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REVIEW ARTICLE

Diffuse Large B-Cell Lymphoma-Review

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Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 30 percent of all NHL cases, involving both nodal and extra-nodal sites. Apart from distinct morphological and clinicopathological subtypes, DLBCL can be dived into molecular subtypes, Germimal Centre Subtype (GCB) and Activated B-Cell (ABC) based on gene expression profiling. IPI (International Prognostication Index) and its variants are used to prognosticate the patients. Limited stage DLBCL is primarily treated with combined modality therapy consisting of abbreviated systemic chemotherapy (three cycles), and involved field radiation therapy, whereas advanced stage disease is treated with full course of chemotherapy with recommendation of addition of novel agents (Bortezomib, Ibrutinib, Lenalidomide) in ABC type DLBCL.

Key words: Diffuse large B-cell lymphoma, germinal center, activated B-cell, rituximab

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 30% of NHL cases.[1] It occurs in both sexes with slight male preponderance. Although DLBCL can occur in childhood, the incidence generally increases with age and roughly half of patients are over the age of 60.[2] DLBCL arises from a mature B-cell and is usually comprised of cells resembling centroblasts or immunoblasts, which are two distinct types of activated B-cells. DLBCL can arise *de novo*, as well as through the transformation of many different types of low-grade B-cell lymphomas, most commonly including B-cell chronic lymphocytic leukemia (e.g., Richter's transformation).

DLBCL is an aggressive (fast-growing) and high-grade lymphoma that can arise in nodal or extranodal sites, such as gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. Although the involvement of nodes in the cervical and abdominal regions is the most common clinical presentation, 40% of cases present with extranodal involvement.[3] In approximately 30% of patients, systemic "B" symptoms (i.e., fever, weight loss, drenching, and night sweats) are observed, which is comparatively less as seen in Hodgkin's lymphoma, where "B" symptoms can be present in up to 70% of cases. The relevance of "B" symptoms is not as clear in prognosis of NHL's but are markers of advanced disease, as that in Hodgkin's lymphoma, where they are poor prognostic factors.[4,5] About 25% of cases of DLBCL have bone marrow involvement which is far less common in comparison to up to 70% involvement in low-grade lymphomas.[6]

SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA

DLBCL has distinct morphological and clinicopathological subtypes. The common morphological subtypes are centroblastic, immunoblastic, and anaplastic. Centroblasts are large noncleaved cells with round or oval nuclei associated with good prognosis, whereas immunoblasts are large cells with prominent nucleoli and plasmacytoid features.

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Plasmablastic lymphoma is a morphological variant that is immunophenotypically distinct from other variants. They express plasma cell markers (CD38, CD138), instead of pan B-cell markers (CD20, CD79a) of typical DLBCL. DLBCL has many clinicopathological subtypes, including four specific subtypes (T-cell/histiocytic LBCL, primary central nervous system [CNS] DLBCL, primary cutaneous DLBCL, and Epstein–Barr virus [EBV] + DLBCL of elderly) and DLBCL, Not otherwise specified (NOS), which include other variants that do not belong to any of the four specific subtypes.

The molecular classification of DLBCL into germinal center B-cell (GCB)-like, non-GCB, and double-hit lymphoma is done by gene expression profiling (GEP) and immunohistochemistry (IHC) algorithms. The gold standard is GEP but is rarely used in view of various IHC algorithms (Tally, Hans, and Choi), with concordance of around 80%. Lymph 2Cx can be performed on formalin-fixed paraffin-embedded tissue and is highly concordant (>95%) with conventional GEP, such as on Affymetrix gene chips. Molecular classification is prognostic, as well as guides therapeutic intervention.

DLBCLs thus can be divided by GEP or various IHC algorithms into GCB-like and activated B-cell (ABC)-like subtypes [Table 1], with the latter having a significantly poorer outcome than the GCB group.[7] These molecular subtypes are associated with different outcomes, even after the introduction of immunochemotherapy.[8] The characteristic features of GCB and ABC DLBCL are tabulated in Table 1. Amplification of 18q21, which contains the BCL2 gene, was more frequent in ABC tumors (18%) than in GCB tumors (5%). The majority of the cases of GCB-DLBCL with amplification of 18q21 also had the translocation t (14;18). As GCB-like and ABC-like tumors arise from B-cells at different stages of differentiation (germinal center cells vs. postgerminal center cells), apparently utilize different oncogenic pathways (t[14;18] [q32;q21] translocation in GCB-like tumors vs. activation of the nuclear factor kappa B pathway in ABC-like tumors) and have different survival rates, it can be assumed that different disease entities are represented by both molecularly defined subgroups. Apart from GCB and ABC DLBCL subtypes, diagnosis of double-hit lymphoma (DHL) is based on the presence of MYC rearrangements in addition to BCL2 and/or BCL6 rearrangements. The cell of origin for DHL is germinal center B-cell and is associated with extensive disease, extranodal involvement, increased propensity to involve BM and CNS in comparison to other subtypes, and associated with poor outcomes with standard chemoimmunotherapy.

Table 1: Characteristics of germinal center B-cell and activated B-cell-diffuse large B-cell lymphoma

	GCB-DLBCL	*ABC-DLBCL*
Postulated normal counterpart	GCB cell	Post-GCB-cell
Clinical outcome (5-year OS)	59%	30%
Immunophenotype	CD10+, BCL2+, BCL6+, IRF4/MUM1−	CD10−, BCL2±, BCL6±, IRF4/MUM1+
Oncogenic mechanism	*REL* amplification *BCL2* translocation	Constitutive activation of NF-κB
Chromosomal alterations	Gain 12q12 t(14;18)	Trisomy 3 (*FOXP1*) Gain 3q Gain 18q21-q22 (*BCL2*) Deletion 6q21-q22 (*BLIMP1*)
Therapy	Better outcome with standard Chemoimmunotherapy (R-CHOP)	Poor outcome with standard therapy Addition of lenalidomide, bortezomib, and ibrutinib recommended.

ABC=Activated B-cell; DLBCL=Diffuse large B-cell lymphoma; GCB=Germinal center B-cell; NF-κB=Nuclear factor kappa B; OS=Overall survival; R-CHOP=Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone

DIAGNOSIS AND STAGING WORKUP

The diagnosis of DLBCL is done on biopsy, with distinct immunophenotype positive for CD20, CD45, and negative for T-cell markers. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD45, BCL2, BCL6, Ki67, IRF4/MUM1, and MYC to distinguish between GCB, non-GCB, and double-hit lymphomas. Patients with expression of MYC along with BCL2 and/or BCL6 should undergo FISH for MYC rearrangement to distinguish between double-hit or double-expression lymphoma. Additional markers such as CD30, CD138, EBV, HHV8, and ALK1 are useful in certain circumstances to establish the subtype. Differential diagnosis of DLBCL includes Burkitt's lymphoma (BL), Hodgkin's lymphoma, anaplastic large cell lymphoma, and gray-zone lymphomas (those intermediate between DLBCL and BL or intermediate between PMBL and HL), as outlined in Table 2.

Further detailed workup includes complete blood counts, metabolic profile including renal and liver function tests, electrolytes (potassium, phosphate, calcium), uric acid, and lactate dehydrogenase (LDH) for considering patient's suitability for cytotoxic chemotherapy, organ reserves/involvement, early indication of tumor lysis, and tumor burden, respectively. Imaging studies include positron-emission tomography/computed tomography (PET/CT) of whole body, which is found to be superior to CT scan in determining the extent of disease, extranodal as well as BM involvement, response to therapy, and distinguishing between treatment-related change and active metabolic disease. Practically, all patients with NHL should undergo a BM aspiration and biopsy before the initiation

Table 2: Differential diagnosis of diffuse large B-cell lymphoma

Entity	Clinical features	Morphology	Immunophenotype	Genotype
DLBCL	Adults >children Nodal >extranodal Often localized	Large cells, prominent nucleoli, basophilic cytoplasm	Pan B-cell antigens (CD 19, CD20, CD79a, sIg+CD10±, BCL2±, BCL6±)	BCL2 and BCL6 rearrangements common
Burkitt's or Burkitt's like	Children >adults Extranodal >nodal Widespread disease	Pleomorphic medium sized cells, multiple nucleoli, starry sky pattern	CD10+, CD20+, BCL6+, sIg+, BCL2−	t(8;14), t(2;8), t(8;22), no BCL2 or BCL6 translocations
ALCL	ALK+, young age ALK−, older adults	Large cells, horseshoe nuclei, abundant cytoplasm	CD30+, one or more T-cell antigen, no B-cell antigen	t(2;5) in ALK+
Hodgkin lymphoma	Bimodal peak, contiguous involvement, extralymphatic rare	Reed–Sternberg cells and their variants in inflammatory background	CD15+, CD30+, CD20±, CD3−, CD45−	No single cytogenetic abnormality is diagnostic
Mantle cell lymphoma	Middle-aged and elderly, prominent extranodal involvement, widespread disease	Medium-to-large cells, scant cytoplasm	CD5+, CD20+, CD10−, BCL2+, cyclin D1+, sIg+	t(11;14)

ALK=Anaplastic lymphoma kinase; DLBCL=Diffuse large B-cell lymphoma; ALCL=Anaplastic large cell lymphoma

of treatment as part of their staging evaluation. A potential exception is patient with evidence of BM positive disease on PET/CT, as sensitivity and specificity of the later determining BM involvement exceeds 88% and 98%, respectively.[9,10] HIV, hepatitis B, and hepatitis C serologies to be done as they have causal relationship, prognostic, and can guide the addition of additional therapy to improve the outcome. Addition of highly active antiretroviral therapy (HAART) improves the outcome in patients of DLBCL as well as addition of entecavir in patients positive for hepatitis B significantly reduces the reactivation rates with chemoimmunotherapy.[11] Cerebrospinal fluid studies to be reserved for patients with high LDH, high International Prognostic Index (IPI), extranodal involvement, involvement of specific sites such as epidural, paranasal, bone/bone marrow, testis, and HIV lymphoma. 2D echo or multigated acquisition scan to be done as anthracyclines are imminent part of the therapy.

PROGNOSIS

The IPI and its variants [Table 3a and b] are the main prognostic tools used in patients with DLBCL. These indices are significantly more accurate than standard staging criteria in predicting event-free survival (EFS) and overall survival (OS).[12] It incorporates age, LDH, stage, Eastern Cooperative Oncology Group performance status (ECOG PS), and number of extranodal sites to calculate IPI score. Age-adjusted IPI is used for patient ≤60 years, where all the prognostic factors in main IPI are used except for age and extranodal involvement to calculate the score. Modifications in IPI has been also made for Ann Arbor Stage I and II disease, since there is marked difference in prognosis of such patients as compared to advanced stage DLBCL.[12] It incorporates age, LDH, presence or absence of Stage II or IIE, and ECOG PS to calculate the stage-modified IPI.

TREATMENT

Treatment options for DLBCL depends on whether its localized (Ann Arbor Stage I-II) or advanced (Ann Arbor Stage III-IV) disease.

Limited stage disease (Ann Arbor Stage I or II)

Limited stage [Table 4] DLBCL is defined as one, which can be contained within one irradiation field, and accounts for 30%–40% of patients with DLBCL. The treatment of limited stage DLBCL is primarily with combined modality therapy consisting of abbreviated systemic chemotherapy (three cycles), the recombinant anti-CD20 antibody rituximab, and involved field radiation therapy (RT). Alternatively, full course (six to eight cycles) systemic chemotherapy plus rituximab without RT may be used. Although in the SWOG 8736 trial, where patients with limited stage aggressive lymphoma were randomly assigned to treatment with either chemotherapy alone (eight cycles of Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone (CHOP)) or three cycles of CHOP plus involved field RT (40–55 Gy) revealed combined modality (chemotherapy plus RT) treatment resulted in higher rates of 5-year progression-free (77% vs. 64%) and overall (82% vs. 72%) survival, but on longer follow-up of this trial revealed no significant difference in progression-free survival or OS.[13,14] Patients with nonbulky limited-stage DLBCL, treatment with abbreviated chemotherapy (R-CHOP × 3) plus involved-field radiotherapy (30–36 Gy) rather than extended

Table 3a: International Prognostic Index

IPI			
Age >60 years			
LDH >ULN			
ECOG PS ≥2			
Ann Arbor III or IV			
No of extranodal sites >1			
Score	Risk group	5-year OS (prerituximab era) (%)	3-year OS (postrituximab era) (%)
0 or 1	Low risk	73	91
2	Low intermediate	51	81
3	High intermediate	43	65
4 or 5	High	26	59

LDH=Lactate dehydrogenase; ECOG=Eastern Cooperative Oncology Group; PS=Performance status; OS=Overall survival; IPI=International Prognostic Index; ULN=Upper limit of normal

Table 3b: Variants of International Prognostic Index

Variants of IPI			
Age-adjusted IPI		Stage-adjusted IPI	
LDH >ULN		Age >60 years	
ECOG PS ≥2		LDH >ULN	
Ann Arbor III or IV		ECOG PS ≥2	
		Stage II or IIE	
Risk	5-year OS (%)	Risk	10-year OS (%)
Low risk (0)	83	Low (0)	90
Low intermediate (1)	69	Intermediate (1 or 2)	56
High intermediate (2)	46	High (3 or 4)	45
High (3)	32		

OS=Overall survival; IPI=International Prognostic Index; LDH=Lactate dehydrogenase; ECOG=Eastern Cooperative Oncology Group; PS=Performance status; ULN=Upper limit of normal

chemotherapy (R-CHOP × 6–8) alone is the preferred modality of treatment. Higher doses of radiation (e.g., 45–50 Gy) may be needed for patients with persistent PET-positive disease after chemotherapy. Patients with bulky (>10 cm) Stage II disease have a prognosis similar to that of patients with advanced (Stage III or IV) disease and therefore need to be treated in a similar fashion as that of advanced disease. Patients with limited stage, bulky disease should be treated with six cycles R-CHOP plus 30–40 Gy involved-field radiotherapy rather than six or eight cycles of R-CHOP alone. Despite this more aggressive approach, survival rates of patients with bulky disease remain worse than for those of patients without bulky disease suggesting a need for trials targeting this population.[15]

Table 4: Staging of diffuse large B-cell lymphoma

Revised staging system for primary nodal lymphomas		
Stage	Involvement	Extranodal (E) status
Limited stage		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky	II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

Advanced stage diffuse large B-cell lymphoma (Ann Arbor Stage III or IV)

Advanced stage [Table 4] patients account for 60%–70% of cases of DLBCL. Treatment of these patients should be individualized on the basis of subtypes. Chemoimmunotherapy has been proven to be the standard treatment for most patients with advanced disease. R-CHOP is the preferred regime based on numerous randomized trials conducted before the advent of rituximab-containing regimens, which compared CHOP with many other anthracycline-based regimens. These regimens failed to show any improvement in remission rate, disease-free survival, or OS and were associated with increased toxicity.[16-18] In MabThera International Trial, randomly assigned patients younger than 60 years of age with DLBCL were treated with six cycles of CHOP-like chemotherapy administered every 21 days with or without rituximab. Patients assigned to R-CHOP had significantly higher rates of remission, event-free, and OS.[19]

Patients with GCB DLBCL identified by GEP, IHC algorithms, have a relatively good prognosis following standard therapy with R-CHOP, in contrast, those with ABC type DLBCL or double-hit DLBCL have unacceptably high rates of relapse and poor survival following treatment with R-CHOP.[20,21] For patients with advanced stage ABC type DLBCL, enrollment in a clinical trial evaluating the incorporation of novel agents (e.g., R-CHOP plus lenalidomide; R-CHOP plus ibrutinib; R-CHOP plus bortezomib) is encouraged. R-CHOP plus lenalidomide in a multicenter, single-arm trial has shown overall response and complete response rates of 92% and 86%, respectively. Two-year PFS and OS in these patients was

80% and 92%, respectively.[22] Patients with double-hit DLBCL are candidates for more aggressive chemotherapy regimens (e.g., Dose-adjusted [DA]-EPOCH-R) given high rates of relapse and poor survival following treatment with standard R-CHOP, based on meta-analysis which showed prolonged PFS with DA-EPOCH-R in comparison to R-CHOP, though no OS benefit was observed. Alternatively, these patients are encouraged to participate in clinical trials.

Central nervous system prophylaxis

Patients with DLBCL have a risk of CNS recurrence of approximately 5%, and CNS prophylaxis to be given in specific situations which include lymphomatous involvement of certain organs (bones, bone marrow, testis, epidural, and paranasal sinuses), raised LDH, extranodal involvement, HIV, or double-hit lymphoma. Prophylaxis includes either six to eight doses of intrathecal methotrexate or systemic high-dose methotrexate (3.5 g/m^2) with leucovorin rescue on day 15 of alternate chemotherapy cycles. CNS relapse rates are significantly reduced in patients receiving CNS prophylaxis, which is substantially lower than the expected relapse rate based on other reports.

AIDS-RELATED DIFFUSE LARGE B-CELL LYMPHOMA

Systemic lymphomas account for 70%–90% of HIV-associated lymphoma, whereas primary CNS lymphoma accounts for rest of the cases. With the advent of HAART, the prognosis of HIV-associated lymphoma has improved, primarily for those with systemic lymphomas. Survival rates for patients with HIV-associated lymphomas remain low as compared to those with lymphoma unassociated with HIV infection. In addition to IPI, other poor prognostic markers include low CD4 counts, high HIV RNA levels, histology, lymphoma arising on HAART, and poor response to HAART. The guidelines recommend the use of HAART and growth factor support with full dose-intensive chemotherapy in patients with HIV-associated lymphomas. AIDS Malignancy Consortium has concluded that DA-EPOCH-R is associated with significant improvements EFS and OS as compared to R-CHOP.[23,24] Since the treatment-related deaths are higher in patients with low CD4 counts (<50/μL) receiving rituximab, it is strongly recommended to omit rituximab in such patients.[23] During treatment with combination chemotherapy, ART should be continued along with prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP, previously *Pneumocystis carinii* pneumonia). *Mycobacterium avium* complex prophylaxis may be appropriate for selected patients with severe immunocompromise (i.e., CD4 <50/μL). Antibiotic prophylaxis for enteric organisms during neutropenia is strongly encouraged. Given the high incidence of recurrent Herpes simplex, Herpes zoster, and Candida infections in this population, many clinicians also advise instituting antiviral and antifungal prophylaxis.

RELAPSED/REFRACTORY DISEASE

Patients with relapsed/refractory disease should be considered for enrollment in suitable clinical trials. High-dose chemotherapy followed by autologous stem cell rescue (HDT/ASCR) is the treatment of choice for patients with chemosensitive disease at relapse. One multicenter randomized trial (PARMA randomized controlled trial) has compared autologous HDT/ASCR with consolidation chemotherapy in patients with chemotherapy-sensitive relapsed aggressive NHL (largely DLBCL).[25] After a median follow-up in excess of 5 years, autologous hematopoietic cell transplant resulted in significantly superior rates of event-free survival (46% vs. 12%, $P = 0.001$) and OS (53% vs. 32%, $P = 0.038$). Patients who are candidates for HDT/ASCR should be treated with second-line chemotherapy like dexamethasone, cisplatin, cytarabine (DHAP), ifosfamide, carboplatin, etoposide (ICE), or methylprednisolone, etoposide, cytarabine, cisplatin with or without rituximab. Incorporation of rituximab results in significantly higher complete response rates than historical controls treated with the second-line chemotherapy without rituximab.[26]

An international randomized intergroup study compared R-ICE versus R-DHAP followed by ASCR in chemosensitive patients and found no significant differences in outcome. In contrast, in a subset analysis of patients with GCB DLBCL (the bioCORAL study), R-DHAP was associated with superior progression-free survival (52% vs. 31%, $P = 0.02$).[27] The second randomization showed no benefit when maintenance rituximab was added following autologous hematopoietic stem cell transplantation.[28] Thus, based on multiple randomized studies, patients with relapsed or refractory DLBCL are treated with systemic chemotherapy with or without rituximab with plans to proceed to HDT/ASCR in those with chemotherapy-sensitive disease. The treatment of patients who are not candidates for HDT/ASCR, who fail to respond to second-line chemotherapy regimens, or who relapse after HDT/ASCR is generally palliative.

MAINTENANCE

This analysis of Phase III randomized controlled REMARC study demonstrated that 2 years of lenalidomide maintenance in patients aged 60–80 years, responding to R-CHOP

significantly improved PFS (primary end point) without an early significant impact on OS. The cell of origin (COO) analysis is currently ongoing. This is the first report finding that using an immunomodulatory agent as maintenance therapy prolongs PFS for patients with DLBCL after first-line treatment with R-CHOP.[29]

CONCLUSION

The most common NHL is DLBCL, with its various morphological and clinicopathological subtypes. GEP and IHC algorithms are used for molecular risk assessment for classifying DLBCL into GCB DLBCL and nongerminal center B-cell lymphoma and for identification of double-hit DLBCL. This molecular classification is not only prognostic but also guides the therapy. The staging determines the treatment of DLBCL, wherein limited stage disease is managed with combined modality of treatment with abbreviated systemic chemoimmunotherapy and involved field RT, and advanced stage disease is treated with systemic chemoimmunotherapy. Novel agents are recommended in the treatment of non-GCB DLBCL, based on promising results in phase II trials. Oncological emergencies and treatment-related hematological as well as nonhematological toxicities are common which require urgent identification and effective treatment.

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Conflicts of interest

There are no conflicts of interest.

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