INTRODUCTION

Non-Hodgkin Lymphomas are a heterogeneous group of malignant neoplasms in which lymphocytes—either of B-cell, T-cell, or natural killer (NK)-cell origin have arrested at various stages of differentiation, have acquired the ability to clonally proliferate, and do not undergo apoptosis in a typical fashion. B cell is the commonest. Tumor clonality is established by demonstrating immunoglobulin gene rearrangement in B-cells, T-cell receptor rearrangement in T-cells, or more sophisticated methods such as the finding of a reciprocal cytogenetic translocation or molecular rearrangements by fluorescent in situ hybridization or polymerase chain reaction (PCR). In US lymphoma is the commonest hematological malignancy. Diffuse large B Cell Lymphoma (DLBCL) is the commonest. The disease is associated with a male dominance.

CLASSIFICATION:

The initial classification of Lymphoma was on the basis of grades—low, intermediate and high grade. But clinicians found out a lot of heterogeneity amongst the different types. The REAL (Revised European American Classification of Lymphoid Neoplasms) classification modified this to an extent and what is followed currently is the WHO classification which takes into account—morphology, immunophenotype, genetics, molecular profiles and clinical presentations. This has helped in identifying “grey zone” lymphomas, which are intermediate between two types of lymphomas.

<table>
<thead>
<tr>
<th>Infectious agents associated with NHL</th>
<th>Type of Lymphoma</th>
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<tr>
<td>Human T cell lymphotropic Virus type I</td>
<td>ATLL</td>
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<td>Helicobacter Pylori</td>
<td>Gastric MALT</td>
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<tr>
<td>Hepatitis C</td>
<td>Splenic marginal zone lymphoma, lymphoplasmacytic Lymphoma, nodal marginal zone lymphoma, DLBCL</td>
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<tr>
<td>Human herpesvirus 8</td>
<td>Primary effusion lymphoma, plasmablastic lymphoma</td>
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<tr>
<td>Human immunodeficiency Virus</td>
<td>DLBCL, Burkitt lymphoma, PCNSL, primary effusion lymphoma, plasmablastic lymphoma</td>
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<tr>
<td>Borrelia burgdorferi</td>
<td>Cutaneous B-cell lymphoma</td>
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<tr>
<td>Chlamydia psittaci</td>
<td>Ocular adnexal MALT</td>
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<tr>
<td>Chlamydia trachomatis</td>
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<tr>
<td>Chlamydia pneumonia</td>
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<tr>
<td>Campylobacter jejuni</td>
<td>Small intestine MALT</td>
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WORK UP

Apart from the conventional biochemical and haematological parameters optional procedures (depending on specific lymphoma type) include beta 2 microglobulin, endoscopic ultrasound (gastric MALT lymphoma), CT Scan or MRI brain and lumbar puncture to analyze cerebrospinal fluid (Mantle Cell Lymphoma and Diffuse Large B Cell Lymphoma). MUGA scan (multigated acquisition scan) or echocardiograms are recommended when anthracyclines and anthracyclinedione containing regimens are used. Discussion of fertility issues and sperm banking ought to be performed under certain circumstances. Hepatitis B reactivation has been reported in several patients treated with rituximab (anti CD 20 monoclonal antibody) in combination with chemotherapy. Hepatitis B testing is a part of essential work-up prior to initiation. Bone marrow biopsy is usually included in the work-up for patients with NHL. However it may be safely omitted in selected patients with early stage DLBCL.

DIAGNOSIS

An incisional or excisional lymphnode biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL.

Diffuse large B Cell Lymphoma (DLBCL), Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) deserve special mention. Mantle Cell Lymphoma is characterised by CD5 positive, CD 23 negative and cyclin D1 positive. Dysregulated expression of cyclin D1, a cell cycle protein that results from the chromosomal translocation, t(11;14) is seen in the vast majority of cases. BCL2 is over-expressed as the consequence of the t(14;18) translocation in 90% cases of Follicular Lymphoma. The increased production of BCL-2 protects the lymphoma cells from apoptosis. Lymphoblastic Lymphoma which are aggressive in nature are commonly of T cell lineages (85-90%). They are positive for immature markers such as CD99 and Tdt (). The monoclonal antibody Ki-67 is used to detect proliferation index (P) which has been found to have significance in FL as well as in other lymphomas.

ROLE OF PET/CT IMAGING:

Fluorodeoxyglucose (FDG)-PET (Positron Emission Technology) scans and PET/CT scans exploit the enhanced rate of glucose utilisation (both uptake and phosphorylation) seen in many tumour cells as compared to normal surrounding cells (the Warburg effect). Thus, FDG-PET scans can provide a semiquantitative measurement of tumour involvement in Nulls, which has proven to have superior sensitivity compared to anatomic imaging alone. PET/CT scans are not without drawbacks, however, FDG uptake in tumour cells and the subsequent appearance on PET scan is dependent on a number of variables related to the tumour such as blood flow, glucose transporters, tumour cell number, and tumour proliferation, and also related to nontumour variables such as the fat content of the patient, technicalities regarding the procurement of the images, resolution of the scanner and clinician interpretation. Nonetheless, PET scans and PET/CT scans have essentially become the standard of care in the US for aiding the initial evaluation and staging of patients with newly diagnosed aggressive lymphomas. They are also utilised for the response evaluation and follow up. False positive results occur at the sites of inflammation and necrotic tissue infiltrated by macrophages. The role of PET/CT in indolent NHL is less as these are slow growing tumors and uptake is variable. Chances of false negative results are high. It is estimated that using PET/CT at diagnosis will upstage about 15% to 20% of patients with NHL, but the impact of this on treatment options or ultimate outcomes has not yet been elucidated.

PROGNOSTIC FACTORS

INTERNATIONAL PROGNOSTIC INDEX (IPI): The prognosis of patients with newly diagnosed NHL is clearly related to more than just Ann Arbor staging, and it is standard practice to determine the IPI at diagnosis in patients with diffuse large cell B-cell lymphoma (DLBCL). The IPI score is based on age, stage, performance status, number of extranodal sites of disease, and lactate dehydrogenase (LDH) level. Each is designated a score of 1. The higher the value, worse is the prognosis. For all patients, 5 year survival was 73% for low risk patients, 51% for low/intermediate risk patients and 26% for high risk patients. For Follicular Lymphoma the prognostic index is called FLIPI (Follicular Lymphoma International Prognostic Index). three risk groups have been identified on the basis of age, stage, haemoglobin, LDH and number of nodal sites.

Gene expression profiling (GEP): Clinical variables maybe dominated by extent of disease burden. So researchers tried to predict the clinical behaviour of lymphomas based on the expression of genes on tissue microarray. With the advent of GEP, it has become possible to predict outcomes based on the molecular profile of the tissue. The best example is DLBCL, which can be subdivided into 3 subtypes; germinal center B-cell (GCB) which responds more favourably to standard chemotherapy regimens, activated B cell subtype (ABC) and primary mediastinal B cell lymphoma (PMBL) with the best overall prognosis.
Functional biomarkers: Patients who have a negative PET after 1 to 2 cycles of chemotherapy have a much more favourable prognosis.1

TREATMENT

Indolent NHL: Watchful waiting is an appropriate strategy in many patients until there is evidence of undesired symptoms. One of the greatest achievements in Lymphoma is the group of monoclonal antibodies. Rituximab is a chimeric monoclonal antibody against CD20 that has revolutionised the treatment of all B-Cell NHLs since early 2000s. Single agent Rituximab is not terribly effective for patients with bulky nodes & should be reserved for patients who are not candidates for combination chemotherapy in Follicular Lymphoma (FL).18 The use of anthracyclines is not mandatory in patients with untreated FL. Common regimens include R-CVP (Rituximab, Cyclophosphamide, Vincristine, Prednisone) and R-FND (Rituximab, Fludarabine, Mitoxantrone, Dexamethasone). Bendamustine-Rituximab has shown surprisingly high response rates & PFS but with less toxicity in a recent randomised study compared to R-CHOP (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Prednisone).20 Other treatments include anti CD 20 Radio-Immuno Conjugates where a radioactive substance is conjugated with antibodies. Example are iodine131 – tositumomab and ibritumomab tiuxetan. They are approved for used as both the initial therapy of indolent NHL as well as in consolidation strategy after initial chemotherapy.21,22,23 Maintenance therapy in indolent NHL with Rituximab has recently reported a benefit in PFS (progression free survival) but no OS (overall survival) benefit as per PRIMA trial. In case of relapse the patients who did not get Rituximab in the first line should get chemotherapy along with Rituximab. Rituximab maintenance or stem cell transplantation should be kept for second remission.24 Gastric MALT lymphomas (Mucosa associated lymphoid tissue) associated with H pylori responds to antibiotic therapy directed at the bacteria alone and does not require either radiation or chemotherapy in early disease.25

Mantle cell lymphoma: shares the worst features of both indolent NHLs and aggressive NHLs. It is sensitive to RCHOP and radiation. But the responses are brief and at the time of relapse are chemotherapy resistant. For fit patients the ideal strategy would be to administer intense chemotherapy regimens with cytarabine based combinations and to consolidate with high dose therapy with stem cell rescue in first Complete Response.26

Peripheral T cell Lymphomas (PTCL): They have poor prognosis except ALK positive ALCL (Anaplastic Large Cell Lymphoma) which responds to CHOP. Agents that seem to have activity are gemcitabine, alemtuzumab (anti CD 52 antibody), pentostatin, histone deacetylase inhibitors and lenalidomide. In 2009, the US FDA approved a drug specifically for the treatment of relapsed or refractory PTCL – pralatrexate an antifolate.1,27

Diffuse large B cell lymphoma: 6-8 courses of R-CHOP has become the gold standard after the results of the GELA Trial in the elderly population (age>60 yrs).28 The MInT study29 demonstrated the superiority of R-CHOP in improving the OS for patients younger than 60. In a German study CHOP given every 14 days with G-CSF support produced a better complete remission rate (77% vs 63.2%) and longer time to treatment failure compared to CHOP every 21 days.30 Radiation is useful for patients presenting with bulky disease along with chemotherapy and in early stages as a solitary modality.31 In case of relapse, patients who have not received Rituximab in the first line should get a regimen with Rituximab. The common regimens are R-ICE (Rituximab, Ifosfamide, Etoposide, and Carboplatin), R-DHAP (Rituximab, Cisplatin, Cytrabine and Dexamethasone) and R-ESHAP (Rituximab, Etoposide, Methylprednisolone, Cytrabine and Cisplatin).32 If the patients show chemo responsiveness then they are taken up for ASCT (Autologous Stem cell Transplantation). There is increased usage of growth factors and pegylated G-CSF (Granulocyte Colony Stimulating Factors. Recent analyses have shown that, by reducing the risk of febrile neutropenia and chemotherapy dose delays and reductions, G-CSF prophylaxis can potentially enhance survival benefits in patients receiving chemotherapy in curative settings. A single dose of Pegylated G-CSF (pegfilgrastim) may provide a more effective, as well as a more convenient, alternative to daily G-CSF.33

LYMPHOBLASTIC LYMPHOMA (LBL) & BURKITT’S LYMPHOMA (BL):

These are highly aggressive lymphomas. LBL is treated with ALL like regimens with CNS prophylaxis and are typically administered in three phases (induction, consolidation and maintenance) with prolonged administration lasting up to 24 to 36 months. Burkitt’s lymphoma is associated with c-MYC translocation in all cases and most commonly arise from reciprocal t(8;14) translocation. R-CHOP is not adequate therapy for BL and Hyper CVAD and CODX-M regimens are preferred.34

LYMPHOMAS NEEDING SPECIAL MENTION

A. Post-transplant lymphoproliferative disorders (PTLDs):

Abnormal expansions of lymphoid cells (either B-cell or T-cell) in patients who have undergone either solid organ or hematopoietic stem cell transplantation are defined as PTLDs. Marked variation ranging from benign expansions to aggressive and fatal NHL. Radiotherapy or surgery can be effective in localised and accessible disease, but for more advanced disease and for disease in which the lymphocytes are monoclonal, combina-
tion chemotherapy with or without rituximab or donor lymphocyte infusions for stem cell transplant patients is often necessary.¹

Risk factors for PTLDs:
Seronegative for EBV pretransplantation (HSCT recipients)
Age>50years at time of transplantation
Use of a second transplantation
Less than 1 year since transplantation
AGT or OKT3 (anti CD3 monoclonal antibody) as prophylaxis
Unrelated or mismatched HLA grafts
Use of a T-cell depleted graft
Acute or chronic GVHD
Cardiac transplant>renal transplant

NHL in the elderly:
Age consistently is important prognostic marker in outcomes in NHL. A common clinical problem involves the selection of appropriate therapy for a patient with intermediate grade NHL over the age of 70 years or older than 60 years with significant comorbid disease. Data regarding patients over the age of 80 years being virtually nonexistent. Empiric dose reductions or dose delays likely compromise the potential for cure. In GELA trial, 399 patients with DLBCL aged 60 to 80 years were treated with R-CHOP versus CHOP. The addition of rituximab was associated with a 15% improvement in CR rate with associated improvements in DFS and OS. In this trial, the most common grade 3 toxicity was infection, grade 3 cardiac toxicities were seen in only 8% of patients, and other toxicities were consistent with those expected with the use of CHOP in younger populations.³⁵

Therapy of Relapsed NHL
Salvage Chemotherapy:
i. Upto 50% of patients with DLBCL will ultimately relapse after initial chemoimmunotherapy, the number is higher with MCL and PTCL. Tumors that have become chemo-resistant or are primarily refractory to initial chemotherapy (defined as duration of response < 6 months) uniformly have a dismal prognosis and are likely incurable. Typically Platinum based regimens are given and after chemosensitivity, are taken up for high dose therapy with stem cell rescue.²⁸ SK PARMA trial in the pre-rituximab era demonstrated an OS for patients undergoing autologous transplant in first relapse versus chemotherapy alone.³⁶ But in the rituximab era biology of disease relapse is less known. The recently presented results of the CORAL study suggest fewer patients (15%) will be salvaged with autologous transplantation done in second CR, suggesting the need for use of novel agents.³⁷ In the era of PET/CT scan – emerging concept is that patients with residual disease in PET prior to transplant may not benefit from high dose therapy and should not be offered this approach. In case of FL the approach of autologous transplant in first CR improves PFS but not OS.

ii. Allogenic transplantation in relapsed NHL:
Myeloablative allogenic transplantation has traditionally been reserved as a last ditch options for select patients with relapsed both indolent and aggressive NHLs that have failed all other therapies. Even though the graft-versus-leukemia effect can be very potent in NHL, incidence of at least grade III GVHD has been a significant barrier to widespread use of this approach. Nevertheless, it appears that allogenic transplantation is a potentially curative approach in carefully selected patients with relapsed NHL; with the use of reduced-intensity preparative regimens, more patients are becoming eligible for this high-risk/high-reward therapy.¹

iii. Novel/targeted agents:
Agents that are currently being studied include immunomodulating agents(such as lenalidomide), proteasome inhibitors(such as bortezomib) in combination with Rituximab, BCL2 inhibitors, histone deacetylase inhibitors, mammalian target of rapamycin inhibitors, PI3K/Akt inhibitors, MEK inhibitors, PARP inhibitors, cyclin dependent kinase inhibitors, and novel monoclonal antibodies targeting both CD20 and CD19, Vaccines.¹

Indian Data: The distribution of NHL is as follows;³⁸
DLBCL-34%
Follicular centre-cell lymphomas-12.6%
B-cell small lymphocytic lymphoma-5.7%
Mantle-cell lymphoma-3.4 %
Marginal zone B-cell lymphomas (including MALT lymphomas)-8.2 %

Survey amongst clinicians regarding awareness of Lymphoma:
Recently a survey was conducted amongst the internists in a metro-city regarding the awareness of role of immunohistochemistry in the diagnosis of Lymphoma. An educational session was conducted and a post session survey revealed that most of the internists would advice histopathology examination followed by immunohistochemistry for a better diagnosis and are convinced that FNAC is not adequate for diagnosis and management of lymphoma. The results are depicted in the charts below.

Chart 1

<table>
<thead>
<tr>
<th>Consideration Of Immunohistochemistry for Work out of NHL</th>
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<tr>
<td>Never</td>
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<td>24%</td>
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Chart 2

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<th>Degree of Agreement in PATIENT Outcome through Diagnosis</th>
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<tbody>
<tr>
<td>Strongly Agree</td>
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<tr>
<td>28%</td>
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</table>

REFERENCES

20. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of profession-free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mant-


