research Consensus Document for the Management of Non-Hodgkin's Lymphoma (High Grade)

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Abstract

This consensus document is based on the guidelines related to the management of Non Hodgkin's Lymphoma (High grade) in the Indian population as proposed by the core expert committee. Accurate diagnosis in hematolymphoid neoplasm requires a combination of detailed history,clinical examination, and various investigations including routine laboratory tests, good quality histology section (of tumor and also bone marrow aspirate/biopsy), immunostaining, cytogenetic and molecular studies and radiology investigations. The staging system used for adult high grade lymphomas is based on the Ann Arbor system and includes various parameters like clinical, haematology, biochemistry, serology and radiology. Response should be evaluated with radiological evaluation after 3-4 cycles and at the end of treatment based on criteria including and excluding PET. Treatment of high grade lymphomas is based on histologic subtype, extent of disease, and age of the patient. Autologous stem cell transplantation after high dose chemotherapy is effective in the treatment of relapsed NHL. Newer RT techniques like 3 dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) can significantly reduce radiation doses to surrounding normal tissues in lymphoma patients. Patients should be followed up every 3 to 4 months for the first 2 years, followed by 6 monthly for the next 3 years and then annually.

Keywords: *Guidelines, Indian Council of Medical Research, Non-Hodgkin's lymphoma (high grade)*

Introduction

Lymphomas are a heterogeneous group of lymphoproliferative disorders originating in B-, T-, or natural killer (NK) lymphocytes. In India, B-cell lymphomas represent 80%–85% of all cases, T-cell approximately 15%–20% and NK cell are rare. The incidence of lymphomas worldwide has increased and is mainly attributed to the human immunodeficiency virus (HIV) epidemic and the development of acquired immune deficiency syndrome-related non-Hodgkin lymphoma (NHL). The increased incidence has been observed in patients in their sixth and seventh decade. It has paralleled a decline in mortality due to other causes. In India too, the incidence of lymphomas has shown an increase in the last decade.

Broadly, lymphomas comprise Hodgkin's lymphoma (HL) and NHL. NHL is subclassified as low grade (indolent) and high grade. The high-grade NHL is generally curable with cytotoxic chemotherapy while the low-grade lymphomas are controllable for long periods. Hence, it is not only important to make the correct diagnosis of the lymphoma but also essential to subclassify them correctly to high-grade NHL or low-grade NHL to give appropriate treatment. The World Health Organization classification of tumors of hematopoietic and lymphoid tissues is followed.[1] This includes mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, HL, histiocytic and dendritic cell

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neoplasms, and posttransplant lymphoproliferative disorders. The common lymphoma subtypes in adults include diffuse large B-cell lymphoma (DLBCL), HL, follicular lymphoma, T-cell lymphoblastic lymphoma (LBL), small lymphocytic lymphoma, Burkitt's lymphoma, anaplastic large cell lymphoma, etc.[1,2] The common subtypes in children include T LBL, HL, Burkitt's lymphoma, DLBCL, and anaplastic large cell lymphoma.[1,3]

Purpose

Although the international consensus guidelines are available for the management of high-grade NHL, it is not entirely feasible to apply these guidelines to the Indian population owing to differences in the incidence of the disease in different parts of India, socioeconomic factors, and availability of resources. Therefore, it is essential to analyze the evidence pertaining to NHL from India, and the rest of the world with an aim to formulate evidence-based guidelines that could be applicable to Indian patients. Taking into consideration, peripheral oncology centers, regional cancer centers, and tertiary cancer centers in major cities, the set of recommendations includes two categories, namely.

Desirable/ideal tests and treatments that may not be available at all centers, but the centers should aspire to have them in the near future, and essential bare minimum that should be offered to all the patients by all the centers treating cancer patients.

Diagnosis

Accurate diagnosis in hematolymphoid neoplasm requires a combination of detailed history, clinical examination, and various investigations including routine laboratory tests (complete blood counts, liver and renal function tests, lactate dehydrogenase [LDH], uric acid, beta-2 microglobulin, erythrocyte sedimentation rate, peripheral blood smear, good quality histology section [of tumor and also bone marrow aspirate/biopsy], immunostaining, cytogenetic and molecular studies and radiology investigations [X-ray chest, abdominal Ultrasound (USG) abdomen, computed tomography (CT) abdomen/thorax, and/or positron emission tomography-CT (PET-CT)]). Diagnostic workup includes testing for various viral markers including HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV).

The organization of a hematopathology laboratory may vary from a large size hematopathology laboratory capable of performing all tests in house (institute based or a private reference laboratory) to a small size laboratory doing only preliminary tests such as morphology on hematoxylin and eosin-stained sections. These laboratories may send samples/paraffin block to reference laboratories for specialized tests such as immunohistochemistry/flow cytometry, cytogenetics, and molecular genetics services. Standard protocols should be followed for processing of tissues.

Staging

The stage of lymphoma is of major therapeutic and prognostic significance in the management of lymphoma. The staging system used for adult high-grade lymphomas is based on the Ann Arbor system. The staging workup includes various parameters including clinical (clinical history with reference to B symptoms and family history; physical examination with particular attention to node-bearing areas, Waldeyer's ring, and size of liver and spleen; performance status Eastern Cooperative Oncology Group [ECOG] including comorbidity), hematology (complete blood counts, differential and film; bone marrow aspirate and trephine; cytogenetics and immunophenotyping of marrow ± blood in low-grade lymphomas and any other lymphomas with morphological evidence of marrow/blood involvement), biochemistry (LDH, urea and electrolyte, creatinine, albumin, aspartate transaminase, bilirubin, alkaline phosphatase, serum calcium, uric acid; pregnancy test in females of child-bearing age), serology (HBV and HCV, HIV status), and radiology (chest X-ray; chest and abdominopelvic CT with oral and intravenous contrast [unless coexistent renal insufficiency]).

Performance Index

The ECOG performance status is related to the scales and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

The International Prognostic Index (IPI) is a prognostic model based on five parameters including age, performance status, stage, LDH, and extranodal sites.[4] The IPI describes a predictive model for patients with DLBCL at presentation. It has been adjusted for use in Follicular lymphoma IPI and is less useful in anaplastic large cell lymphoma, mediastinal B-cell lymphoma, and T-NHL. It should not be used in Burkitt's lymphoma or LBL.

The risk factors for age-adjusted IPI are ECOG performance status 2, Stage III/IV, and LDH > upper limit of normal. The revised-IPI and Mantle Cell-International Prognostic Score have also been developed.[5]

Response Evaluation

Response should be evaluated with radiological evaluation after 3–4 cycles and at the end of treatment. Infiltration of marrow or cerebrospinal fluid (CSF) at diagnosis needs to be rechecked at the end of treatment. The response criteria not including PET defines the response categories as complete remission (CR), CR unconfirmed, partial remission (PR), and relapse/progression on the basis of parameters including physical examination, lymph node (LN), LN masses, and bone marrow.[6] Response criteria including PET defines the response categories as CR, PR, stable disease, relapse/

progressive disease on the basis of nodal masses, spleen, liver, and bone marrow.[7]

Treatment Regimens

Treatment of high-grade lymphomas is based on histologic subtype, extent of disease, and age of the patient. In the case of discordant (two separate sites of disease with differing lymphoma types), composite (one site of disease with two discrete types of lymphoma at that site) or transformed (a second lymphoma developing out of a background of previously known lymphoma) lymphoma, treatment must be directed at the most aggressive phase of the disease.

Diffuse large B-cell lymphoma

DLBCL accounts for approximately 30% of NHLs diagnosed. Transformed DLBCL, Follicular lymphoma Grade 3B, intravascular DLBCL, anaplastic lymphoma kinase-positive DLBCL, Epstein–Barr virus-positive DLBCL, and T-cell/histiocyte-rich large cell lymphoma are also managed according to the DLBCL guidelines. Treatment options vary between patients with localized (Stage I–II) and advanced (Stage III–IV) disease. Prognosis is extremely good for patients with no adverse risk factors (normal LDH, Stage I or II nonbulky disease, age less than 60 years or ECOG performance status less than 2). For patients with nonbulky (<10 cm) Stage I or II disease, cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) ± Rituximab (R) for 3 cycles with involved field radiotherapy (IFRT) or 6 cycles of CHOP ± R alone is recommended (Category 2A). Patients with bulky disease (10 cm or more) should be treated with 6 cycles of CHOP ± R with or without IFRT (Category 1). CHOP ± R for 3 cycles followed by IFRT has been the standard treatment for patients with Stage I–II based on the results of the SWOG 8736 study,[8] in which 3 cycles of CHOP with IFRT produced significantly better progression-free survival (5-year PFS: 77% vs. 64% for 3 cycles of CHOP alone). The efficacy of the addition of rituximab to CHOP and IFRT has also been reported in the SWOG 0014 study[9] (CHOP–R for 3 cycles followed by IFRT). For Stage III–IV patients with advanced stage disease, treatment with 6 cycles of CHOP ± R repeated every 21 days is recommended (Category 1). In selected cases, radiation therapy (RT) to bulky sites may be beneficial (Category 2B). Patients at increased risk of central nervous system (CNS) relapse (those with involvement of the paranasal sinuses, testes, bone-marrow involvement with large cells or having two or more extranodal sites with elevated LDH) should receive CNS prophylaxis with 4–8 doses of intrathecal methotrexate (MTX) or 3–3.5 g/m^2 of systemic MTX. Response should be evaluated with radiological evaluation after 3–4 cycles and at the end of treatment. Infiltration of marrow or CSF at diagnosis needs to be rechecked at the end of treatment. Patients who are not PET negative at the end of treatment have primary refractory disease and should be considered for salvage therapy.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a B-cell neoplasm composed of monomorphic small to medium-sized lymphoid cells with irregular nuclei which most closely resemble centrocytes/follicle center cells but with less irregular nuclei. MCL accounts for 6% of all newly diagnosed cases of NHL. Very few Stage I–II patients present with localized MCL. Local radiotherapy (30–36 Gy) alone or combination chemoimmunotherapy is recommended (Category 2A). If the patient received initial treatment with RT alone and relapses after CR; then, the patient can be treated with first-line induction chemo-immunotherapy. The majority of patients with MCL will have advanced stage disease and require systemic therapy. In highly selected patients with asymptomatic disease, close observation without any therapy is a reasonable option, especially for those with good performance status and lower IPI.[10] The standard treatment regimen for MCL is not yet established. Most commonly used aggressive therapies are hyper-CVAD ± R[11,12] or high-dose (HD) Ara-C-based regimens and less aggressive therapies are CHOP ± R[13,14] or bendamustine and rituximab.[15] Second-line options include bendamustine ± rituximab, bortezomib ± rituximab, fludarabine-based therapy or lenalidomide ± rituximab. Myeloablative or reduced intensity allogeneic transplantation is an appropriate option for patients who are in remission after second-line therapy.[16]

Burkitts lymphoma and Burkitt leukemia (acute lymphoblastic leukemia-L3)

Burkitts lymphoma is a rare lymphoma in adults, except in HIV-positive patients. It constitutes 1% to 2% of all non-HIV adult lymphomas in Western Europe and the United States. A strategy, developed in children, using brief very intensive chemotherapy can produce long-term survival in approaching 90% of adult patients, including patients with bone marrow and CNS involvement.[17,18] There is a high incidence of tumor lysis syndrome (TLS) and measures should be taken to prevent and treat this complication. Patients with bulky disease and organ dysfunction may be treated with modified dose therapy (e.g., "mini-CHOP"), in an attempt to modify the effects of tumor lysis. They will proceed to more intensive therapy. All patients will require a peripherally inserted central catheter line or Hickman catheter which should be inserted at the earliest opportunity. The patient should be treated using one of the brief, high-intensity therapies that have been developed for this disease: CODOX-M/IVAC (National Cancer Institute protocol 89-C-41);[17,19,20] the Berlin-Frankfurt-Münster protocol (B-NHL 86);[21] LMB-86 protocol;[18] R-Hyper CVAD[22] and CALGB 9251.[23] These protocols include strategies for the treatment of patients with CNS disease at diagnosis.

Lymphoblastic lymphoma

LBL is a rare disease that represents only <2% of NHL in adults. The majority of patients are young men with T-cell phenotype. T-LBL is a clinically aggressive disease with frequent involvement of extranodal sites, particularly the bone marrow and CNS. Patients with LBL have typically been treated with regimens appropriate for acute lymphoblastic leukemia (ALL). The therapeutic regimens for adult patients with LBL are based on the treatment protocols designed for ALL and often include various phases of treatment including induction, consolidation/intensification, and maintenance. Patients with systemic LBL can be treated with any one of the chemotherapy regimens (MCP-841, CALGB 8811, GM ALL T-ALL, LMB-86 regimen, or hyper-CVAD).[18,24-26] Patients with CR to induction therapy should be continued with other components of the treatment protocols. HD therapy followed by autologous stem cell transplant (ASCT) has also been investigated as consolidation. Patients with relapsed disease should be considered for allogeneic SCT. The relapse rate is higher after autologous transplantation, and therefore, patients with high-risk features (such as marrow involvement) and a matched sibling donor should be offered an allogeneic transplantation in the first remission.

Special Problems in High-Grade Lymphomas

Human immunodeficiency virus-associated lymphoma

Lymphomas are an important complication of HIV infection and are a significant cause of morbidity and mortality. Most of these are aggressive B-cell lymphomas and are histologically heterogeneous. The common HIV-associated lymphomas are DLBCL, which includes primary CNS lymphoma (PCNSL), and Burkitt lymphoma, whereas primary effusion lymphoma, plasmablastic lymphoma, and classic HL are far less frequent. Since the introduction of combination highly active antiretroviral therapy (HAART), HIV-associated lymphomas have fallen in incidence and improved in outcome, in large part because of better control of HIV replication and improved immune function. Early introduction of HAART therapy is associated with superior outcomes. The addition of rituximab to CHOP has been associated with improved CR rates with manageable toxicities. Patient should receive HAART and growth factor support along with full-dose chemotherapy. In patients with persistently low CD4 counts (<100/mcl), rituximab should be omitted to reduce the risk of serious infections. CNS prophylaxis can be considered for all patients or selected patients. Treatment options for HIV-associated Burkitt lymphoma include CODOX-M/IVAC, dose-adjusted EPOCH, or hyper-CVAD with or without rituximab. DLBCL should be treated CHOP ± R or dose-adjusted EPOCH. Most cases of primary effusion lymphoma are CD20-negative; the addition of rituximab to CHOP is not indicated. Plasmablastic lymphoma can be treated with regimens recommended for Burkitt lymphoma. HD MTX or RT can be considered for patients with PCNSL.

Primary central nervous system lymphoma and primary intraocular lymphoma

PCNSL is usually an aggressive form of NHL arising in and confined to the brain, spinal cord, and leptomeninges. The intraocular manifestation of PCNSL, which typically occurs in the retina, vitreous humor and rarely, optic nerve, is termed "primary intraocular lymphoma" (PIOL). PIOL is a variant of PCNSL that can appear prior to, concurrent with, or subsequent to the cerebral disease. Although relatively rare, the incidence of both PCNSL and PIOL seems to be increasing. Over the last three decades, survival has improved, mainly because of the introduction of MTX-based combination chemotherapy. Long-term treatment-related neurological toxicity, however, remains a major problem. All patients should be offered chemotherapy as first-line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD MTX (3–5 doses) of ≥3 g/m^2 delivered over a maximum of 2–3 h at intervals of not more than 2–3 weeks. The efficacy of HD MTX may be improved by using it in combination with other CNS-penetrating chemotherapeutic agents such as cytarabine but such treatment should be based on established protocols.[27-32] Consolidation whole brain radiotherapy (WBRT), 45 Gray in 25 fractions, should be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits. There is no evidence supporting a role for intrathecal chemotherapy as an adjunct to HD intravenous MTX in patients with PCNSL.[32] Rituximab administered through the intrathecal or intraventricular route should not be used in the routine treatment of PCNSL except in a clinical trial. Dexamethasone is the treatment of choice for short-term palliation but should be avoided before biopsy. WBRT can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy. There is no role for CHOP-like chemotherapy in the treatment of PCNSL relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone should be considered for short-term palliation. Alternative chemotherapeutic regimens such as temozolomide[33] or HD chemotherapy with ASCT[34] show promise but require further evaluation in clinical trials. Concurrent intraocular and CNS lymphoma should be treated with systemic HD MTX-based chemotherapy followed by radiation to both globes. Isolated intraocular disease should be treated in the same way. Intravitreal MTX is an effective treatment option for patients with

recurrent disease confined to the eyes. Timely referral to rehabilitation and supportive care services is imperative and is dependent on rapid, comprehensive communication between medical and rehabilitation team.

Primary testicular lymphoma

NHL of the testis (primary testicular lymphoma [PTL]) is an uncommon and rare disease that represents 1% to 2% of all NHLs and about 5% of all testicular neoplasms.[35-37] However, it represents the most frequent testicular cancer in men older than 60 years of age (85% of PTLs are diagnosed in men >60 years of age). Standard management guidelines for patients with PTL have not been yet established. PTL patients with limited disease should be managed with primary orchidectomy followed by R-CHOP treatment, CNS prophylaxis (intrathecal chemotherapy ± HD MTX or HD cytarabine), and prophylactic scrotal radiotherapy. In patients with Stage-II E disease, irradiation of involved LNs is advisable. PTL patients with Stage III or IV should be treated according to the guidelines for the treatment of advanced stage nodal DLBCL.[38,39] The usual therapeutic option for these patients is conventional-dose anthracycline - containing chemotherapy with rituximab along - with prophylactic scrotal radiotherapy and intrathecal chemotherapy. The addition of intermediate-HD MTX might improve CNS prophylaxis, especially in the younger patients but this has never been formally demonstrated.[40] HD chemotherapy followed by SCT may be an investigational option. Management guidelines should be the same as for other aggressive NHLs. Therapeutic decision should be strongly influenced by age, performance status, and clinical condition of the patient. HD chemotherapy followed by autologous stem cell rescue is the treatment of choice in patients less than 60 years with chemosensitive relapse.

Primary gastrointestinal lymphoma

Gastrointestinal tract is the most common extranodal site involved by lymphoma accounting for 5%–20% of all cases. Primary gastrointestinal lymphoma, however, is very rare, constituting only about 1%–4% of all gastrointestinal malignancies. Gastrointestinal lymphoma is usually secondary to the widespread nodal diseases. Treatment of gastrointestinal lymphoma is according to histological subtype. Previously, resection of gastrointestinal lymphoma to prevent hemorrhage or perforation was recommended, however, earlier diagnosis and current management techniques seem to have reduced this risk. Thus, resection of gastrointestinal lymphoma is no longer recommended, unless necessary to establish a definite diagnosis, or to control the complications of hemorrhage or perforation.

Management of Relapsed Lymphomas

Aggressive or high-grade NHLs are associated with responses in approximately half the patients treated with combination chemotherapy including anthracyclines, alkylating agents, vinca alkaloids, and steroids. Despite these initial responses, about one-third of patients are either refractory to, or relapse after standard therapy. Patients with higher IPI scores are more likely to respond poorly to therapy and have worse PFS than others. Attempts to predict poor response have been made using gene-expression profiling and early PET imaging, i.e., after 1–3 cycles of chemotherapy, however, clear guidelines are not available for the same. The majority of relapses occur during the first 2 years after completion of treatment. Relapsed NHL may be classified as early or late (occurring >5 years after therapy). The choice of chemotherapy regimen depends on whether the patient is a transplant candidate or not. ASCT after HD chemotherapy has been shown to be effective in the treatment of relapsed NHL.[41] Therefore, the first step in the planning of therapy is the assessment of whether or not the patient is eligible for autologous hematopoietic SCT (HSCT). Although no clear guidelines exist regarding the eligibility criteria for autologous HSCT, common exclusion criteria include advanced age (typically >60–65 years), presence of significant organ dysfunction (pulmonary, cardiac, hepatic, or renal), poor ECOG performance status, and the unavailability of adequate financial and social support for posttransplant care.

Supportive Care

Tumor lysis syndrome

TLS is an oncological emergency. The incidence of TLS in all patients with malignancies ranges from 5% to 20%. It is a series of life-threatening complications after the lysis of tumor cells in patients undergoing treatment for malignancies. Because of the significant morbidity associated with TLS, early recognition in patients with lymphoma is critical for good outcomes. Mild consequences of TLS may delay treatment, and severe consequence may result in death; thus, identification of risk factors and prevention is of paramount importance. Risk factors for the development of TLS include tumor type (Burkitt's lymphoma, LBL, ALL), large tumor load, LDH 2 times upper normal limit, white blood cell count 25,000 cmm/L, preexisting renal failure or oliguria, uric acid level, and effective or prompt cytoreductive therapy. Although uncommon, TLS can occur with rituximab administration. It may be possible to prevent TLS or reduce TLS-related mortality by identifying patients at high risk for TLS and making preparations (such as hospitalization, hydration, starting allopurinol, and urinary alkalinization) before starting treatment. Close monitoring of renal parameters in initial part of treatment is strongly recommended.

Viral reactivation

For cancer patients, who have chronic HBV infection, there is a high rate of hepatic complications during cytotoxic chemotherapy, and this has mainly been attributable to HBV reactivation. The condition is manifested with

abnormal liver function tests confirmed by raised levels of serum HBV DNA. The clinical spectrum ranges from symptomatic hepatitis to fatal hepatic failure. The incidence of HBV reactivation in hepatitis B surface antigen seropositive cancer patients undergoing cytotoxic chemotherapy has been reported to be 20% or higher. With the increasing incidence of neoplastic diseases and the more widespread use of cytotoxic chemotherapy, the occurrence of HBV reactivation is likely to increase further. Identified risk factors include detectable prechemotherapy HBV DNA load (using real-time polymerase chain reaction measurement), use of steroids, diagnosis of lymphoma or breast cancer, use of anthracyclines, male sex, younger age, and hepatitis B e antigen positivity. By implementing good medical practice, virtually all patients should be prevented from contracting or reactivating HBV, in view of the potentially serious consequences of this infection.

Fertility issues in high-grade non-Hodgkin lymphoma

Since the introduction of aggressive chemotherapy alone and in combination with irradiation, long-lasting remissions, and cures has been obtained in patients with high-grade NHL. Although a more aggressive therapy may result in an improved remission rate, it is usually associated with amenorrhea and infertility in 33%–75% patients. Therapy-induced gonadal toxicity has become an issue of clinical concern to these patients for several reasons. First, many patients are young adults concerned about their reproductive potential after therapy. Second, cure rates have gone beyond 40%–50% in high-grade NHL, thus exposing a large group of long-term survivors to this potential toxicity. Third, gonadal injury may not only result in reduced fertility but also affect gonadal steroid synthesis, which may be associated with cardiovascular, sexual, and emotional disorders. Gonadal toxicity following cancer therapy in female patients mainly involves endocrine gonadal functions and in men primarily spermatogenesis. They may be detrimental even to resting and immature oocytes and possibly damage pregranulosa cells of primordial follicles. Particularly, radiotherapy and the use of agents such as mechlorethamine, cyclophosphamide, or procarbazine have been held responsible for the gonadal damage in patients with lymphoma. Normal pregnancies can occur after oophoropexy and pelvic irradiation without increased risk of fetal wastage or spontaneous abortion. No increase in birth defects could be observed in offspring of survivors when compared with those of sibling controls. Sperm banking before treatment commences is available for males, but unfortunately, cryopreservation of ovarian tissue is not yet established for females. The use of gonadotropin-releasing hormone analog in combination with chemotherapy may possibly have a protective effect on oocytes in some female patients exposed to conventional dose chemotherapy; however, its efficiency may be limited in patients undergoing HD chemotherapy with stem cell rescue.

Non-Hodgkin lymphoma during pregnancy

NHL in pregnancy is a rare event. MRI can replace staging CT but is not advisable in the first trimester. Patients with aggressive NHL usually have Stage II–IV disease and present at a median of 23 weeks of gestation. Prolonged delay in treatment is likely to have serious consequences for the patient. If the patient is diagnosed in the first trimester, termination before the commencement of chemotherapy should be offered. For those patients diagnosed after 32 weeks, it may be possible to delay treatment until safe delivery of the child is possible. For those patients that fit into neither of the above categories, a decision will have to be made as to when treatment should start. The risks appear higher in the first trimester.

Immunization

Patients who have lymphoma should receive certain immunizations to help boost or maintain their immunity. However, immunizations using live organisms are theoretically dangerous and should be avoided unless advised by hematooncologist, to have one (exception, Zostavax®, see below). Patients who are currently receiving chemotherapy or radiation should wait until 6 months after treatment before receiving immunizations, except for influenza vaccine, which can be taken every year.

Radiotherapy

Lymphomas in general are very sensitive to ionizing radiation. RT has remained an integral part in the combined modality treatment (CMT) of malignant lymphomas. Currently, most patients with localized DLBCL and a significant proportion of patients with disseminated disease with bulky nodes are treated with CMT approach using multiagent chemotherapy and RT. The optimal radiation dose after chemotherapy has not been determined. The optimal treatment volume or field size for RT of localized NHL is also a matter of some controversy. Conclusions regarding appropriate field size are extrapolated from information regarding the patterns of failure. In patients with large residual masses in proximity to critical organs, a shrinking field technique can be used where the radiation field size is reduced as the treatment progresses/tumor shrinks and thereby restricting the RT dose to the nearby critical structures. Newer RT techniques such as 3 dimensional conformal RT and intensity modulated RT can significantly reduce radiation doses to surrounding normal tissues.

Follow-up

Most cured patients experience minimal long-term toxicity from the treatments; however, certain predictable and unpredictable late effects may occur and require preventive measures and/or recognition and treatment. Patients should be followed up every 3–4 months for the first 2 years, followed by 6 monthly for the next

3 years, and then annually. The following format shall be followed: Accurate history, careful physical examination, hematological investigation, documentation of side effects: Late effects of treatment, documentation of second primary, and documentation of any other findings. Late effects of lymphoma or its treatment should be considered when patients are reviewed in follow-up.

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Conflicts of interest

There are no conflicts of interest.

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