Review

Diffuse large B-cell lymphoma – a new look and old prognostic factors

Limfomul difuz cu celulă mare B – aspecte actuale şi factori de prognostic

Camelia Dobrea[1*], Hamed Al Salamat[2,3*], Anca Roxana Lupu[2,4*]

1. "Victor Babeş" National Institute, Bucharest, Romania
2. "Carol Davila" University of Medicine, "Fundeni" Department of Haematology, Bucharest, Romania
3. Alsamed Medical Center, Colentina 22, Bucharest, Romania
4. Colţea Hospital, Department of Haematology, Bucharest, Romania

Abstract

Diffuse large B-cell lymphoma (DLBCL) accounts for about 30% of non-Hodgkin's lymphoma (NHL) cases. The 2008 WHO Classification of Lymphoid Neoplasms recognizes several clinicopathological variants, subtypes and distinct disease entities of DLBCL. We present a review of clinical, pathological and molecular factors with implication in DLBCL behavior. Even if the golden standard therapy for CD20-positive DLBCL is still represented by R-CHOP, prognostic factor assessment could open new therapeutic perspectives.

Keywords : *diffuse large B cell lymphoma, prognostic factors*

Rezumat

Limfomul difuz cu celulă mare B reprezintă aproximativ 30% dintre cazurile de Limfoame NonHodgkin. Clasificarea OMS din 2008 a neoplasmelor limfoide recunoaşte câteva variante clinico-patologice, subtipuri şi entităţi distincte în cadrul limfoamelor difuze cu celula mare B. Prezentăm o trecere în revistă a factorilor patologici şi moleculari, precum şi clinici, implicaţi în evoluţia limfoamelor difuze cu celulă mare B. Deşi R-CHOP rămâne tratamentul standard pentru cazurile de limfom difuz cu celulă mare B CD20 pozitive, aprecierea factorilor de prognostic ar putea deschide noi perspective terapeutice.

Cuvinte cheie: *limfom difuz cu celulă mare B, factori de prognostic*

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Introduction

Diffuse Large B-cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin's Lymphoma (NHL), comprising about 30% of all NHL cases in all epidemiological reports (1, 2), and it accounts for 80% of aggressive lymphomas (3). The 2008 WHO Classification of Lymphoid Neoplasms (4, 5) recognizes

[*]The three authors have an equal contribution to this article.

Corresponding author: Camelia Dobrea, Institutul Clinic Fundeni, Clinica de Hematologie, Şoseaua Fundeni 258, Bucharest, 022328, Sector 2
E-mail : cameliadobrea@yahoo.com

Table 1. DLBCL: variants, subtypes, and other entities (4, 5)

DLBCL, NOS: **- Common morphologic variants:** • centroblastic; • immunoblastic; • anaplastic; **- Rare morphologic variants** **- Molecular subgroups:** • germinal center B-cell like; • activated B-cell like.. **- Immunohistochemical subgroups:** • CD5+ DLBCL; • germinal center B-cell like; • non-germinal center B-cell like.	**DLBCL histogenetic variants:** • T-cell/histiocyte-rich large B-cell lymphoma; • Primary mediastinal; • ALK+ DLBCL; **DLBCL extranodal variants:** • Primary of the central nervous system; • Primary cutaneous leg-type; • Intravascular. **DLBCL associated with viral infection** • EBV- associated of the elderly; • Lymphomatoid granulomatosis; • Associated with chronic inflammation; • Plasmablastic; • Primary effusion; • Arising from HHV8-associated multicentric Castleman's disease; **Borderline cases:** B-cell lymphomas, unclassifiable with features intermediate between: • DLBCL and Burkitt's lymphoma; • DLBCL and classical Hodgkin's lymphoma.

several clinicopathological variants, subtypes and distinct disease entities of DLBCL. Cases not conforming to these defined subtypes are given the diagnostic label DLBCL-NOS (Not Otherwise Specified). DLBCL-NOS are a very heterogeneous group, divided in several morphological variants, molecular and immunohistochemical subgroups (*Table 1*) (5).

Patients with similar DLBCL diagnoses can have varied molecular profiles, heterogeneous clinical presentations, and clinical outcomes. Standard therapy for newly diagnosed CD20 positive DLBCL is a chimeric monoclonal antiCD20 antibody (rituximab) associated with an anthracycline-based chemotherapy regimen, usually cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) (6). Although DLBCL can be cured with the current chemotherapy regiments, the long-term survival is estimated at only 50% for high-risk patients (3). Several immunohistochemical algorithms and gene profiling sets have been developed to identify DLBCL subgroups with unfavorable prognosis (7, 8). Despite the sustained research in recent years, risk-adapted therapies based on DLBCL phenotype are still in the development stage.

Pathological and molecular prognostic factors in DLBCL

Characteristics and variations of biological features in DLBCL seems to refine prognostic impact of IPI (which remains the most important prognostic factor). Several biomarkers (CD10, BCL6, MUM1, BCL2, CD5, Ki67, etc) appear to be useful to discriminate distinct subgroups, with different outcome, within IPI categories. In addition to prognostic impact, biomarkers may also define more homogeneous subsets of DLBCL, suitable for future targeted therapies (9).

Morphologic variants

Among the morphologic subtypes determined by WHO Classification (*Table 1*), the immunoblastic subtype (*Figure 1a and 1b*) is the one that

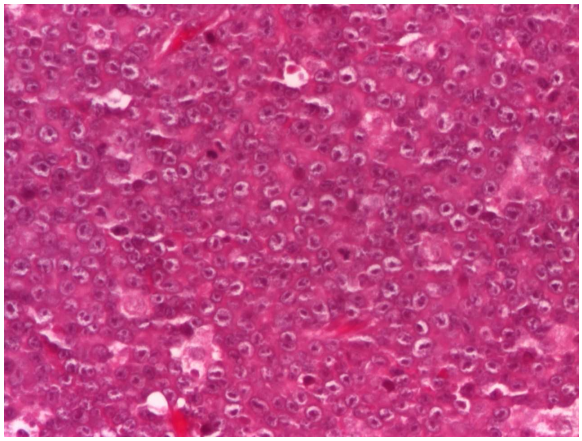

Figure 1a. DLBCL, immunoblastic variant (HE, 200x)

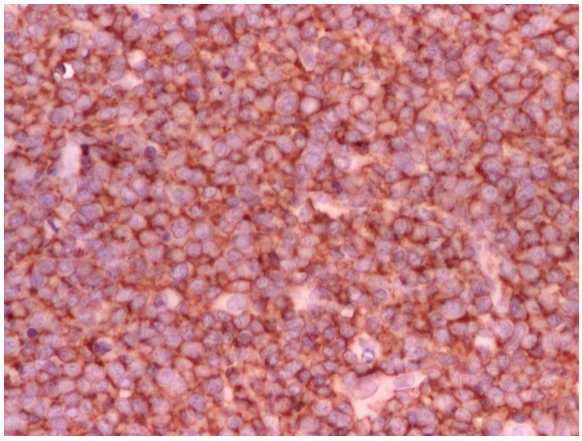

Figure 1b. DLBCL, immunoblastic variant, CD20 positive (IHC stain for CD20, 200x)

has generated most discussions. Immunoblastic variant lymphomas are lymphomas with greater than 90% immunoblasts (however most DLCL contain a mixture of centroblasts and immunoblasts or cells with intermediate features). In the RICOVER-60 trial (including 949 patients with DLBCL treated with CHOP-14 with / without Rituximab) the German High-Grade Lymphoma Study Group (DSH-NHL) concluded that immunoblastic morphology is a significantly adverse prognostic factor in multivariate analysis (10). An explanation would be that patients with immunoblastic morphology had more frequently (94%) a non-GCB (non-germinal center B-cell like) phenotype (11).

CD20 expression

The large majority of DLBCL express CD20, an important target for the treatment. CD20 negative DLBCL are very rare. CD20 negativity is associated with an immunoblastic / plasmablastic morphology, a non-GCB phenotype, and a poor prognostic (median survival < 1 year) (*Table 2*) (5, 12 - 16).

Table 2. DLBCL CD20 positive *vs* DLBCL CD20 negative: frequency, median survival (5, 12-16)

CD20 positive DLBCL			**CD20 negative DLBCL**		
DLBCL subtype	***% NHL***	***Median survival***	***DLBCL subtype***	***% NHL***	***Median survival***
DLBCL NOS	30%	~5 years	Associated with chronic inflammation	< 1%	< 2 years
Primary mediastinal	2-4%	> 5 years	ALK+ DLBCL	< 1%	< 1 year
H/TCRBCL	1%	~ 5 years	Plasmablastic	< 1%	< 1 year
Primary cutaneous leg-type	<1%	< 5 years	Arising in HHV8-associated multicentric Castelman's disease	< 1%	< 1/2 year
Primary of the central nervous system	<1%	< 2 years	Primary effusion	< 1%	< 1/2 year
EBV+ of the elderly	2-3%	< 2 years			
Lymphomatoid granulomatosis	<1%	< 2 years			
Intravascular	<1%	< 2 years			

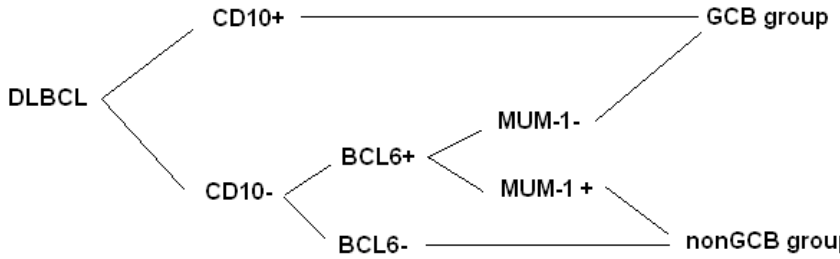

Figure 2. HANS' ALGORITHM to discriminate GCB and non-GCB/ABC group of DLBCL (15)

Gene profiling

Gene expression profiling (GEP) using cDNA microarray identified two distinct molecular subgroups of DLBCL: with germinal centre B cell-like (GCB) profil and non-germinal centre B cell-like (non-GCB) gene or activated profil. Unfortunately, although GEP provided important information about the molecular heterogeneity of DLBCL, is not routine because of the high cost. For this reason, several groups (8, 17, 18) developed identification methods using immunohistochemistry of paraffin-embedded tissue as a substitute. Because it is relatively simple (the algorithm uses only three markers: CD10, BCL6 and MUM-1/IFR4) and feasible (about 80% concordance with the GEP), Hans' algorithm (*Figure 2*) (8) has been the first widely accepted in discriminating GCB group and non-GCB, activated (ABC) group (*Figure 3 a-d*). When treated with CHOP or CHOP-like regimens, patients from GCB group have a better survival, independent of IPI (19). Even in Rituximab era, the prognostic values of this classification remain significant: a National Cancer Institute phase II trial (20) with dose-adjusted DA-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) in untreated DLBCL showed, at 62 months, time to progression and EFS (event-free survival) of GCB group were 100% and 94%, respectively, and non-GCB group were 67% and 58%, respectively (p=0.008). In 2009, Choi et al (7), using two additional markers (GCET1 and FOXP1), propose a new algorithm (*Figure 4*) to discriminate GCB and non-GCB/ABC groups of DLBCL, with 93% concordance with GEP.

Stromal signature

After Rituximab addition to CHOP therapy for DLBCL, the survival parameters were significantly improved. In 2008, G Lenz et al (21) studied prognostic impact of stromal signature (extracellular matrix, histiocytes, fibrosis, blood vessel) in DLCL patients treated with CHOP and R-CHOP respectively. Two types of stromal signature were identified by GEP. **Type 1 stromal signature**, with a more favorable prognosis, is characterised by overexpression of genes associated with a normal mesenchimal tissue, like fibronectin (SPARC), GTCF (connective-tissue growth factor), that can initiate fibrosis, MMP9 (mtrix-metallopeptidase 9) deposition, macrophage, PMN and histiocytes infiltration (21). GTCF may represent a target therapy for these patients. **Type 2 stromal signature**, with a poor prognosis, is associated with overexpression of genes involved in stimulating neoangiogenesis, like chemokine CXCL12 (21). Antiangiogenetic therapy (anti VEGF – Bevacizumab) could by a therapeutic alternative for these DLBCL.

De novo CD5 positive DLBCL

T-cell marker, CD5 is also expressed in some B-cell NHL, such as small lymphocytic lymphoma / chronic lymphocytic leukemia (B-

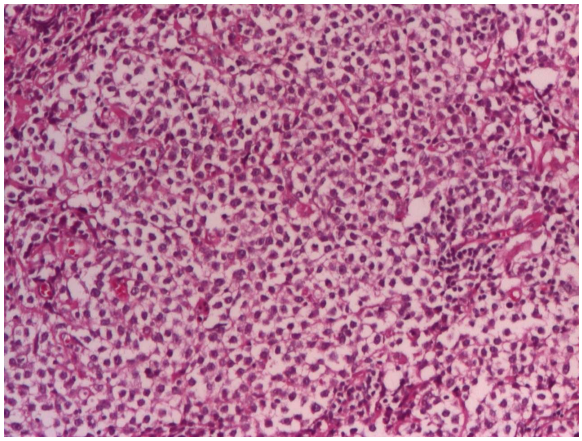

Figure 3a. Non-GCB/ABC case of DLBCL according Hans' algorithm (HE, 100x)

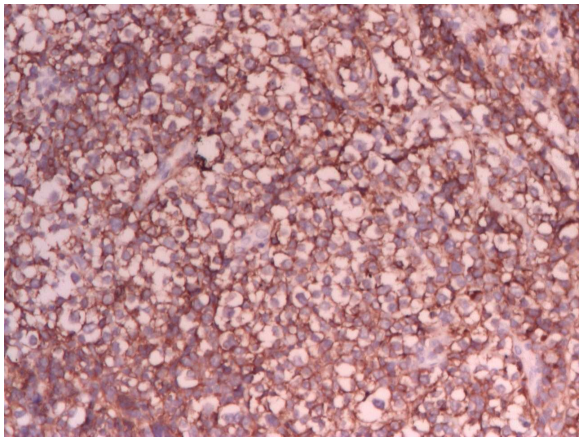

Figure 3b. Idem, CD20 positive (IHC stain for CD20, 100x)

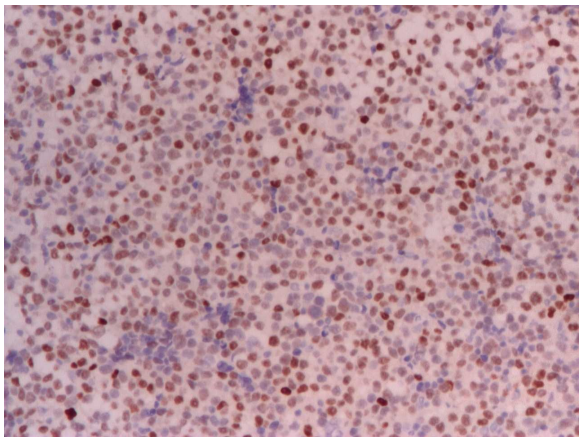

Figure 3c. Idem, BCL6 positive (IHC stain for BCL6, 100x)

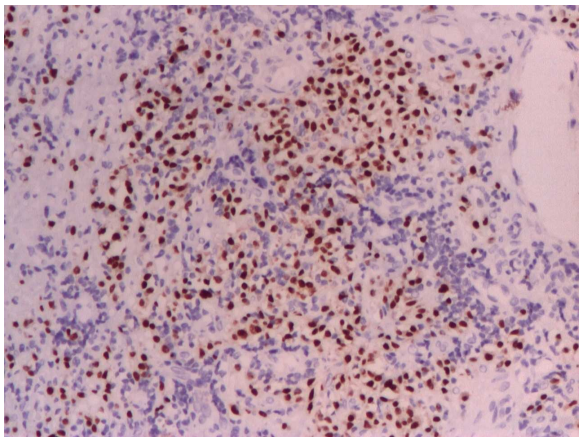

Figure 3d. Idem, MUM-1 positive (IHC stain for MUM-1, 100x)

SLL/B-CLL), mantle cell lymphoma (MCL) and rare cases of "*de novo*" CD5+ DLBCL (CD5+ DLBCL not preceded by any other lymphoproliferative disease). In 1995, Matolcsy et al (22) first described *de novo* CD5+ DLBCL, which are now recognized by WHO as an immunohistochemical subgroup of DLBCL NOS (*Table 1*) (5). *De novo* CD5+ DLBCL comprise approximately 10% of DLBCL (23).

De novo CD5+ DLBCL is clinicopathologically and genetically distinct from CD5 negative DLBCL. Four morphologic variants were identified: monomorphic, giant cell-rich, polymorphic and immunoblastic (24). This type of DLBCL is mainly included in the non-GCB-cell subgroup. Immunohistochemistry, the lymphoma frequently showed MUM1/IFR4 expression; BCL6 transcription factor is positive in about half of cases and BCL2 is expressed in the majority of cases (25, 26). Cytogenetically, a subgroup of patients with *de novo* CD5+ DLBCL with chromosomal abnormalities at 8p21 or 11q13, displaying a poor prognosis was identified (27). Clinical, *de novo* CD5+ DLBCL is associated with old age onset at diagnosis, female predominance, and frequent involvement of extranodal sites (bone marrow, liver,

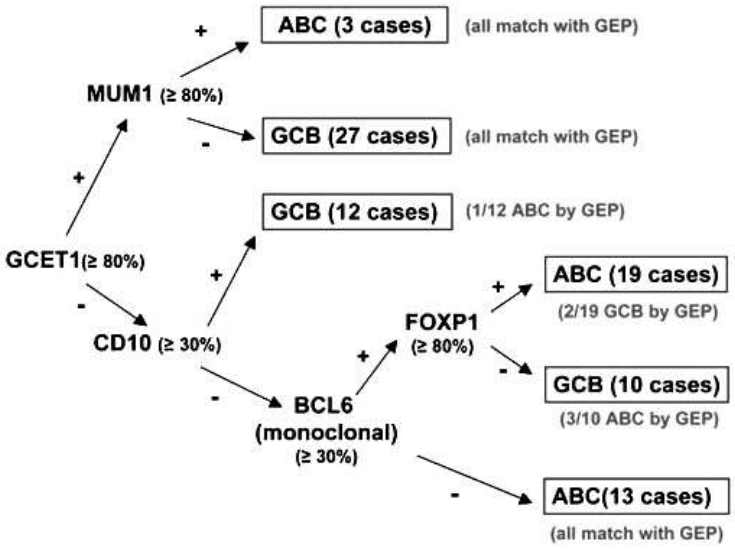

Figure 4. CHOI' ALGORITHM to discriminate GCB and non-GCB/ABC group of DLBCL (7)

spleen, lung, etc). About a third of patients are categorized in the high-risk IPI group, indicating a highly aggressive subtype of DLBCL (23). The prognosis of *de novo* CD5+ DLBCL is significantly poor compared to CD5 negative cases, with a 5-year overall survival (OS) rate of only 38% (26). The incidence of central nervous system recurrence in this form of DLBCL is high (26).

BCL2 expression

BCL2 overexpression (an antiapoptotic protein) is well known to confer chemotherapy resistance (28). Therapeutic targeting of this protein (BL193) is under development (29). In DLBCL, BCL2 expression and OS were not significantly correlated within the GCB subgroup, but BCL2 had a significant adverse effect on OS within the ABC subgroup (30, 31). BCL2 was found to discriminate the outcome of low- or intermediate IPI risk patients treated with (and without) Rituximab (9). Rituximab modulates the significance of BCL2 expression in DLBCL (32). For gastric DLBCL, BCL2 expression does correlate with worse prognosis (31).

Ki67 expression

The prognostic impact of Ki-67 protein overexpression in DLBCL is still unclear. Some immunohistochemical studies have suggested a correlation between Ki67 level, GCB / non-GCB DLBCL phenotype and BCL2 expression, but the prognostic relevance of these findings remain unclear. Hasselblom S et al (33) suggest that low rather than high Ki-67 protein expression confers an adverse prognostic in DLBCL, independent of non-GCB phenotype and bcl-2 expression. Others authors (9) consider that Ki67 overexpression (>80%) appears to confer a poor prognosis in intermediate IPI DLBCL patients treated with R-CHOP (34).

Other biomarkers with prognostic impact in DLBCL

The Signal Transducers and Activators of Transcription 3 (STAT3) plays a critical role in regulation of cell proliferation and survival (35). STAT3 is more frequently expressed in non-GCB DLBCL, and its strong nuclear expression is correlated with a poor OS (24). The study of Chen Z et al (36) found Topoisomerase IIα (Topo IIα) overexpression in >89% cases with DLBCL, while gene amplification was absent in all cases.

Clinical prognostic factors in DLBCL

International Prognostic Index

The International Prognostic Index (IPI) is the first prognostic model used in the management of patients with DLBCL (37). Based on the number of negative prognostic features present at the diagnostic (age > 60 years, advanced clinical stage III/IV, elevated LDH level, ECOG performance status ≥ 2, > 1 extranodal site of disease) four groups (with low, low-intermediate,

Table 3: DLBCL outcome according to IPI, R-IPI and SIL index in DLBCL (3, 32)

Risk group	No factors	4-year PFS %	4-years OS %
Standard IPI			
1. low	0-1	85	82
2. low-intermediate	2	80	81
3. high-intermediate	3	57	49
4. high	4-5	51	59
Revised IPI			
5. very-good	0	94	94
6. good	1-2	80	79
7. poor	3-5	53	55
SIL index			
8. standard	0-1	83	91
9. high	2-3	52	67

IPI, R-IPI: age > 60 years, advanced clinical stage III/IV, elevated LDH level, ECOG performance status ≥ 2, > 1 extranodal site of disease; SIL: clinical stage; sIL-2R level > 2,500 U/mL, LDH level

high- intermediate and high-risk) were identified, with a 5-year overall survival ranging from 26% to 73% (38). In the GELA trial (39), following addiction of Rituximab to CHOP regiment, low-risk patients seemed to have a greater benefit than high-risk patients Elevated beta2-microglobulin level, >1 extranodal site of disease and bulky disease are the most important negative prognostic factors in the GELA trials. In 2007, LH Sehn et al (3) propose a Revised IPI (R-IPI) which identifies 3 distinct prognostic groups of DLBCL: "very-good", with zero risk factor (90% chance of long-term PFS); "good", with 1-2 risk factors (80% chance of long-term PFS); "poor", with 3-5 risk factors (50% chance of long-term PFS). Other predictors must be elucidated to identify patients with less than 50% chance of survival, who need alternatives therapies. In 2012, Tomita et al (32) proposed to add soluble interleukin-2 receptor (sIL-2R) level >2,500 U/mL to the factors comprising the R-IPI. This SIL index (S=clinical stage; I=sIL-2R level > 2,500 U/mL, L=LDH level) identifies 2 risk groups: standard (0-1 risk factors, 4-year PFS 83%, OS 91%) and high-risk (2-3 risk-factors, 4-year PFS 52%, OS 67% (*Table 3*). However, the Lunenburg Lymphoma Biomarker Consortium study, published in 2011 (9) demonstrate that the IPI remains the best available index in patients with DLBCL treated with rituximab and chemotherapy.

Conclusion

A more complex, clinical, morphologic, immunohistochemical and cytogenetic assessment of prognostic factors could help in orienting the therapeutic strategy in this very heterogenous group of NHL.

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