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Recent Advances in Diffuse Large B Cell Lymphoma

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Abstract

More recently, DLBCL has witnessed advances in the molecular profiling and treatment of patients with refractory and relapsed disease. DLBCL is biologically and clinically a heterogeneous disease. Despite its aggressive behavior, DLBCL is a potentially curable disease with overall survival of 94 and 55% in patients with low and high rIPI scores, respectively. The combination of anti-CD 20 monoclonal antibody rituximab and cyclophosphamide, doxorubicin, oncovin (vincristine) and prednisone (R-CHOP) chemotherapy every 3 weeks is the first line treatment. Radiotherapy is reserved for the patients with bulky disease who fail to achieve complete remission after first line treatment. CNS prophylaxis is reserved for the patients with high lactate dehydrogenase (LDH) levels and involvement of more than one extranodal sites and for the patients with involvement of selective extranodal sites like testes and orbits (the sanctuary sites). Patients who suffer relapse after first line treatment receive high-dose chemotherapy supported by autologous stem cell transplantation (HDC/ASCT). Variants of DLBCL like double-hit (presence of MYC and BCL2/BCL6) and triple-hit (presence of MYC, BCL2 and BCL6) lymphomas are treated differently and these patients have worse outcome. Several novel immunotherapeutic agents like checkpoint inhibitors and chimeric antigen receptor T cell (CART) are being investigated in randomized trials on patients with DLBCL.

Keywords: diffuse large B cell lymphoma, double-hit lymphoma, update, triple-hit lymphoma, R CHOP, DA-R EPOCH

1. General information

1.1. Epidemiology

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL). It constitutes for approximately 25% of patients with NHL [1].

The incidence of NHL is 19.5 per 100,000 men and women per year. Approximately 2.1% of men and women will be diagnosed with NHL at some point based on 2012–2014 SEER database [2] (SEER data). The incidence of DLBCL is approximately 7 cases per 100,000 persons per year. Males have a higher incidence with (M/F) incidence ratio of 1.5–1.6. Incidence is higher among whites than blacks or Asians and increases steeply with age. The overall incidence of DLBCL has declined 0.5% per year during 1992–2001 [2]. This decline was observed predominantly in men aged 25–54, on contrary in the elderly, the incidence of DLBCL increased 1.4% per year during the same time-period.

1.2. Etiology and risk factors

DLBCL is a mature B cell neoplasm arising from germinal center and post germinal center B cells. Etiology of DLBCL is complex and multifactorial. DLBCL can arise de-novo or from transformation of indolent diseases like chronic lymphocytic lymphoma/small lymphocytic lymphoma (so-called Richter's transformation), follicular lymphoma, and marginal zone lymphoma. Those that originate from previous hematological malignancies are generally more aggressive and carry a poor prognosis. Chemical substances such as pesticides, herbicides, alkylating agents, ionizing radiation have been implicated as risk factors. An association has been found between inherited immune deficiency disorders such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disorder [3]. Patients with acquired immunodeficiency states such as AIDS, organ or stem cell transplantation, autoimmune or rheumatologic diseases also have a higher incidence of DLBCL [4].

2. Pathology and biology

2.1. Pathogenesis

DLBCL is composed of large B cells with a diffuse growth pattern arising from mature B cells at different stages of differentiation. Normal B cell development takes place in the bone marrow and results in the transformation of a B-progenitor cell into mature B cell. Mature B cells have undergone immunoglobulin VDJ gene rearrangement and express a complete IgM antibody molecule on the cell surface [4]. After release from the bone marrow, antigen naïve mature B cells are exposed to antigen in the interfollicular area of the secondary lymphoid tissues. Majority then migrate into the germinal center. Mature antigen exposed B cells proliferate in the center of a primary follicle to form the germinal center. The centroblasts mature into centrocytes as they transition into light zone of the germinal center. In the germinal center, B cell undergoes class-switch recombination and somatic hypermutation. Centroblasts are thought to give rise to germinal center B cell (GCB) DLBCL. After transition through the germinal center, B cells can become memory cells or plasmablasts which undergo further development to become plasma cells. Plasmablasts are thought to give rise to activated B cell like (ABC) DLBCL [4].

2.2. Cell of origin

The cell of origin classification (COO) has been the most significant development in the understanding of DLBCL biology. The gold standard test to identify COO is Gene expression profiling (GEP). GEP divides DLBCL into germinal center B cell (GCB), activated B cell (ABC) or unclassifiable (Type 3) types. GCB DLBCL is derived from normal GC centroblasts. Various mechanisms have been elucidated that drives pathogenesis of these subclasses based on COO [5]. GCB like tumors contain the (14;18) translocation (IgH/BCL-2 fusion gene) typical of follicular lymphoma and amplifications of the locus on chromosome 2 which codes for the c-Rel oncogene. BCL2 is dysregulated by t (14;18), PTEN deletions and amplification of miR-17-92 leading to deregulation of PI3K/mTOR pathway which are activated further promoting cell survival, proliferation and growth. GCB is further characterized by gain or amplification of MDM2, a negative regulator of the tumor suppressor p53 as well as deletions of the known tumor suppressor genes TP73 and ING1 that lead to genomic stability. The GEP of ABC DLBCL suggests that it is derived from B cells that are in the process of differentiating into plasma cells. Most of the genes expressed by normal GCB cells are down regulated in ABC DLBCL. There is upregulation of many genes normally expressed by plasma cells including XBP-1, amplification of BCL2, CD79A/CD79B ITAM mutation/deletion leading to chronic active BCR signaling, CARD11/A20 mutation, MYD88 mutation, STAT3 activation which lead to NFkB activation, FOXP1 activation. ABC-like DLBCL is associated with loss of 6q21, trisomy 3, and gains of 3q and 18q21–22. This locus on 6q encodes suppressor gene PRDM1 (Blimp-1) which is a master regulator in the differentiation of mature B lymphocytes to plasma cells, loss of which may lead to inhibition of terminal differentiation. ABC DLBCL has high expression and constitutive activity of the nuclear factor kappa B (NF-κB) complex involved in the B cell receptor signaling pathway. This classification not only defined subgroups with distinct biology and pathogenesis but also identified groups of patients with different outcomes after treatment [4]. In a study done at British Columbia looking at outcomes in patients treated with R-CHOP, there were 56% patients with GCB subtype and 32% with ABC subtype. The ABC group experienced significantly inferior outcomes as compared to the GCB group [6]. A third type, type III DLBCL (Unclassifiable as per GEP profiling) is also identified in which tumor cells have gene expression profiles that do not resemble either germinal center or post germinal center B cells [4, 7].

2.3. Double-hit lymphomas/double expressor

DLBCL with MYC gene rearrangement in addition to BCL2 and/or BCL6 gene rearrangements by Fluorescent in Situ Hybridization (FISH) or standard cytogenetics are known as double-hit lymphomas. MYC is rearranged in 5–15% of DLBCL and is frequently associated with BCL2 or to a lesser extent, BCL6 translocation. They are more aggressive and have a much poorer prognosis. Double-hit lymphomas are now recognized as a distinct entity in the 2016 WHO classification [8]. MYC and BCL2 are the key regulators of cellular proliferation and apoptosis, respectively. Dysregulation of MYC and BCL2 can cause chromosomal translocation or gene amplification but it may also occur by transcriptional upregulation downstream of NFkB pathway signaling [9]. This leads to a highly aggressive clinical behavior with very high Ki67 and overlapping pathologic features with Burkitt's lymphoma. These patients have an inferior

prognosis compared to those with DLBCL without these mutations. FISH for MYC, BCL2 and BCL6 gene rearrangements should be tested for patients with expression of MYC and either BCL2 or BCL6 by IHC and a GCB like immunophenotype to identify these double- (or triple-hit) lymphomas [10]. They have very poor outcomes with standard R-CHOP-based chemotherapy [11]. While the cases identified by FISH positive results are called double- (or triple-hit) lymphomas, those patients with high expression of MYC and BCL2 protein by Immunohistochemistry (IHC) alone in the absence of gene rearrangements by FISH are labeled as double expressor and they seem to have an intermediate prognosis.

In a study on 193 patients who were double expressor the 3 year OS rate was 46 vs. 75% and the 3 year PFS rate was 46 vs. 65% [11].

2.4. Morphology

Under light microscopy, the normal architecture of lymph nodes is completely effaced by the sheets of atypical lymphoid cells. The tumor cells resemble normal centroblasts or immunoblasts with nuclei size at least twice the size of a small lymphocyte. While the centroblasts are large,

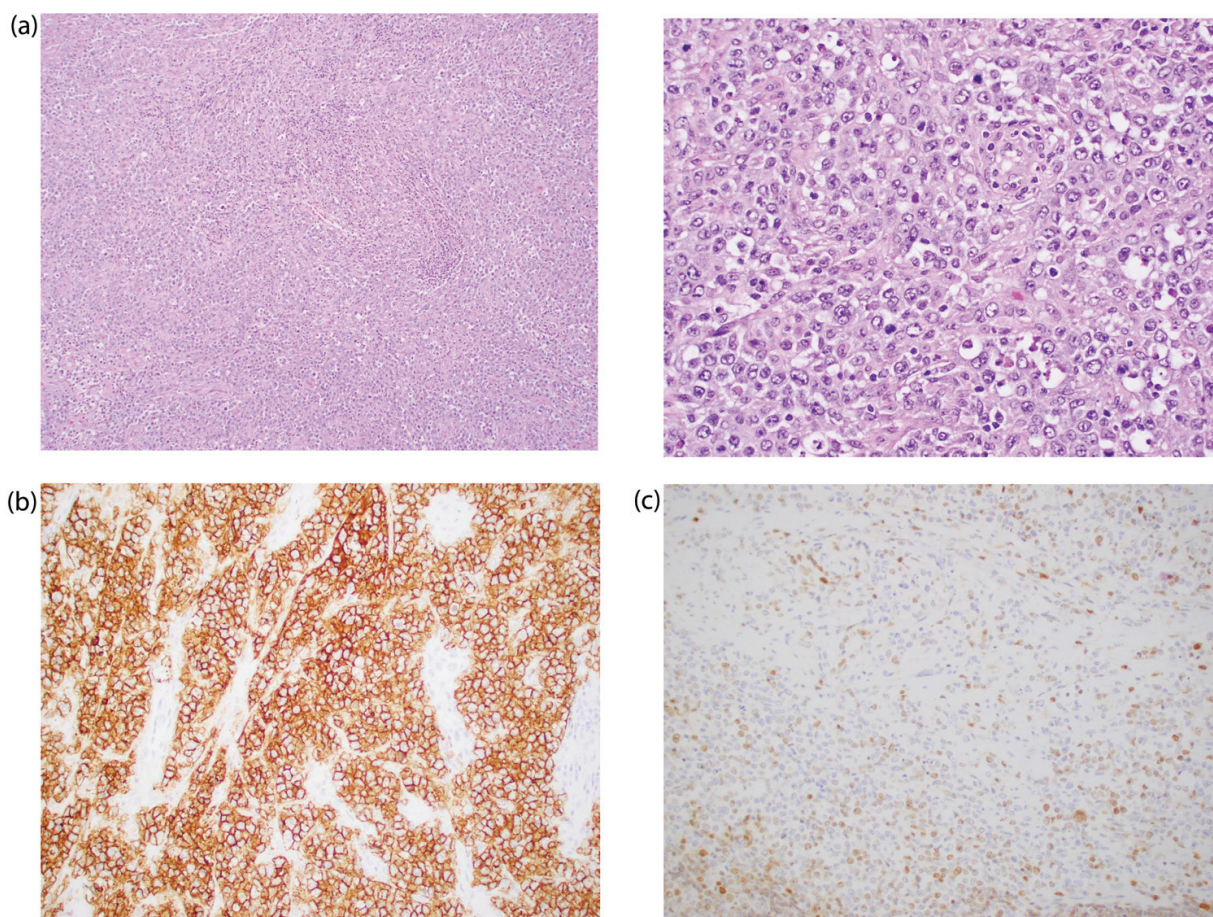


Figure 1. Lymph node sections showing GC type DLBCL (a) The H&E stained sections of lymph node showing diffuse infiltration of atypical lymphoid cells that are large in size with irregular nuclear contours, vesicular chromatin, and some with prominent nucleoli (X10 and X40 magnification). (b) On immunohistochemistry, CD20 highlights the infiltrating cells (X20 magnification) (c) cells are negative for MUM1 (major subset) (X20 magnification).

noncleaved cells, with round to oval nuclei with multiple nucleoli and thin rim of basophilic cytoplasm, the immunoblasts are larger cells with more prominent nucleoli and abundant cytoplasm. Other less common cytological variants include multilobated and anaplastic forms. However the clinical significance of less common forms is debatable. Due to inter- and intra-observer variability in the characterization of DLBCL based on the appearance of tumor cells, all the morphological subtypes are grouped as one category in the current WHO classification except for plasmablastic lymphoma. The plasmablastic lymphoma displays immunophenotype characteristics which allows its distinction from other morphological subtypes of DLBCL (**Figures 1–3**).

Histopathological and immunohistochemistry slides of diffuse large B cell Lymphoma showing characteristics of DLBCL of germinal center origin (GC) in **Figure 1** and activated B cell origin (ABC) in **Figure 2**.

2.5. WHO classification

The revised WHO classification 2016 [8] classifies DLBCL NOS into GCB and ABC/non-GC subtypes based on cell of origin. The use of IHC algorithm is accepted [8]. We also now have a

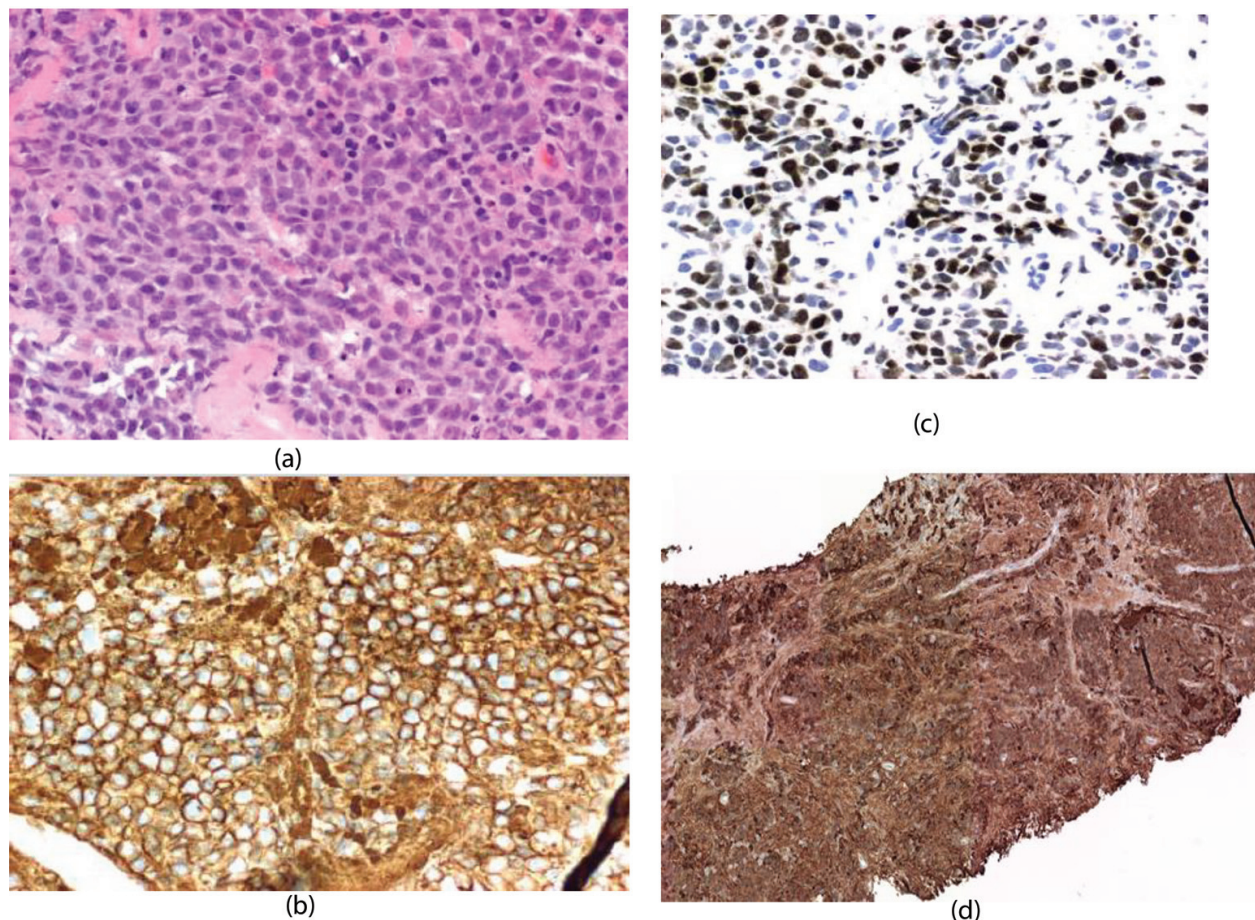


Figure 2. Lymph node sections showing ABC type DLBCL (a) The H&E stained sections showing diffuse infiltration of large atypical lymphoid cells with irregular nuclear contours and vesicular chromatin (X40 magnification). On immunohistochemistry cells are (b) CD20 positive (X20 magnification) (c) MUM1 positive (X20 magnification) (d) CD 79A positive (X20 magnification).

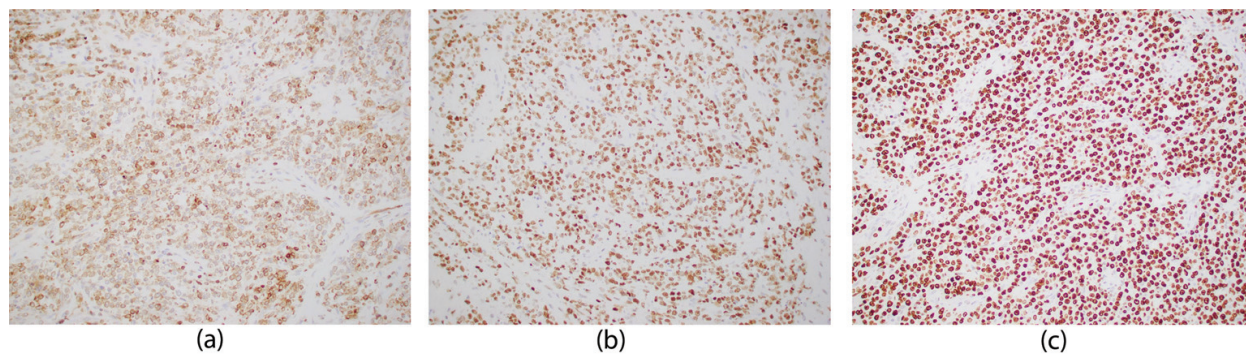


Figure 3. Lymph node sections showing very aggressive DLBCL on immunohistochemistry. (a) bcl-2 positive (X20 magnification) (b) bcl-6 positive (X20 magnification) (c) ki 67 proliferation index is approximately 70-80% positive (X20 magnification).

better understanding of MYC alterations in DLBCL. These are included in a new category of “High grade B cell lymphoma with MYC and BCL2 and/or BCL6 translocations”. Co-expression of MYC and BCL2 is considered a new prognostic marker (double-expressor lymphoma). High grade lymphoma, NOS replaces B cell lymphoma unclassifiable (BCLU) category. It includes blastoid appearing large B cell lymphomas and cases lacking MYC and BCL2 or BCL6 that would formerly have been called BCLU.

2.6. Other distinctive clinicopathological subtypes of DLBCL

2.6.1. T cell histiocyte-rich large B cell lymphoma

As the name suggests this variant is characterized by the predominance of infiltrating reactive T cells and macrophages (histiocytes). Presence of <10% cellularity, has been suggested to label this diagnosis. This pathological subtype does not appear to affect the outcome when adjusted for IPI. In a study of 40 patients comprising of predominantly middle-aged males, splenomegaly, bone marrow involvement, and hepatomegaly were present in 60, 43, and 40%, respectively [12]. The International Prognostic Index (IPI) (Table 3) was ≥ 2 in 77% of the patients. Tumor cells were uniformly positive for CD20 and negative for CD5, CD10, CD15, and CD138. Although these patients were relatively young, the use of combination chemotherapy, led to complete remission in only 40%, with an overall survival of 50% at 3 years. On multivariate analysis, only the IPI and deletions or point mutations in p53 were predictive of survival. In another study, the 5-year overall or event-free survival between this variant and DLBCL was not different among the IPI matched patients [13].

2.6.2. Plasmablastic lymphoma

The tumor cells in plasmablastic lymphoma have large eccentrically placed nuclei, usually with single placed nucleoli and abundant basophilic cytoplasm. However these cells are distinct immunophenotypically. Instead of pan B cell markers which are present in typical DLBCL (CD 20, CD 79a), these tumors comprise of late B cell and express plasma cell markers like CD 138. MYC rearrangement is present in up to 50% of cases and 70% of these patients are Epstein-Barr virus (EBV) positive. Some tumors in this subtype are distinct genetically and clinically. For

example oropharyngeal plasmablastic lymphomas occur most frequently in HIV-patients and are positive for EBV. Another rare variant of plasmablastic lymphoma is characterized by rearrangements of the ALK tyrosine kinase gene [7].

2.6.3. Primary mediastinal large B cell lymphoma

Primary large B cell lymphoma of the mediastinum is a distinct clinicopathological entity that arises from the thymic (medullary) B cell. It has clinical and pathologic features that differ from DLBCL.

2.6.4. Intravascular large B cell lymphoma

This is variously known as intravascular lymphomatosis, angiotropic large cell lymphoma, and malignant angioendotheliomatosis. It usually presents with disseminated intravascular proliferation of large lymphoid cells involving small blood vessels without an obvious extravascular tumor mass or leukemia. It commonly affects central nervous system, kidneys, lungs, and skin, but virtually any site may be involved.

2.6.5. Diffuse large B cell lymphoma, leg type

It manifests as red or bluish (violaceous) nodules or tumors on one or both legs, usually below the knee; 10–15% develop outside of the lower extremities. Contrary to other cutaneous B cell lymphomas, these tumors frequently disseminate to extracutaneous sites and pursue an aggressive course. MYD88 L265P mutations are seen in ~50% of cases.

2.6.6. Diffuse large B cell lymphoma associated with chronic inflammation

Also known as pyothorax-associated DLBCL, it usually develops in patients with a long standing history of pyothorax; however it may also arise at other sites with chronic inflammation [14]. It is seen worldwide but is more common in Japan and China. Clinically, it is an aggressive tumor. These tumors are almost always EBV-positive and are believed to arise from EBV-infected post germinal center B cells. The pattern of EBV gene expression present in this type of lymphoma (LMPI and EBNA2 positivity) suggests the role of local immunosuppression within the sites of chronic inflammation.

2.6.7. Lymphomatoid granulomatosis

This is also an EBV-positive large B cell lymphoma with a T cell-rich background which is clinically and pathologically distinct from DLBCL [15]. The usual manifestations are cough and fever (60%), rash/nodules (40%), malaise and weight loss (35%), neurological abnormalities and dyspnea (30%), or chest pain (15%) [16]. Extranodal involvement is common. The lungs are commonly affected. Other commonly involved sites include kidney, liver, brain, and skin. Lymph nodes and splenic involvement is rare. Histologically, the infiltrates are either angiocentric or angioinvasive. Often extensive necrosis is present with only a few atypical large B cells in a pleomorphic background of lymphocytes, plasma cells, and histiocytes. The large atypical B cells represent the neoplastic component and show evidence of EBV infection with in situ hybridization. Pulmonary nodules exhibit central necrosis and cavitation.

2.6.8. EBV-positive DLBCL, NOS

EBV-positive DLBCL, NOS is a variant of DLBCL that replaced the entity, EBV-positive DLBCL of the elderly and was added in the 2016 WHO classification. It may affect persons of all ages [17–21]. This is seen in patients without known immunodeficiency or prior lymphoma. It is seen most commonly in Asian countries where it accounts for 8–10% of DLBCL among patients without a known immunodeficiency. The majority of patients present with extranodal disease, with or without nodal involvement. While the initial reports were in adults >50 years old, this entity has been increasingly recognized in younger patients [17, 22].

2.6.9. EBV-positive mucocutaneous ulcer

It is considered a provisional entity in the 2016 revision of the WHO classification. This is characterized by the presence of isolated circumscribed ulcerative lesions, typically affecting elderly individuals [23, 24]. Its association with immunosuppression is not clear. Usually, the oropharynx is affected but lesions may also occur in the skin or in the gastrointestinal tract. Histologically, a polymorphous inflammatory infiltrate mixed with scattered EBV-infected B cells is seen in the lesions, which frequently include cells resembling Hodgkin/Reed-Sternberg cells both morphologically and immunophenotypically. This entity is distinguished from Hodgkin lymphoma by its extranodal presentation and has a benign disease course which is characterized by frequent spontaneous regressions and its excellent response to conservative treatment.

2.7. Molecular subtypes

As noted above, the classification of DLBCL NOS, into GCB vs. ABC subtypes is important for the prognostication. The prognosis of GCB-type DLBCL is considered to be better than ABC-type DLBCL. In the rituximab era the 5-year survival of GC type DLBCL is 87–92% as compared to 44% in the ABC-type DLBCL [7, 25]. Moreover, response to novel therapies may be different for the two subtypes. The classification into GCB- vs. ABC-type is best conducted by genomic expression profiling [26]. The DNA microarray is an effective tool to characterize the molecular features of DLBCL and specific genes associated with response to therapy. Though microarray GEP are gold standard for profiling of DLBCL to determine COO, they are expensive and not readily available. Moreover, they have poor flexibility and reproducibility in evaluating low quality RNA samples from formalin-fixed paraffin-embedded (FFPE) tissues and for high quality data, they require RNA extraction from the frozen tissues [27]. Thus their implementation in the routine clinical practice is limited [28]. IHC-based methods are rapid, cost effective and thus are widely used in the clinical practices. Different algorithms have been developed to improve the accuracy. These algorithms use different combinations of antibodies to identify germinal center or activated B cell-related proteins [4, 7, 29]. The relatively simple and most well-known is the Hans algorithm which is based upon the application of 3 antibodies, CD10, BCL6, IRF4/MUM1 and has a reasonable correlation with the GEP [30]. Cases are considered positive if 30% or more of the tumor cells are stained with an antibody (CD10, BCL6, and MUM1). The overall concordance with gene expression array is 80%. The Choi algorithm added FOXP1 and GCET 1 to Hans algorithm and showed 93% concordance with GEP [25, 31]. A Tally classifier substituted BCL6 for the LMO2 antibody which predicted COO better than rest of the IHC algorithms [32].

However, it was not superior in predicting the outcome. In a study on 108 patients, it was shown that Hans and Choi algorithms predicted OS and PFS significantly better than the Tally method [33]. Other algorithms use combinations of other markers (Muris et al.: BCL2, CD10, MUM1 [34]), (Natkunam et al.: LMO2 [35]), (Nyman et al. 50: MUM1, CD10, GCET1, MUM1, FOXP1, LMO2 [36]) and have been described in detail in **Figure 4**.

However, the utility of IHC methodology is also limited by its poor concordance to GEP, inferior accuracy and reproducibility and a lack of prognostic utility. IHC algorithms do not recognize the 10–15% of tumors and are not always reproducible [37]. Lymph2Cx is a 20-gene version of a Nanostring code set for a COO typing assay of DLBCL. This represents GEP like

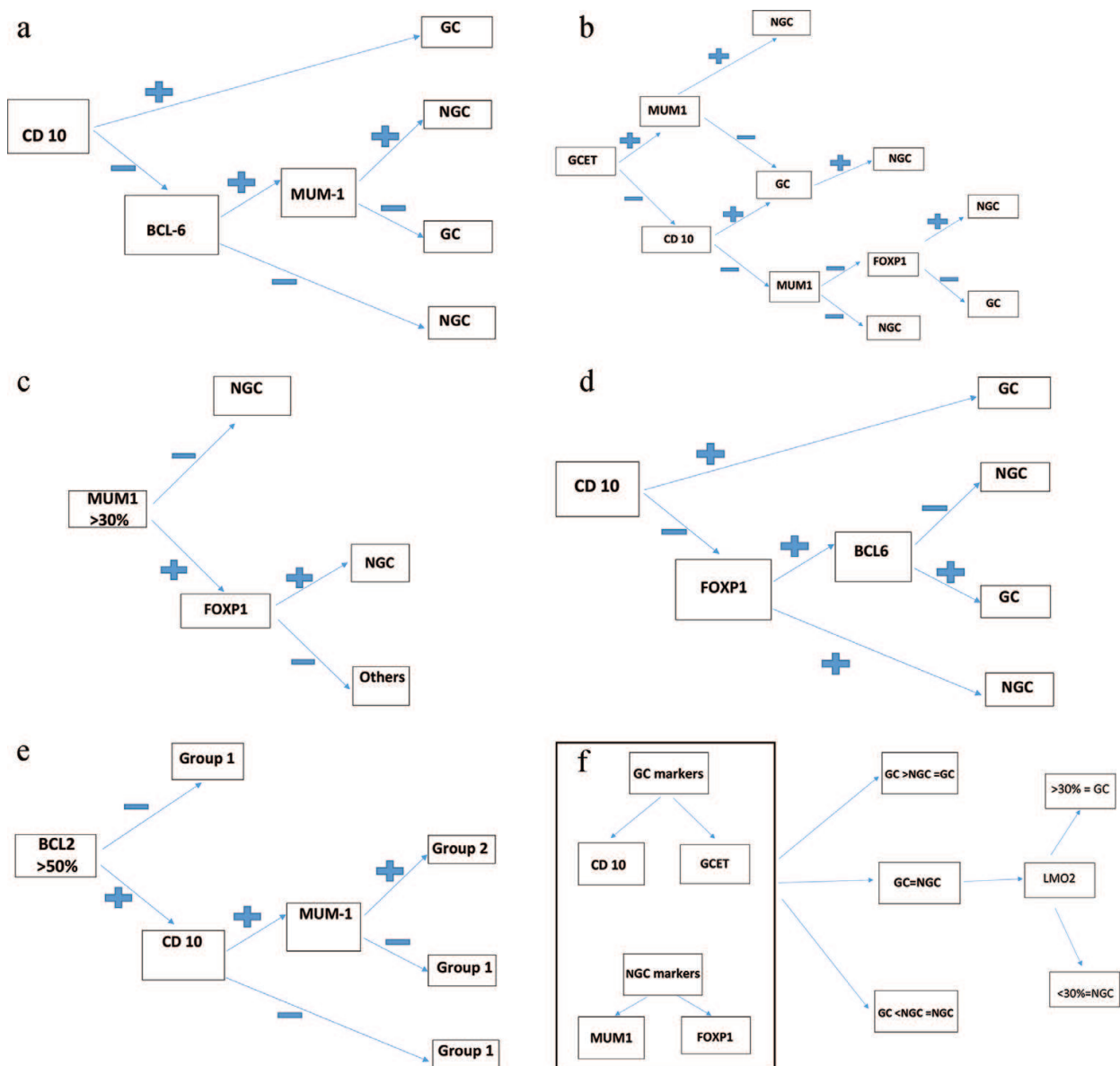


Figure 4. Immunohistochemistry algorithms for the characterization of diffuse large B-cell lymphoma on the basis of cell of origin. (a) Hans algorithm; (b) Choi algorithm; (c) Nyman algorithm; (d) Visco-young algorithm; (e) Muris algorithm; and (f) Tally algorithm.

platform that can run on FFPE tissue. Twenty genes have been selected out of 93 candidate genes [38, 39] to identify COO using this platform. In NanoString technology, digitally colored code sets are attached to the sequence-specific probes to directly measure mRNA [28, 40]. This technique offers highly sensitive, quantitative and reproducible results on FFPE and frozen tissue samples. This requires a very small amount of RNA and covers a large number of genes enabling complex genetic analysis. Studies have demonstrated strong concordance between patient-matched frozen and FFPE materials. It showed 98% concordance for ABC/GCB and 95% in the unclassifiable cases when compared with GEP [38]. In a study on 82 patients, who were treated with R-CHOP the concordance rate between Lymph2Cx assay and Hans algorithm was 73.6%. The outcome of Lymph2Cx-defined ABC (77.1%) was significantly poor as compared to the GCB type (96.6%). On contrary, there was no difference in the outcome of two groups classified by the Hans algorithm [41].

3. Clinical presentation, diagnosis and staging

3.1. Clinical presentation

Patients typically present with a rapidly enlarging single or multiple masses. In case of lymph nodes, enlargement usually involves cervical or the abdominal lymph nodes. The primary mediastinal DLBCL presents as a mediastinal mass. Patients with early stage (I/II) disease often presents with extranodal involvement. These comprise of about 40% of cases [42], while remainder 60% present with stages III/IV disease [43]. Extranodal disease is often seen in elderly patients with poor performance status and lower disease burden [42]. In a series published by Guillermo et al. extranodal gastrointestinal tract involvement was noted to be the most frequent in 12% of all cases, with majority of the lesions being in stomach; other regions included 4.5% soft tissue, 2.5% central nervous system (CNS), 2% each of liver and bone, 1% of skin, breast, kidney, testis/ovaries, and the remainder <1% each of thyroid, bone marrow, lung, prostate, uterus and pericardium [44]. Presenting symptoms may be related to the rapidly enlarging mass depending upon the site of the mass; B symptoms such as fever, night sweats, weight loss may be seen in about 30% of patients [43]. Some may present with hypercalcemia of unknown origin with imaging work up leading to diagnosis of lymphoma. Others may present with oncologic emergencies such as spinal cord compression, superior vena cava syndrome, acute airway obstruction, CNS mass lesions, renal failure due to hydronephrosis and liver failure.

3.2. Diagnosis

Diagnosis of DLBCL needs an expert hematopathologist with expertise in hematologic malignancies. An incisional or excisional lymph node biopsy is recommended when possible, to establish the diagnosis. This allows evaluation of the lymph node architectural details. Core needle biopsy is not encouraged. FNA is not suitable for the initial diagnosis although it may be sufficient to establish the relapse.

3.3. Immunophenotype

It is essential for the differentiation of various subtypes of DLBCL. This is established either by flow cytometry or IHC. Flow cytometry can be employed in determining bone marrow involvement [45] when PET/CT is not readily available for staging and in determining CNS involvement by CSF flow cytometry [46]. Immunophenotype findings are usually combined with morphologic findings to arrive at a diagnosis. Tumor cells in DLBCL generally express pan B cell antigens (CD19, CD20, CD22, and CD79a) as well as CD45. The typical immunophenotype is CD20+, CD45+, and CD3-. The panel should include CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, and MYC. 50–75% of tumors express surface and cytoplasmic monoclonal immunoglobulin (Ig). The proliferative fraction of cells is usually higher than 40% and may occasionally be >90%. CD5 positive tumors are associated with a more aggressive disease and a higher incidence of CNS involvement and a worse prognosis. CD10+ and BCL6+ indicates GCB lymphoma while MUM1+ indicates ABC lymphoma. The three most common translocations noted in DLBCL include MYC, BCL2 and BCL6. MYC is an oncogene involved in pathogenesis of aggressive lymphomas based on partner gene translocation. MYC protein is a transcription regulator for cellular proliferation acting on metabolic and angiogenic mechanism. Genetic translocation involving MYC are considered primary events in 5–15% of DLBCL [47] and in around 20% on first relapse [48]. In DLBCL frequently the partner gene is BCL-2 or to a lesser extent BCL-6 or both, in the so-called double-hit or triple-hit lymphomas. Overexpression of MYC protein can be tested with IHC which can occur independent of translocation in 30% of cases; however for confirmation of specific translocation FISH studies are required [49]. Both, overexpression and translocation confer adverse outcome as documented in different studies [50]. More information on this translocation and their effect on outcome is detailed in Sections 2.3 and 6.2.

3.4. Workup

Initial work up includes thorough physical examination with special attention to node bearing areas and evaluation of performance status (PS) and constitutional symptoms. Appropriate site for excisional/incisional biopsy should be earmarked as stated above. Laboratory assessments include complete blood count (CBC) with differential, complete metabolic profile (CMP), lactate dehydrogenase (LDH) and Beta-2 microglobulin. Additional tests including uric acid and phosphorus, in patients with high tumor burden. Hepatitis B virus (HBV) testing is also warranted as there is an increased risk of HBV reactivation in patients who may require Rituximab. Positron emission tomography (PET)/computed tomography (CT) scan is recommended for initial staging as upstaging can result in altered therapy. Also baseline PET/CT is necessary to confirm the response on the post treatment PET scans. A systematic review and meta-analysis by Adams et al. showed that sensitivity and specificity of PET/CT for detection of bone marrow involvement ranged from 70.8 to 95.8% and from 99.0 to 100%, respectively [51]. There were 3.1% patients who were PET negative but had bone marrow involvement on bone marrow biopsy. On contrary 12.5% patients with negative bone marrow biopsies had marrow involvement on PET scan and PET/CT [51]. Bone marrow biopsy is not needed if the PET/CT is negative unless finding another concomitant lymphoma is important

in treatment decision. Another study showed that the incidence of bone marrow involvement was 3.6% in 192 patients with stage I and II DLBCL [52]. Echocardiogram or multigated acquisition (MUGA) scan if required if anthracycline-based regimen is being considered. In selected cases discussion of fertility issues and sperm banking should be considered. Consider lumbar puncture if there is suspicion of CNS disease or if patient is at high risk of CNS involvement such in patients with testicular lymphoma, aggressive histology, human immunodeficiency virus (HIV) lymphoma, double-expressor lymphoma and in patients with 4–6 factors on the prognostic score which is discussed in the section on CNS prophylaxis. The role of various imaging modalities has been reviewed in detail elsewhere [53].

3.5. Staging

Ann Arbor staging system was originally introduced for Hodgkin's lymphoma and was later adopted for NHL. Lister et al. classified patients with NHL into stages I (localized) to IV (extensive) disease [54]. Patients are classified into A or B depending on the absence or presence of B symptoms, respectively. B symptoms mainly include fevers, drenching night sweats or weight loss of 10% or more within 6 months of diagnosis. DLBCL is a non-contiguous disease while Hodgkin's lymphoma involves contiguous sites hence the Ann Arbor staging has limited utility in DLBCL. In 2014, the Lugano classification was proposed (**Table 1**) [55]. According to this classification, patients with stage I or II disease can be grouped and considered as having limited disease while patients with Ann Arbor stage III or IV disease can be grouped as advanced stage disease. The suffix A and B is only reserved for Hodgkin's lymphoma. The X for bulky disease is now replaced with the recording of the largest nodal diameter by CT scan. Limited evidence suggests that 6–10 cm should be considered as bulky disease in the rituximab era for DLBCL. National comprehensive cancer network (NCCN)

Stage	Involvement	Extranodal (E) status
<i>Limited</i>		
I	Single lymph node or a group of adjacent nodes	One extranodal lesion without nodal involvement
II	Two or more lymph nodal groups on the same side of the diaphragm	Stage I or II by nodal involvement with limited contiguous extranodal extension
II bulky ¹	II as above with "bulky" disease	Not applicable
<i>Advanced</i>		
III	Lymph nodes on both sides of the diaphragm or lymph nodes above the diaphragm with splenic involvement	Not applicable
IV	Wide spread extralymphatic involvement	Not applicable

Note: Extent of disease in DLBCL is determined by PET-CT or CECT if former is not available. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

¹The decision to treat stage II bulky disease as limited or advanced disease is determined by the histology and IPI.

Table 1. Revised staging system for primary nodal lymphomas.

considers more than or equal to 7.5 cm as bulky disease. A single nodal mass of 10 cm or greater than third of the transthoracic diameter is the definition of bulky disease only for Hodgkin's lymphoma.

Staging has limited prognostic value due to the heterogeneity of the disease. To fully incorporate prognostic information several models have been developed to predict survival. The staging should generally be used with these prognostic models for accurate information.

3.6. Role of PET/CT in management of DLBCL

In oncology, the focus of imaging modalities is drifting from morphological to functional imaging and combined PET/CT is making its foray in each step of DLBCL management. Bone marrow evaluation is a part of staging that upstages DLBCL to stage IV if positive. Focal positivity on PET/CT scan can obviate the need for bone marrow biopsy in staging these patients. In a study where it was compared to standard bone marrow biopsy, PET/CT showed higher sensitivity, accuracy and negative predictive value (94, 98 and 98%, respectively, for PET/CT vs. 24, 80 and 81% for bone marrow examination) [56]. Similarly PET/CT has established its role in response assessment (see Section 7.6). Interim PET/CT can be used as a predictive marker for prognosis with PET response in the interim denoting better outcomes. In a study [57] negative PET/CT after 2 cycles when compared to those who had positive scans, showed significantly higher CR (97.3 vs. 33.3%), 3-year PFS (75.8 vs. 38.2%) and 3-year OS rates (93.5 vs. 55.6%). This advantage was also seen in those patients whose PET/CT was negative after 4 cycles and showed higher CR (96.9 vs. 16.2%), 3-year PFS (75.3 vs. 24.7%) and 3-year OS rate (91.6 vs. 49.4%).

4. Differential diagnosis

Includes wide range of pathologies that cause lymphadenopathy such as infectious mononucleosis, Carcinoma, anaplastic large cell lymphoma, gray zone lymphoma, Burkitt's lymphoma, rarely pathologies that cause small blue round cells such as Ewing's sarcoma may be in the differential diagnosis.

5. Subtypes

Several distinct subtypes of large B cell lymphoma need to be distinguished from DLBCL, NOS (see sec 2.6 above) [8].

1. Primary mediastinal (thymic) B cell lymphoma
2. Gray zone lymphoma.
3. T cell/histiocytes rich large B cell lymphoma.
4. DLBCL associated with chronic inflammation.

5. Primary cutaneous lymphomas, leg type.
6. ALK positive large B cell lymphoma.
7. EBV-positive DLBCL NOS.
8. Primary cutaneous B cell lymphomas.
9. Primary DLBCL of the CNS.
10. Lymphomatoid granulomatosis.
11. Intravascular large B cell lymphoma.

6. Prognosis

6.1. International Prognostic Index (IPI)

Staging in DLBCL has a limited value. The original IPI was developed to identify variables that could predict OS and PFS (Table 2). The factors included were age >60 years, elevated serum lactate dehydrogenase (LDH), Eastern Cooperative group (ECOG) performance status ≥ 2 , clinical stage III or IV, more than 1 involved extranodal disease sites. One point was given for each of the characteristics ranging from zero to five. Five-year survival rates worsened as the scores increased. Five-year overall survival rates for patients with scores of zero to one, two,

Original IPI (1 point to each)	Age adjusted IPI (1 point to each)	NCCN IPI
Stage III or IV disease	Stage III or IV disease	Stage III or IV disease—1 point
Elevated serum LDH	Elevated serum LDH	¹ LDH ratio > 1—3—1 point LDH ratio > 3—2 points
PS of 2, 3, or 4	PS of 2, 3, or 4	PS of 2 or more—2 points
Age greater than 60 years		Age 41–60 years—1 point 61–75 years—2 points >75 years—3 points
More than 1 extranodal site		Extranodal sites involving bone marrow, CNS, liver/GI tract or lung—1 point
Low risk—0–1	Low risk—0	Low risk—0–1
Low-intermediate risk—2	Low-intermediate risk—1	Low-intermediate risk—2–3
High-intermediate risk—3	High-intermediate risk—2	High-intermediate risk—4–5
High risk—4 or 5	High risk—3	High risk—6 or above

¹Ratio of patient's LDH level to the labs upper limit of normal.

Table 2. Original and modified International Prognostic Index.

three, four to five were 73, 51, 43, 26%, respectively [58] (project TIN-HsLPPF). This was before the rituximab era. The utility of IPI was reassessed in a retrospective analysis of patients with DLBCL treated with R-CHOP in the province of British Columbia to assess the value of IPI [5]. They redistributed the IPI into revised IPI which identified 3 distinct prognostic groups of very good (score-0), good (scores 1, 2) and poor (scores 3, 4, 5) with a 4 year OS of 94, 79 and 55%, respectively. The NCCN incorporated detailed information about the variables in the original IPI and the location of extranodal disease is used rather than the number of extranodal disease as the lymphomatous involvement in major organs (bone marrow, CNS, liver/GI tract or lung) appeared to be a stronger predictor for a worse prognosis. It stratifies patients into four risk groups low—0–1 points, low-intermediate risk—2–3 points, high-intermediate risk—4–5 points and high risk—≥6 points with OS of 94, 72, 54, 35%, respectively. Both the R-IPI and the NCCN-IPI predict clinical outcome with accuracy and the use of R-IPI or the NCCN-IPI routinely to better understand the prognosis of these patients is recommended [59].

6.2. Double-/triple-hit lymphoma

Several strategies with intense regimens have been tried to mitigate this risk. **Table 3** illustrates the studies of these regimens. Additional randomized control trials are needed to evaluate the efficacy of intense regimens. Based on these small data sets, R-CHOP is associated with inferior outcome. Current literature indicates better outcomes when treated with DA-EPOCH-R in this group of patients [60]. The regimen is a dose adjusted regimen combining etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin in an infusional manner targeting prolonged drug exposure to reduce resistance and dynamic dose adjustments allowing for highest acceptable doses.

Study	Number of patients	Treatment	PFS	OS
Petrich et al. [44] Induction therapy with HDST	311	R-CHOP (32%) Hyper CVAD/MA (2%) R-EPOCH (21%) R-CODOX-M/IVAC (14%)	10.9 months PFS (R-CHOP): 7.8 months vs. 26.6 months (intensive regimen) p = 0.001	21.9 months (p = 0.14)
Oki et al. [43]	129	R-CHOP R-Hyper CVAD/MA R-EPOCH	25% 32% 67%	OS with R-EPOCH vs. R-CHOP (p = 0.057)
Dunleavy et al. [45]	52	DA-REPOCH	79% (14 months follow up)	77%
Howlett et al. [46]	394	R-CHOP R-EPOCH R-Hyper-CVAD/MC R-CODOX-M/R-IVAC	12.1 months 22.2 months* 18.9 months 18.9 month	

*p = 0.032 (significant at p <0.05).

Table 3. Intense regimen studies for MYC rearranged with/without BCL2 rearrangement.

7. Treatment

Treatment for DLBCL includes chemo-immunotherapy with an anthracycline backbone. Options differ for patients with limited vs. advanced disease.

7.1. Initial treatment of limited stage DLBCL

Limited stage DLBCL which is usually Ann Arbor stage I or II (usually non-bulky stage II which may be included in one irradiation field) accounts for 30-40% of patients with DLBCL. Combined modality therapy is considered the standard of care for these patients. This was initially established by a large randomized SWOG 8736 trial which was conducted in the pre-rituximab era. The trial compared 3 cycles of CHOP plus RT (radiotherapy) vs. 8 cycles of CHOP alone in localized stage IE, non-bulky stage IIE aggressive lymphoma. The PFS for patients receiving CHOP plus RT and for patients receiving CHOP alone were 77 and 64%, $p = 0.03$, respectively. The 5 year OS for patients receiving CHOP plus RT vs. CHOP alone were 82 and 72%, $p = 0.02$, respectively [61]. However, further follow up showed that the advantage negated. Patients with RT had more late relapses while patients with CHOP alone had increased toxicity. Addition of rituximab to combination chemo showed improved responses in patients with early stage disease. In a multicenter randomized clinical trial, MInT, which comprised of at least 2/3rd early stage patients, 3-year event-free survival (EFS) in R-Chemo arm (79% [95% CI 75–83]) was higher as compared to chemo alone arm (59% [54–64]) and 3-year overall survival (OS) in R-chemo arm was also higher than the chemo alone arm (93 vs. 84%) [62]. The SWOG S0014 study [63] was a phase II study where patients with limited stage disease and at least 1 adverse feature, based on stage modified-IPI were given rituximab with 3 cycles of CHOP followed by involved field radiation therapy (IFRT). The study showed 2-year PFS of 93% and 4 years PFS of 88%. OS was 95% at 2 years and 93% at 4 years. These results were better than SWOG 8736 trial where CHOP+ RT without rituximab was given. R-CHOP \times 3 followed by RT remains the standard of care for patients with limited stage non-bulky disease while R-CHOP \times 6 cycles with or without RT remains the standard for patients with limited stage bulky disease (NCCN guidelines).

7.2. Initial treatment of advanced stage DLBCL

60–70% of patients present with advanced disease. R-CHOP every 21 days is the standard of care for this group of patients. About 60% of patients are cured with this approach. The beginnings of modern chemotherapy dates back to the use of nitrogen mustard with remarkable tumor response in a patient at Yale in 1942. The initial use of Adriamycin containing drug combinations (CHOP) was reported in 1979 by Miller et al. in 45 patients with localized NHL [61]. In Phase III trials, a complete remission (CR) rate was 53% and the survival rate was 30% after 12 years of follow up [64]. Several intense regimens such as m-BACOD; proMACE-CytaBOM and MACOP-B were investigated to improve on the results of CHOP. SWOG and ECOG did a prospective randomized phase III trial to compare these with CHOP and found no difference between these regimens but higher toxicity with the intense regimens [65]. It

remained the standard of care for two decades until the introduction of first monoclonal antibody Rituximab which improved the OS by 10–15%. In the landmark GELA trial, 399 DLBCL patients 60–80 years old were randomly assigned to receive either 8 cycles of CHOP every 3 weeks vs. 8 cycles of CHOP plus rituximab every 3 weeks. There was an improvement in all endpoints including complete response rate, event-free and overall survival without significant increase in toxicity. R-CHOP became the standard of care [66]. (Table 4). Recent follow up of the study reported 10 year OS of 43.5%. The Mabthera International trial (MInT) studied R-CHOP for 6 cycles vs. CHOP for 6 cycles in young patients 18–60 years who had IPI score of 0 or 1, advanced disease or stage I bulky disease. The EFS was 79 vs. 58% and OS of 93 vs. 84% which established 6 cycles of R-CHOP as the standard of care in advanced stage disease. Eight cycles of R-CHOP 21 has not been compared with 6 cycles of R-CHOP 21, 6 cycles is recommended in most patients (NCCN guidelines).

An attempt to intensify R-CHOP-21 by giving it every 14 days in a dose dense manner has been tried in several trials. The first trial by Cunningham et al. assigned 1080 patients to R-CHOP 21 × 8 or R-CHOP 14 × 6 along with two more infusions of rituximab along with G-CSF support. There was no significant improvement in OS and PFS [67]. Another study, LNH03-6B also showed no difference in EFS in elderly patients treated with R-CHOP-14. R-CHOP-21 has thus remained the standard of care.

Maintenance Rituximab has shown some benefit in some subtypes of lymphoma. This was tested in ECOG intergroup 4494 study comparing CHOP vs. R-CHOP in elderly patients. Patient who had a CR had a second randomization to maintenance rituximab every 6 months for 2 years vs. no maintenance. There was no difference in OS or PFS. The maintenance was only useful in patients who did not receive it during induction. Based on these results, there is no role for maintenance Rituximab in DLBCL therapy [68].

7.3. Role of transplant

High-dose therapy with autologous stem cell rescue (HDT/ASCR) has shown significant improvement in OS and PFS in pre-rituximab era [69, 70]. However in the era of chemo-immunotherapy with addition of rituximab to chemotherapy, the indication for HDT/ASCR has significantly become limited with many studies showing no statistical significant advantage of proceeding to transplant in first remission except may be in patients with high risk score [71, 72].

7.4. Treatment in the elderly

Conventionally, very elderly patients are not considered candidates for aggressive therapy for various reasons. This population is not represented well in the clinical trials that form the basis for standard treatment. To address this issue GELA study group undertook a phase II study where 149 patients age 80 years and above were administered reduced dose CHOP with conventional dose rituximab (so-called R-mini-CHOP). The extended follow up from this study revealed 4-year OS and PFS rates of 49 and 41% with neutropenia being most frequent

Initial evaluation

- | | |
|----------------------|---|
| History | <ul style="list-style-type: none"> • Demographics including age and gender • Clinical including fever ($>38.3^{\circ}\text{C}$ or 101°F), night sweats, significant weight loss ($>10\%$ in 6 months) of unknown etiology and swelling. • Assessment of comorbidities which could affect the lymphoma management and outcome. |
| Physical examination | <ul style="list-style-type: none"> • Specifically assessment of nodal regions and size of spleen and liver. CT imaging is more accurate for organomegaly. |
| Diagnosis | <ul style="list-style-type: none"> • FNAC is inadequate for initial diagnosis. Incisional and excisional biopsy is the standard if feasible core needle biopsy is acceptable if excisional biopsy cannot be done. • Morphology, IHC and flow cytometry in most of the cases and molecular studies in selected cases. • Additional tissue or cell suspension should be preserved for future research. |

Staging

- | | |
|-------------------------|---|
| | <ul style="list-style-type: none"> • PET-CT is the preferred imaging modality over CT scan wherever available. Chest X-ray is not required. • CECT should be included in selected cases for more precise measurement of lymph nodes, to distinguish bowel from lymph nodes, in cases with compression or thrombosis of mediastinal or central vessels and for planning of radiation. • If CT is used for imaging, up to 6 of the largest lymph node masses or other lesions should be measured (largest diameter LDi] and smallest diameter) as marker of disease burden. It should include mediastinal and retroperitoneal regions, if affected. Significant lesions are lymph node with LDi > 1.5 cm and extranodal masses with LDi >1 cm • Instead of classical, modified Ann Arbor staging is used in which bulky stage II is a separate stage. |
| Bulky disease | <ul style="list-style-type: none"> • Exact size for bulky tumor is not clear for DLBCL. 6–10 cm is reported as bulky in various studies in the rituximab era. |
| Splenic involvement- | <ul style="list-style-type: none"> • The exact cut off is affected by ethnicity, body size and height. No consensus. More than 10–12 cm has been used in various studies. Current recommendations are >13 cm. • Normal size does not rule out lymphomatous involvement. PET-CT is the best modality which could show homogenous splenomegaly, diffuse infiltration, miliary lesions, nodular or solitary mass. |
| Hepatic involvement | <ul style="list-style-type: none"> • Size is not a reliable marker of lymphomatous involvement. Presence of focal or diffuse uptake, with/without focal or disseminated nodules support involvement. |
| Bone marrow involvement | <ul style="list-style-type: none"> • Routine bone marrow biopsy is not required in DLBCL. • Involvement of BM on DLBCL is sufficient to label advanced stage disease. In patients with negative PET • CT, BM may be required to r/o simultaneous presence of other histologies or when malignant transformation is suspected. |

Response assessment

- Should be done with PET-CT wherever available.
- 5-point scale should be used both for interim analysis (for early treatment response) and end of treatment assessment (to establish the remission).
- Score of 1 (no uptake) and 2 (uptake $<$ mediastinum) = complete metabolic response at interim or end of treatment
- Score of 3 (uptake $>$ mediastinum but $<$ liver) = good response in real practice but in clinical trials should be considered as inadequate response.
- Score of 4 (uptake moderately $>$ liver) and 5 (uptake markedly $>$ liver) = in interim analysis, if uptake is decreased from baseline, is considered as chemosensitive disease. However, if it persists till end of treatment, it is considered as treatment failure. New foci of lymphoma at any time is also considered treatment failure.

-
- In Waldeyer's ring uptake may be more than mediastinum with complete response but should not be higher than the uptake in surrounding normal tissues.

Follow up evaluation

- Every 3 months for first 2 years, then every 6 months for 3 years followed by annually afterwards.
 - Physical assessment and lab investigations including CBC, metabolic panel and LDH should be checked.
 - No role of imaging and it should be discouraged.
-

Table 4. Summary of updated recommendations for the initial evaluation, staging, response assessment and follow up evaluation of patients with DLBCL as suggested in Lugano classification.

high grade toxicity [73]. Comprehensive geriatric assessment may help in identifying patients suitable for chemotherapy [74].

7.5. Supportive care

Supportive care is imperative to mitigate the toxic effects of the chemotherapy. Care must be taken during initial cycles of chemotherapy and patients should have prophylactic allopurinol to prevent tumor lysis syndrome with highly effective regimens used currently. Patients should be screened for and appropriately treated for underlying hepatitis B infection if rituximab use is contemplated [75].

7.6. Assessment of therapeutic response

Assessment of response to therapy is accomplished by PET scans. Interim PET scans after 2 cycles may have prognostic significance. In a study 2-year PFS and OS were shown to be significantly better for the patients with PET negative disease after 2 cycles of therapy than those with positive scans [69]. Interpretation of PET scans should be done according to 5-point scoring system—Deauville criteria [76]. As per Deauville criteria score of 1, 2 or 3 with or without residual mass is considered a complete response, while a score of 4 or 5 with reduced uptake from baseline, represents responding disease when PET-CT is performed in the interim or residual disease if the PET-CT is performed at the end of the treatment. A score of 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment is regarded as no response or stable disease. New lesions or a score of 4 and 5 with increase in intensity of uptake from baseline at interim or end of treatment, signify disease progression [77]. There is not enough evidence that this can be used to change the therapy when performed in the interim. Re-biopsy should be performed if contemplating change of therapy due to positive scans, since false positive scans may be encountered [78]. Additional imaging with MRI or biopsy is also recommended when bone marrow only findings are evident on PET-CT.

7.7. Surveillance and follow up

Routine imaging in patients after complete remission (CR) without any symptoms can safely be deterred, in a study by Guppy et al. only 6% relapses were noted in asymptomatic patients as

against 86% in those who had symptoms [79]. However, imaging can also pick up changes early on when disease recurs. Although imaging can diagnose recurrence earlier, it has not been shown to alter the outcomes. The current work up and follow up recommendations for DLBCL are summarized in **Table 4**.

7.8. CNS prophylaxis

The rate of secondary CNS involvement is 3–5% but it is much higher with certain risk factors. Risk factors for CNS involvement include [80] elevated LDH, >1 extranodal site, involvement of testis, renal, breast, epidural space or adrenal gland, high CNS-IPI or MYC + BCL2/BCL6 gene rearrangement. Patients with 3 or more of these risk factors have a risk of CNS recurrence of as high as 25%. Prognosis is very poor with CNS recurrence and death is inevitable with median overall survival of 2–5 months. Hence patients at high risk of CNS recurrence should be considered for intrathecal chemotherapy with methotrexate or ara-C or high-dose IV methotrexate with leucovorin rescue. The intrathecal chemotherapy can be incorporated once in each cycle; alternatively, IV high-dose methotrexate can be given on Day 15 of 21-day R-CHOP. CNS prophylaxis has been reviewed elsewhere in detail [81].

8. Therapy of relapsed refractory DLBCL

Patients with relapsed/refractory disease have traditionally been treated with HDT/ASCR as per PARMA trial in the pre-rituximab era [82]. However, many chemotherapy regimen combinations with rituximab have since been shown to be active. For instance, R-ICE (rituximab, ifosfamide, carboplatin and etoposide) when given in out-patient setting has shown ORR of 71% with an estimated 1-year EFS rate and OS rate of 60 and 72%, respectively [83]. More recently lenalidomide monotherapy in a phase II trial in patients not eligible for transplant, showed improvement in RR, PFS and OS in non-GCB subtype DLBCL [84]. Brentuximab vedotin, a CD30-directed antibody-drug conjugate has shown ORR of 44% (CR17%) in a planned subset analysis in a phase II study [85]. Bruton's tyrosine kinase (BTK) inhibitor ibrutinib is proposed to be active in DLBCL and is being tried in combination with R-ICE in relapsed patients [86] (clinical trials.gov-NCT02955628).

8.1. Novel therapies and future directions

Many novel targeted agents are under trial and have been reviewed elsewhere [5]. A brief description of novel immune and cellular therapies has been presented below and in **Table 5**. Some novel therapeutic strategies being tested in double-hit lymphoma include the BCL2 inhibitor, PI3K inhibitor and mTOR inhibitor. The INK α /ARF deletion cause genomic instability. Constitutive activation of NF κ B is being targeted in several trials of proteasome inhibitors, immunomodulatory agents, and B cell receptor signaling pathway inhibitors.

Drug	MOA (target)	Eligibility (and design)	Phase	Subjects (N)	Results
<i>Chemotherapeutic agents</i>					
Pixantrone [95]	Aza-anthracenedione	Ist line CHOP-R vs. CPOP-R	II	N = 124	ORR 82% for the CPOP-R arm vs. 90% for the CHOP-R arm, and median PFS not reached in the CPOP-R arm and was 40 months in the CHOP-R arm; median OS not reached in either arm. OS inferior for CPOP-R (hazard ratio 2.37, p = 0.029), with more deaths occurring in the CPOP-R arm (30% vs. 14%)
Liposomal vincristine [96]	Chemotherapy	Refractory/relapsed	II	N = 60	ORR: 95%; (CR/CRu: 92%, PR: 3%) 5 years OS 87% and PFS 81%
<i>Monoclonal antibodies</i>					
Obintuzumab Plus Lenalidomide plus CHOP [97]	Anti-CD 20	Refractory/relapsed	I	N = 6	CR 100%; neutropenia (grade 3: 50%, grade 4: 33%), thrombocytopenia (grade 3: 17%), and Rash (grade 2: 17%).
Veltuzumab plus Milatuzumab [98]	Anti-CD20 plus anti-CD74	Heavily pretreated NHL	II	N = 7	PD in all DLBCL: 100%
Blinatumomab [99]	Single chain bispecific T cell engaging antibody anti-CD19 and anti-CD3 mAb	Refractory/relapsed	II	N = 25 stepwise (9–28–112 µg/d with weekly dose increases; n = 23) or flat (112 µg/d; n = 2)	ORR 43%, CR 19%. Three patients had late CR in follow up without other treatment
<i>Antibody drugs conjugates</i>					
I-131 tositumomab [100]	Anti-CD20 radio-immunotherapy	Previously untreated DLBCL (with R-CHOP)		15	CR rate increased from 60% post-CHOP to 80% post TST/I-131 TST. At 120.0 months, median DOR was 58.4 months. PFS and time to treatment failure were 63.0 months. OS was not reached. Grade 3/4 hematologic adverse events were decreased absolute neutrophil count (47%), white blood cell count (40%), platelet count (27%), and hemoglobin (20%)
		Consolidation therapy after first line R-CHOP	II	71	2 year event-free survival was 75%; grade 3–4

Drug	MOA (target)	Eligibility (and design)	Phase	Subjects (N)	Results
⁹⁰ Y-epratuzumab tetraxetan [101]	Radiolabeled humanized anti-CD22 mAb	in DLBCL in untreated patients aged 60–80 years			thrombocytopenia in 84% and neutropenia in 79%
Brentuximab vedotin (SGN-35) [102]	Antitubulin monomethyl auristatin E (MMAE) anti-CD30 mAb conjugate	Refractory/relapsed	II	49 DLBCL	ORR 49% for DLBCL, including 17% CR with a DOR of 16.6 months
<i>Immunomodulatory agents</i>					
Lenalidomide [103]	Immunomodulator	Lenalidomide as maintenance therapy vs. placebo in elderly patients with DLBCL who achieved a complete response (CR) or partial response (PR) to R-CHOP induction	III	650	At 39 months median PFS was not reached for lenalidomide maintenance vs. 58.9 months for placebo. At 52 months OS was similar between the two arms. Most common grade 3 or 4 adverse events associated with lenalidomide vs. placebo maintenance were neutropenia (56 vs. 22%) and cutaneous reactions (5 vs. 1%), respectively
<i>Targeted therapies</i>					
Bortezomib [104]	Proteasome inhibitor	Previously untreated non-GCB DLBCL (R-CHOP vs. VR-CHOP)	II	206	PFS 25% with R-CHOP and 18% with VR-CHOP. 2-year PFS rates were 77.6% with R-CHOP and 82.0% with VR-CHOP; ORR with R-CHOP and VR-CHOP was 98% and 96%, respectively. 2-year OS was 88.4 and 93.0%
Panobinostat [105]	Deacetylase inhibitor	Refractory/relapsed	II	40	28% response. DOR 14.5 months. MEF2B positive were significantly associated with response
<i>Immune checkpoint inhibitors</i>					
Ipilimumab [106]	CTLA-4 inhibitor	Refractory/relapsed	I	18	2 patients had clinical responses, 1 CR at 31+ months
Nivolumab [93]	PD-1 inhibitor	Refractory/relapsed	I	11	ORRs 36% (CR, 18%; PR, 18%)
Pembrolizumab [107]	PD-L1 inhibitor	PMBCL	Ib	19	ORR 41% (12% CR and 29% PR). 35% SD. DOR not reached

Drug	MOA (target)	Eligibility (and design)	Phase	Subjects (N)	Results
<i>Kinase inhibitors</i>					
Fostamatinib [108]	Spleen oral tyrosine kinase (Syk) inhibitor	Refractory/relapsed	II	68	The most common treatment-related adverse events of all patients were diarrhea (21% total, 6% grade 3/4), nausea (19% total, 3% grade 3/4), and, fatigue (18% total, 9% grade 3/4). The ORR rate was 3% across both arms and clinical benefit (\geq stable disease) was achieved for 13% of all patients
Enzastaurin [109]	Protein kinase beta inhibitor	For maintenance among high risk patients after CR to first line therapy	III	758	At 48 months, DFS hazard ratio for Enzastaurin vs. placebo was 70 vs. 71%, respectively

Table 5. Novel therapies undergoing clinical trials for the treatment of DLBCL.

8.2. CAR T cells

Chimeric antigen receptor (CAR) confers antigen specificity to T cells for antigens expressed by lymphoma cells in a non-MHC restricted fashion. The typical CAR T cell in clinical practice has an antigen binding pocket or single chain variable fragment (scFv) derived from an immunoglobulin molecule and a spacer or a hinge region and a range of different co-stimulatory molecules (CD 28, OX 40, 4-1BB). CD19 is expressed during all stages of B cell differentiation and is absent in any other cell types. Kochenderfer et al. reported the initial results on 15 patients with advanced B cell malignancies of which 8 achieved complete remissions (CR), 4 achieved partial remissions (PR) [87]. Some of the patients had a durable response. This led to the single arm, phase II JULIET study of CTL09 in adult patients with relapsed or refractory DLBCL. The overall response rate (ORR) was 45 with 37% achieved a complete response, and 80% achieving a partial response (PR), respectively [88]. This overall response rate was impressive in this heavily pretreated population. 57% of all treated patients experienced cytokine release syndrome (CRS) and 26% experienced grade 3, 4 CRS. The CAR T cell therapy received FDA breakthrough designation for treatment for relapsed refractory lymphoma in the United States based on the interim results of the JULIET trial. United States FDA finally approved axicabtagene ciloleucel for DLBCL following 2 prior therapies based on phase II Zuma-1 study [89] that showed 82% ORR and 54% CR rate. Development of the CAR T cells takes time and that becomes a limitation of this therapy in patients with rapidly progressive disease. Also cytokine release syndrome (CRS) and neurotoxicity (grade 3 or more CRS in Zuma-1 in 13% and neurotoxicity in 28% patients) can be life threatening and requires considerable expertise and critical care support which may be a limitation to the wide use of CAR T cells in

the community hospital setting [90]. The use of humanized anti IL-6 receptor antibody tocilizumab have been successfully used to manage these toxicities. Pretreating these patients with lymphotoxic agents such as cyclophosphamide or fludarabine is helpful for the survival of the infused T cells. Targeting of normal B cells results in B cell aplasia which may require intermittent infusion of immunoglobulin as prophylaxis from infectious complications. Upregulation of PD-1 expression has been shown among responders to CD19 CAR T cells. This may be vital in developing further strategies including combination therapies [91].

8.3. Immune checkpoint inhibitors

Checkpoint proteins such as PD-1 on T cells and PD-L1 on tumor cells help keep immune responses in check. The binding of PD-L1 to PD 1 keeps T cells from killing tumor cells in the body. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor allows T cell to kill tumor cells. PD L-1 expression has been variable in different subsets of lymphomas. PD-L1 expression in follicular lymphomas is seen but the role in DLBCL is not that clear [92]. Lesokhin et al. did a phase 1b study of Nivolumab every 2 weeks in patients with relapsed refractory B cell, T cell, Multiple myeloma patients. 11 patients had DLBCL. ORR were 36% in the DLBCL patients [93]. Genetic alterations in 9p24.1 are known to upregulate PD-L1 and PD-L2 expression. This is seen in Hodgkin's lymphoma and also in patients with primary mediastinal B cell lymphoma. This was studied in a phase 1b trial of pembrolizumab in relapsed refractory primary mediastinal B cell lymphoma. ORR of 41% was seen among the 18 patients enrolled with 35% of patients had stable disease [94]. Patients with EBV-associated DLBCL and T cell rich B cell lymphomas express high levels of PD-L1 and warrant further studies with checkpoint inhibitors.

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