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Non-Hodgkin's Lymphoma Current Treatment Strategies

M. Thomas, K. Pavithran

Introduction

Currently Non Hodgkin's Lymphoma (NHL) comprises all malignancies of the lymphoid system except Hodgkin's disease (HD). Development of the lymphoid system is a highly complex but regulated process. It is characterized by differential expression of a number of cell surface and intracytoplasmic proteins as well as T-cell receptors or immunoglobulin gene rearrangements. This happens to the lymphoid cells. Dysregulation of this orderly process results in humoral deficiencies, auto immunity or malignancy. A systematic classification of the NHL has been difficult and often confusing. A new classification the Revised American-European Lymphoma (REAL) was proposed in 1994[1] and more recently this has been updated by the World Health Organization (WHO). WHO classification which incorporates morphologic, immunophenotypic and genetic information is the universally used classification (Table 1).[2]

This also includes many newly identified entities.

NHL forms 5% of all malignancies and is the fifth common cancer and 8th leading cause of cancer deaths in USA. In India non-Hodgkin's Lymphoma (in all urban registries, except Bhopal) is one of ten leading sites of cancer in either sex[3]. NHL forms the fifth, sixth and eighth common cancer among males in Delhi, Bangalore and Chennai respectively. Though there are many entities listed under the WHO classification a comprehensive description of many of them are not yet available. B-cell lymphomas formed 79.1% of the NHLs, whereas T-cell lymphomas formed 16.2% of the total. The most common subtypes of NHL seen in India are[4]

1. Diffuse large B cell Lymphoma (DLBCL) - 34%.
2. Follicular lymphoma (FL) - 12.6%
3. Small lymphocytic lymphoma (CLL) - 5.7%
4. Mantle cell lymphoma - 3.4%
5. Marginal zone B cell lymphoma (including mucosa- associated lymphoid tissue (MALT) type - 8.2%.
6. T-cell lymphoblastic lymphoma - 6%
7. Anaplastic large-cell lymphomas of T/null-cell type - 4.3%
8. Other peripheral T-cell lymphomas - 2.9%

Management of only the major types will be discussed in this article.

Management

Ideal and evidence based management of NHL depends on

Table 1 : World Health Organization classification scheme for lymphoma

B-cell lymphoma/leukemias
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma/leukemia
- Pre-B-cell lymphoblastic leukemia/lymphoma

T-cell and NK-cell lymphomas/leukemias
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell leukemia/lymphoma (human T lymphotropic virus type 1-positive)
- Extranodal NK-cell/T-cell lymphoma, nasal type
- Enteropathy type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Blastic NK-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis
- Angioimmunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Anaplastic large cell lymphoma
- Pre-T-cell lymphoblastic leukemia/lymphoma

Hodgkin's lymphoma
- Nodular lymphocyte-predominant
- Classic Hodgkin's lymphoma
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depleted
- Lymphocyte rich

1. A proper diagnostic workup with an accurate histologic diagnosis.
2. Clinical staging and restaging especially after treatment.
3. Stratification into prognostic groups.

1. *Proper diagnostic workup :* This should include a careful history and physical, laboratory studies including hematological parameters, screening chemical studies, (specifically a serum LDH), appropriate imaging-CT abdomen, chest, pelvis and a PET scan if available. The most crucial aspect of the diagnosis is an adequate sample of tissue preferably obtained by an excisional biopsy of an abnormal lymph node or a generous incisional biopsy of an involved organ. Fine needle aspiration (FNA) is not considered adequate for an initial diagnosis of NHL. Sometimes morphology and flow cytometric studies may be enough as in CLL. Additional diagnostic workup includes bone marrow biopsy (preferably both iliac crests), flowcytometry, and occasionally spinal fluid study, cytogenetics and fluorescent in situ hybridization (FISH). It is to be noted that there can be a histologic transformation of indolent lymphoma into the more aggressive types. This has to be taken into consideration when the patient is on a follow up so that more aggressive treatment protocols should be introduced for these patients.
2. *Staging :* Staging has undergone Cotswolds modification of Ann Arbor staging system which was originally used for HD[5,6] (Table 2). Restaging is usually done after some or all of the patient's treatment to see extent of the curative effects of the treatment.
3. *Prognostic groups :* Many NHL including DLBCL are stratified into prognostic groups based on the International Prognostic Index (IPI)[7] (Table 3). Gallium scanning

Table 2 : Cotswold staging classification

Stage	Description
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same site of the diaphragm (II) or localized contiguous involvement of only one extranodal organ or side and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)
	Note: The number of anatomic regions involved may be indicated by a subscript (e.g., II3).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by involvement of the spleen (IIIS) or by localized contiguous involvement of only one extranodal organ side (IIIE) or both (IIISE)
Stage IV	Disseminated (multifocal) involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement
Designations applicable to any disease stage	
A	No symptoms
B	Fever (temperature > 38° C), night sweats, unexplained loss of more than 10% of body weight during the previous 6 months.
X	Bulky disease
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

is now increasingly used to prognosticate NHL. This is positive in nearly all cases of aggressive lymphoma and in approximately 50% of the indolent ones. Those patients who remain gallium avid at the end of the treatment are likely to relapse than those who become gallium negative. Early assessment of response to chemotherapy with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is becoming a routine part of management in patients with aggressive NHL. Changes in FDG uptake can occur soon after the initiation of therapy and they precede changes in tumor volume[8].

Table 3 : International Prognostic Index (patients of all ages)

Risk group*	Risk factors CR rate (%)	Survival rates	5 yrs(%)
Low	0,1	87	73
Low-Intermediate	2	67	51
High-intermediate	3	55	43
High	4,5	44	26

Risk factors include- Age > 60 yrs, LDH > normal, Performance status > 1, stage III/IV, Extranodal involvement > 1 site; score 0 or 1 for each factor; 0 = absent, 1 present

Management of Diffuse Large B-Cell Lymphomas (DLBCL)

This is the most common form of NHL. Currently for management purposes two or three other major categories of aggressive lymphomas are also treated according to the DLBCL practice guidelines. They are anaplastic large cell lymphoma, peripheral T cell lymphoma and follicular lymphoma grade 3.

The goal of treatment of DLBCL is a cure since 50% of the patients with this disease can be cured with conventional therapy. Treatment may be divided into the following groups.[9-12]

1. Patients with localized disease (Ann Arbor stage I-II) with nonbulky disease (less than 10 cm). who do not have adverse risk factors such as an elevated LDH, stage II disease, age above 60 years or ECOG (Eastern Cooperative Oncology Group) performance status equal or more than 2.
2. Patients with localized disease with non bulky disease who have one or more adverse risk factors.
3. Patients with bulky disease (more than 10 cm).
4. Patients with advanced-stage disease who fall into low or low intermediate risk category.
5. Patients with advanced-stage disease who fall into the IPI high-intermediate or high-risk category.

6. Patients with partial remission and relapsed disease.

Patients with localized non bulky disease without adverse risks may be treated with an abbreviated course (three cycles) of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and perdinosone) combined with involved field RT (radiotherapy). The dose and time schedule of R-CHOP is as follows.

Rituximab	375 mg/m^2 on day 1 intravenously (IV)
Cyclophosphamide	750 mg/m^2 day 1 IV
Doxorubicin (adriamycin)	50 mg/m^2 day 1 IV
Vincristine	1.4 mg/m^2 (max 2 mg/ dose) day 1 IV
Prednisone	100 mg/day orally for 5 days. This cycle is given once in 21 days.

Patients with localized non bulky disease with adverse risks may be treated with 6 – 8 cycles of CHOP+R. Patient should also receive additional adjuvant RT.

Patients with localized but bulky disease and/or local extra nodal disease may be effectively treated with a full course of CHOP chemotherapy (6-8 cycles) with rituximab and involved field RT.

Patients with advanced stage disease with low or intermediate risk (as indicated by normal LDH serum level and normal performance status, ECOG 0 or 1) are given full course R-CHOP (6 - 8 cycles).

Patients with advanced stage disease who fall into the IPI high-intermediate or high-risk category have less than 50% chance of being cured with standard chemotherapy. For this reason the general consensus is that if possible these patients should be treated or should be placed in different clinical trials. If they cannot get a chance in a clinical trial, the alternative would be 6-8 cycles of CHOP with rituximab.

Patients who are receiving induction chemotherapy should undergo repeat radiographic evaluation after 3-4 cycles of treatment. This early restaging is done to identify at the earliest possible point, patients who do not respond or has progressed despite induction treatment. After completing the induction therapy, all positive radiographic studies should be repeated. Functional imaging (gallium or PET scans) may be useful in determining whether residual masses represent fibrosis or active tumor. A repeat biopsy of the residual mass is always warranted if they remain positive on functional imaging scan after completing the induction therapy. This repeat biopsy may yield other diagnosis like tuberculosis, sarcoidosis, fungal infection, a different lymphoma, desmoid tumor, nonspecific inflammatory process, follicular hyperplasia etc.

Patients who have completed the chemotherapy and is in complete remission should undergo periodic follow up because there is a good chance for a recurrence. Most patients who relapse will do so in the first 2-3 years. Patients may be reviewed at 2 monthly interval for the first year, 3 monthly intervals for the second year, 4 monthly intervals for the third year, twice a year for the 4th and 5th years and then annually indefinitely.

For patients with partial remission, autologous stem cell transplantation or therapy with higher RT dose may be considered. Appropriate clinical trails are also recommended for partial remission.

Those patients who relapse after initial remission or those who have refractory disease are candidates for non-cross-resistant combination chemotherapeutic regimens. Some of these are ICE (ifosfamide, carboplatin and etoposide), DHAP (dexamethasone, cytarabine, and cisplatin), MINE (mitoxantrone, ifosfamide, mesna, etoposide) etc. Patients responding to this chemotherapy should be considered for further consolidation with high dose therapy and stem cell support. Additional RT can be given before or after stem cell transplant to sites of bulky disease. Those who relapse after this should enter a clinical trial or treated individually. Disease

progression after 3 successive chemotherapeutic regimens is not likely to benefit from currently available standard therapy except for patients with a long disease free interval.

Management of Follicular Lymphoma

Follicular Lymphoma (FL) is the next common form of NHL and its characteristic immunophenotype includes CD 10+,bcl 2+, CD 23±, CD 43-, CD 5-, CD 20+, cyclin D1-. 90% of cases have a chromosome translocation, t(14:18).

Treatment of Grade 1 and 2 follicular lymphoma depends on the extent of the initial disease.[13,14] Grade 3 FL is treated according to the guidelines for DLBCL.

Patients are grouped into the following.

1. Patients with non bulky localized (Ann Arbor stage I-II).
2. Patients with localized bulky (Ann Arbor stage II), abdominal or stage III or IV disease.
3. Patients with relapsed disease.

Radiotherapy alone (with doses of 30 to 36 Gy) is standard treatment for patients with CS I to II follicular grade I to II lymphoma. 10-year over all survival ranges from 43% to 79%, with a median survival of 11.9 to 15.3 years. If patients relapse following localized RT or have no response to initial therapy, they should be managed in the same manner as patients with systemic presentation of FL.

Patients with more extensive disease should be treated based on the following indications: symptoms, threatened end organ dysfunction, cytopenia secondary to lymphoma, bulky disease at presentation, and steady progression of the disease and/or patient preference. Patients should also be given a chance to enter a clinical trial. In the absence of an appropriate clinical trial numerous treatment options are available including loco regional RT and single agent or combination chemotherapy. The selection of treatment should be highly individualized taking into consideration the age, extent of disease, co-morbid conditions and the goals of therapy. Lack of survival advantage and an early use of an anthracycline are not universally accepted by NCCN (National Comprehensive Cancer Network) panel. However the addition of rituximab to chemotherapy regimens for follicular lymphoma has consistently improved overall response rate, complete response rate and progression free survival. Clear evidence supporting a survival advantage is still lacking. Currently rituximab with combination chemotherapy is the preferred mode of treatment. Maintenance treatment with rituximab has been shown to improve survival but many questions remain to be answered.[15]

Single agent drugs include : cyclophosphamide, rituximab, and chlorambucil

Combination drugs include : CVP (cyclophosphamide, vincristine, prednisone); FND±R (fludarabine, mitoxantrone, dexamethasone, rituximab); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combined with rituximab.

Patients who are responding to the treatment are usually followed until their disease recurs. At recurrence, a repeat biopsy is usually indicated to find out if there is a histologic transformation especially when there is a rising LDH levels, disproportional growth in one area, development of extranodal disease or new "B" symptoms. If repeat biopsy shows transformation to DLBCL, patient may be given anthracycline based therapy or chemotherapy ± rituximab if the patient has had minimal prior chemotherapy or did not have one. This may be followed by consideration of either an autologous or allogenic stem cell transplant.

Two new radio immunotherapy agents, 90Y-ibritumomab tiuxetan (Zevalin) and iodine-131I-tositumomab (Bexxar) directed against the CD20 surface antigen found on normal mature B cells are available for therapeutic use and have significant activity in the treatment of relapsed and refractory disease. Both compounds produce similar clinical outcomes (approximately 20%-40% complete response rates and 60%-80% overall response

Table 4 : Staging of Chronic lymphatic leukemia

Rai Stage	Modified Rai Stage	Description	Binet Stage	Description
0	Low risk	Lymphocytosis only	A	Two or fewer lymphoid-bearing areas
1	Intermediate risk	Lymphocytosis and lymphadenopathy	B	Three or more lymphoid-bearing areas
2	Intermediate risk	Lymphocytosis and splenomegaly with/ without lymphadenopathy	–	–
3	High risk	Lymphocytosis and anemia (hemoglobin, < 11 g/dL)	C	Anemia (hemoglobin, < 10 g/dL) or thrombocytopenia (platelets, 100 x 10^6/dL)
4	High risk	Lymphocytosis and thrombocytopenia (platelets, < 100 x 10^6/dL)	–	–

rates for patients with indolent B-cell NHL).[16] High dose chemotherapy with an autologous or allogenic source of stem cell support may also be an appropriate option.

Management of chronic lymphocytic leukemia/ Small lymphocytic lymphoma (CLL/SLL)

These are considered to be the different manifestations of the same disease and managed almost in the same manner. The typical immunophenotype include CD5+, CD19+, CD20 dim, CD23+, CD43±, CD10-, and cyclin D1-. Mantle cell lymphoma is differentiated from these by the point that CLL/ SLL is cyclin D1-. Cytogenetics like t(11:14) also distinguishes mantle cell lymphoma (MCL) from CLL. Prognostic stratification of CLL can now be made depending on FISH, gene mutation and flow cytometric studies.

Patient stratification for treatment is:

1. Patients with localized (Ann Arbor I-II).
2. Patients with advance (Ann Arbor III-IV) disease.

Loco regional RT or observation is an appropriate option for localized disease. Patients are treated as needed for symptoms, threatened end organ function, cytopenia, bulky disease at presentation, steady progression of the disease, histological transformation and or according to the patient's preference, if the disease progresses. Since the disease is incurable with the currently available standard therapy patient may be given a chance to enter a clinical trial. Patients with advance disease are also treated as needed in keeping with the above indications. Patients with recurrent infections may benefit from intravenous immunoglobulin. Rai good risk disease does not need treatment (Rai staging Table 4). Intermediate risk disease can be observed and high risk disease is treated at presentation.

Currently options for systemic chemotherapy include the following groups of drugs.

1. An alkylating agent – chlorambucil
2. Purine analog with or without rituximab – fludarabine with or without rituximab
3. An alkylating agent based combination chemotherapeutic regimen – Cyclophosphamide with or without prednisone, CVP (cyclophosphamide vincristine and prednisone), FCR (fludarabine, cyclophosphamide with or without rituximab).

Different centers use one of the above regimens. It is generally observed that addition of rituximab to fludarabine prolongs progression free and over all survival.

The dose schedules of the different drugs are given below:

Chlorambucil- Different doses and schedules are used. Commonly used dose is 10 mg daily for 2 weeks, repeated every month.

FC - Fludarabine, 25 mg/m^2 and Cyclophosphamide, 250 mg/m^2, were given for 3 days

FND - Fludarabine 25 mg/m^2/d, x 3; mitoxantrone 10 mg/m^2/d, x 1; dexamethasone 20 mg/d, x 5; monthly cycles

FCR - Rituximab -375 mg/m^2 on day 1 intravenously (IV), fludarabine at a dose of 25 mg/m^2 IV and cyclophosphamide at a dose of 300 mg/m^2 IV daily for 3 consecutive days, repeated every 3 weeks. So far FCR has been shown to produce the best response rates.[17]

Patients who achieve a complete or partial response are generally monitored and additional therapy should be given only if he enters a clinical trial.

Treatment options for patients with disease progression are similar to those available as initial therapy. In addition, alemtuzumab is now approved for the therapy of relapsed or refractory CLL. A combination on pentostatin and cyclophosphamide with or without rituximab (PC ± R) has shown significant activity in relapsed and refractory patients.

The three forms of autoimmune cytopenia that occur in CLL are treated by targeted therapy. Auto immune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) are treated with steroids. Intravenous immunoglobulin may be used for refractory cases. Rituximab and splenectomy are the options for selected patients. Immunosuppressive agents like prednisone, cyclosporine and ATG (Anti Thymocyte Globulin) are indicated for treatment of pure red cell aplasia.

Rest of the entities included in NHL is uncommon and only very elementary points will be discussed regarding this.

Management of marginal zone lymphoma (MZL)

This is a heterogeneous group of disorders consisting of

1. Mucosa associated lymphoid tissue lymphoma (MALT) which is further divided into gastric and non gastric. The gastric MALT lymphoma is associated with H. pylori infection which has a critical role in the pathogenesis of the disease and its eradication can lead to tumor emission
2. Nodal MZL (this is considered as a systemic indolent lymphoma under follicular lymphoma) and
3. Splenic MZL.

The typical immunophenotype of MZL is CD5- , CD10- , CD20+ , CD23±, CD43±, cyclin D1-, bcl-2 follicles. In addition a Helicobacter pylori stain is considered essential in gastric malt lymphoma. Molecular, cytogenetic or FISH evaluation for the t (11; 18) chromosomal translocation fusing the AP12 and MALT1 genes may be helpful.

Gastric MALT lymphoma

About 2/3rds of the patients with localized gastric MALT lymphoma have a complete tumor remission after eradication on H. pylori infection with antibiotic therapy.[18] Relapses can occur and a long duration of follow up is necessary.

Stages 1E-H. pylori positive

Here the disease is confined to the stomach and treatment begins with antibiotics in combination with a proton pump inhibitor to block gastric acid secretion. An endoscopy is done at the end of 3 months. If there is evidence of t (11;18) chromosomal translocation, treatment of the H. pylori infection with antibiotics may be ineffective and treatment with involved field radiation therapy is appropriate.

Stages 1E or II H. pylori negative

They could also be treated with an empiric course of antibiotic and reevaluated at 3 months with endoscopy. Preferred method of treatment of these patients is involved field RT especially if they have t (11;18) translocation. Rituximab is an option if radiation therapy is contraindicated.

Endoscopic reevaluation after antibiotics

Four distinct outcomes are observed.

1. Patients who have both microbiologic and tumor response are just observed
2. Patients who have no evidence of H. pylori but have persistent lymphoma. RT is indicated for patients with significant disease progression or symptoms. Other asymptomatic patients may be observed every 3 months or loco regional RT is appropriate.
3. Patients with persistent H. pylori and regressing or stable symptoms are treated with second line antibiotics.
4. Patients with H. pylori positive and persistent lymphoma. RT is given for progressive disease and second line antibiotics if the disease is stable.

All the patients should be followed up for a long time with repeat endoscopy. Generally recurrence of lymphoma is treated with loco regional RT if not previously treated. Those who do not respond to radiation may be treated with single agent or combinational chemotherapy. Surgery is reserved for those who do not respond to other therapeutic modalities.

Stages III/IV

These patients with disseminated disease, management is similar to the management of other advanced stage follicular lymphoma.

Non-gastric MALT Lymphoma

They can arise from a large number of sites including skin, lung, salivary gland, conjunctiva, prostate, ovary, small bowel and colon. For patients with 1E or II disease, loco regional RT is appropriate. For certain sites of the disease (e.g.: lung, colon, skin, thyroid, small intestine, breast) primary surgery is appropriate. Patients with advanced stage disease are treated in the same way as follicular lymphoma.

Management of splenic MZL

The diagnosis is often presumptive based on the findings of splenomegaly with peripheral blood flow cytometry usually revealing a monoclonal B cell population. This is distinguished from CLL with the absence of CD5 expression and strong CD20 expression. Patients who are positive for hepatitis C should have appropriate consultation to determine if there are indications for treatment of the viral infection. If antiviral treatment is given, the patient should be monitored for tumor response. All other patients should be observed if in the absence of cytopenias or symptoms. Splenectomy is indicated if there are cytopenias or symptoms and they should be monitored at regular basis. If splenectomy is contraindicated, they are treated as advanced stage follicular lymphoma.

Management of Mantle cell Lymphoma

The diagnosis is established by histological examination in combination with immunohistochemistry. The profile includes CD5+, CD10±, CD20+, CD23±, CD43+ and cyclin D1+. Mantle cell lymphoma has the worst characteristic combination of both indolent and aggressive NHL. Like many other indolent lymphoma it is incurable with conventional chemotherapy but it does not have an indolent natural history. It has a shorter disease free and overall survival more like an aggressive lymphoma. Therefore there is no established standard of care. Patients should be referred for participation in prospective clinical trials. Outside a clinical trial the recommendation is that patient should have either combined modality therapy or involved field radiation therapy. Advanced stage disease requires systemic therapy. Several regimens have shown significant activity including R-Hyper CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with methotrexate and cytarabine, R-CHOP and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin). Adjuvant stem cell transplant may be given or initial remission may be followed by stem cell transplantation. The optimal approach for

recurrent disease remains to be defined. Entry into clinical trials is strongly encouraged. Single agents like cladribine and bortezomib, or combination chemotherapy including a number of drugs have been suggested. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed/refractory MCL. Radio immunotherapy has been shown to be active for both untreated and relapsed MCL.[19]

Highly aggressive lymphomas

Burkitt's lymphoma and lymphoblastic lymphomas are included in this category as they have an exponential growth rate and a tendency to disseminate to the bone marrow and the meninges. They are aggressive B cell tumors involving extra nodal disease sites. These tumors pose a high risk for tumor lysis. So appropriate treatment includes allopurinol and hydration. Patients with Burkitt's lymphoma who have a completely resected abdominal lesion or a single extra abdominal mass and a normal LDH level are considered to have low risk disease. All others have high risk disease and should be treated by combination chemotherapy regimen including intensive alkylating agent, anthracycline, intrathecal chemotherapy and high dose methotrexate with or without rituximab.[20] Patients with relapse should be treated in the context of a clinical trial whenever possible. Lymphoblastic lymphoma is treated with regimens appropriate for acute lymphoblastic leukemia (ALL).

AIDS related B-Cell Lymphoma

Patients with AIDS can develop several forms on NLH e.g.: Burkitt's lymphoma, DLBCL and primary CNS lymphoma. Patients who develop Burkitt's lymphoma generally have a good CD4 count while patients with CNS lymphoma have very low CD4 count and uncontrolled AIDS. Optimal management of HIV associated lymphoma has not been established. Several key features have emerged which are critically important. Early introduction of HAART has good long term results. Prophylactic intrathecal chemotherapy is very important. Inclusion of rituximab appears to increase the risk of neutropenia and infection and is found to have no benefit in patients with HIV associated lymphoma.[21]

Peripheral T cell lymphoma

The term peripheral T cell lymphoma means, lymphoma of a mature T cell phenotype and not the site of involvement by lymphoma. Majority of these patients present with stage IV disease. The clinical course is aggressive, and relapses may be more common than in large B-cell lymphoma. Treatment regimens used for peripheral T-cell lymphoma are same as that used for DLBCL, with the omission of rituximab. Because of the poorer OS in peripheral T-cell lymphoma as compared with DLBCL, bone marrow transplantation is more frequently required. Bone marrow transplantation may be as effective in peripheral T-cell lymphoma as in DLBCL. In the setting of recurrent disease, purine analogs may have modest activity.[20]

In summary, a great progress has been made in the understanding and management of NHL which are relatively common neoplasms. It is strongly recommended that a correct and most appropriate diagnosis should be made before starting the treatment. This has been made possible by various morphologic, cytogenetic, molecular and FISH techniques. One should know thoroughly regarding all aspects of commonly occurring NLH like DLBCL, FL, CLL/SLL, MZL and mantle cell lymphoma. Other rare entities should be kept in mind so that appropriate diagnosis and treatment are instituted. The most consoling aspect of treatment of NHL is that more than 50% of DLBCL (the most common form of NHL) can be cured with modern treatment. Future of NHL includes a general awareness of the disease so that the disease could be diagnosed at a very early stage with the possibility of cure in many more patients. Newer and less toxic chemotherapeutic agents are on the horizon and radio immunotherapy has shown good promise. To improve the Indian situation,

there should be an online NHL registry under the responsibility of some good center where all NHL cases in India should be reported including diagnosis, management and outcome. This would give us a strong footing in the international arena.

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