

Mini Review

Types of Diffuse Large Beta Cell Lymphoma: A Mini Review

Ayesha T^{1*} and Azhar K²¹Department of Pharmaceutical Services, Ghurki Trust Teaching Hospital, Pakistan²Department of Pharmaceutical Services, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan***Corresponding author:** Tariq Ayesha, Department of Pharmaceutical Services, Ghurki Trust Teaching Hospital, House #27, Muslim Street, Itahad Colony Samanabad, Lahore, Pakistan**Received:** March 13, 2016; **Accepted:** July 25, 2016;**Published:** July 27, 2016**Abstract**

Diffuse large B-cell lymphoma, is the most frequent subtype of lymphoma (non-Hodgkin's lymphoma). Instead of a single clinic pathologic entity, DLBCL is a heterogeneous disease with known inconsistency in cells of origin, inherited attributes and variable clinical outcome. Depending on the basis of histological features. On the basis of gene expression profiling, DLBCL is classified in to at least 3 distinctive molecular subtypes of DLBCL. One is Germinal center B-cell (GCB) subtype, having illustration profile comparable to typical germinal center B cells; second is Activated B-cell (ABC) subtype, imitator of activated peripheral-blood B cells and third subtype is primary mediastinal large B-cell lymphoma (PMBCL), characteristically representing with mediastinal lymphadenopathy and exhibiting some molecular genetics resemblance to Hodgkin lymphoma. In this review, we briefly cover the molecular subtypes of diffuse large beta cell lymphoma and WHO classification of lymphoma.

Keywords: DLBCL; Germinal center B-cell (GCB)-DLBCL; Activated B-cell (ABC)-DLBCL

Introduction

Among all types of blood cancers, lymphoma is the most common one [1]. Hodgkin and Non Hodgkin lymphoma are the two major forms of lymphomas. DLBCL is the most frequent type of NHL in which B lymphocytes have potential to grow and proliferate abnormally [2,3]. Lymph node and outside of the lymphatic system are main arising points for development of DLBCL [4]. Large mass of B cells, B- symptoms and extranodal sites are the main features of DLBCL [5]. In Pakistan, DLBCL reaches to an epidemic proportion [6]. In 2008, WHO had classified the DLBCL according the involvement sites [7].

Germinal center B-cell (GCB-DLBCL)

The GCB subgroup is mainly described by representation of molecular signature of germinal center B-cell, because it tends to develop from germinal center B-cells [2]. GCB-DLBCL have improved prognosis than other subgroups of DLBCLs [8]. GCB-DLBCL has frequent association with translocation of gene on chromosome 14 and 18 [9]. BCL-2 protein is highly expressed in GCB because of the presence of bcl-2 gene nearby to heavy chain gene enhancer [10]. This placement of bcl-2 gene makes possible through the gene translocation on chromosome 14 and 18 [11]. Over expression of Bcl-2 blocks the apoptotic death of a pro-B-lymphocyte cell line. Thus, Bcl-2 is unique among proto-oncogenes, being localized to mitochondria and interfering with programmed cell death independent of promoting cell division. Caspases belong to endoproteases family and having control on inflammation and programmed cell death [12]. Clinically distinguishing features of GCB-DLBCL [13]:

1. Gene translocation (t) at chromosome 14 and 18 (q32;q21)
2. Gain/amplification of oncogenic mir-17-92 micro RNA cluster(in the MIHG1 locus) on chromosome 13

3. Removal of PTEN, a tumor suppressor gene on chromosome 10
4. Gain/amplification of a 7.6-Mb region on chromosome12
5. Amplification of the REL locus on chromosome 2

Activated B-cell (ABC-DLBCL)

ABC-DLBCL have markedly different molecular signature. This signature is characterized by over expression of genes cluster that have tendency to up regulate in peripheral-blood B cells, triggered by mitogenic stimulation in vitro [14]. FOXP1 appeared as a potential oncogene associated with ABC- DLBCLs [14]. It was highly up-regulated by trisomy 3 and focal high-level amplifications.

From recent studies, it has been demonstrated that, most of ABC-DLBCLs expresses amplicon on chromosome 19 [9]. SPIB is highly expressed up-regulated gene involved in this amplicon. SPIB (Spi-B Transcription Factor) is the mean of encoding the transcription factor (an ETS family) [15]. It is strongly implicated by Knockdown of SPIB via RNA interference that SPIB is an oncogene that is highly engaged in the pathogenesis of ABC DLBCLs [9]. Clinically distinctive features associated with ABC-DLBCLs are [11]:

1. Detection of amplicon on chromosome 19 (gain/amplification of a 9-Mb region on chromosome 19)
2. Removal of tumor suppressor locus INK4a/ARF
3. Presence of trisomy 3/amplification of chromosome arm 3q
4. Recurrent gain of 18q arm of chromosome and loss of 6q (chromosome arm)

Primary mediastinal large B-cell lymphoma (PMBL)

On the basis of distinguishing clinical and morphological features, Primary mediastinal B cell lymphoma (PMBL) has been described

as DLBCL's subtype [16]. Pathologically, tumors of PMBL are often highly sclerotic and are differentiated by a diffuse proliferation of large cells, frequently with a clear cytoplasm [5]. In PMBL, lymphoma involvement site is the mediastinum but the lymphoma has capability to spread locally to affect other thoracic structures and infrequently propagate to distinctive extranodal sites for example kidney and the brain.

PMBLs are usually diagnosed in young patients with a mean age of about 30-35 year at stage of diagnosis as compared to other DLBCL patients having age > 60yr at diagnostic stage. There is undefined relationship between PMBL to other DLBCL subtypes [16]. GCB-DLBCL is likely to maintain the gene expression program of normal germinal center B cells while ACB-DLBCL exhibit genes characteristic of activated B cells and plasma cells [17,18]. CD10, an indicator of germinal center stage of B cell differentiation, is not highly expressed in PMBL which makes it distinctive from other subtypes [19].

Pathologically, PMBL is a distinctive subgroup of DLBCL [5]. In more than half of the PMBL cases, chromosome arm 9p gains have been identified, and this karyotypic idiosyncrasy is just infrequently detected in other subgroups of DLBCLs [5]. Clinically, PMBL is a destructive type of lymphoma, and its responsiveness to standard treatment is relatively contentious [20]. It has been concluded from some recent studies that patients of PMBL have a comparatively poor prognosis, but further study revealed 46% overall survival at 5-yr by use of chemotherapy that is anthracycline-based, comparable to that of other subtypes of DLBCLs [21]. Another recent study demonstrated 3yr overall survival rate of 82% when chemotherapy used in combination with radiotherapy, this rate is comparatively higher to a large extent than in other DLBCLs [22]. Three most important clinical and molecular features of PMBL are [5]:

1. PMBLs are more intended to develop in young patients [23]
2. Instead of mediastinum, these lymphoma spread to other thoracic structures [24]
3. MAL and FIG1, two molecular markers that are highly expressed in PMBLs [5]

The International Prognostic Index that is vigorous clinical diagnostic model can be employed to recognize patients of PMBL (less likely to be managed with standard treatment). But such models do not propose specific insights about biology of cancerous cells, efficient treatment approaches or in addition novel therapeutic targets. In addition, latest studies imply that subsets of DLBCL might be different from normal cells on the basis of cell origin, clinical presentation and outcome as well as genetic bases for alteration.

WHO classification of lymphoid neoplasms

In 2008, WHO had précised the definitions of well-known diseases, recognized new entity and alternatives, as well as introduced the integrated novel promising conception in the recognition of lymphoid neoplasms. This report of WHO classification condenses the procedures and underlying principles of lymphoid neoplasms and highlighting those diseases for which modification have had an influence on practice guidelines. These lesions are classified according to the lymphoma to which they conformed [25].

DLBCL classification according to WHO

Mature B-cell neoplasms

- 1) Chronic lymphocytic leukemia/small lymphocytic lymphoma [25,26]
- 2) Monoclonal B-cell lymphocytosis*
- 3) B-cell prolymphocytic leukemia
- 4) Splenic marginal zone lymphoma
- 5) Hairy cell leukemia
- 6) Splenic B-cell lymphoma/leukemia, unclassifiable
- 7) Splenic diffuse red pulp small B-cell lymphoma
- 8) Hairy cell leukemia-variant
- 9) Lymphoplasmacytic lymphoma
- 10) Waldenstrom macroglobulinemia
- 11) Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- 12) M heavy-chain disease
- 13) G heavy-chain disease
- 14) A heavy-chain disease
- 15) Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- 16) Plasma cell myeloma
- 17) Solitary plasmacytoma of bone
- 18) Extraoesous plasmacytoma
- 19) Monoclonal immunoglobulin deposition diseases*
- 20) Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
- 21) (MALT lymphoma)
- 22) Nodal marginal zone lymphoma
- 23) Pediatric nodal marginal zone lymphoma
- 24) Follicular lymphoma
- 25) In situ follicular neoplasia*
- 26) Duodenal-type follicular lymphoma*
- 27) Pediatric-type follicular lymphoma*
- 28) Large B-cell lymphoma with IRF4 rearrangement*
- 29) Primary cutaneous follicle center lymphoma
- 30) Mantle cell lymphoma
- 31) In situ mantle cell neoplasia*
- 32) Diffuse large B-cell lymphoma (DLBCL), NOS
- 33) Germinal center B-cell type*
- 34) Activated B-cell type*

- 35) T-cell/histiocyte-rich large B-cell lymphoma
- 36) Primary DLBCL of the central nervous system (CNS)
- 37) Primary cutaneous DLBCL, leg type
- 38) EBV1 DLBCL, NOS*
- 39) EBV1 mucocutaneous ulcer*
- 40) DLBCL associated with chronic inflammation
- 41) Lymphomatoid granulomatosis
- 42) Primary mediastinal (thymic) large B-cell lymphoma
- 43) Intravascular large B-cell lymphoma
- 44) ALK1 large B-cell lymphoma
- 45) Plasmablastic lymphoma
- 46) Primary effusion lymphoma
- 47) HHV81 DLBCL, NOS*
- 48) Burkitt lymphoma
- 49) Burkitt-like lymphoma with 11q aberration*
- 50) High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
- 51) High-grade B-cell lymphoma, NOS*
- 52) B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and
- 53) Classical Hodgkin lymphoma
- 17) Lymphomatoid papulosis
- 18) Primary cutaneous anaplastic large cell lymphoma
- 19) Primary cutaneous gamma/delta T-cell lymphoma
- 20) Primary cutaneous CD81 aggressive epidermotropic cytotoxic T-cell lymphoma
- 21) Primary cutaneous acral CD81 T-cell lymphoma*
- 22) Primary cutaneous CD41 small/medium T-cell lymphoproliferative disorder*
- 23) Peripheral T-cell lymphoma, NOS
- 24) Angioimmunoblastic T-cell lymphoma
- 25) Follicular T-cell lymphoma*
- 26) Nodal peripheral T-cell lymphoma with TFH phenotype*
- 27) Anaplastic large-cell lymphoma, ALK1
- 28) Anaplastic large-cell lymphoma, ALK2*
- 29) Breast implant-associated anaplastic large-cell lymphoma*

Mature T and NK neoplasms

- 1) T-cell prolymphocytic leukemia
- 2) T-cell large granular lymphocytic leukemia
- 3) Chronic lymphoproliferative disorder of NK cells
- 4) Aggressive NK-cell leukemia
- 5) Systemic EBV1 T-cell lymphoma of childhood*
- 6) Hydroa vacciniforme-like lymphoproliferative disorder*
- 7) Adult T-cell leukemia/lymphoma
- 8) Extranodal NK-/T-cell lymphoma, nasal type
- 9) Enteropathy-associated T-cell lymphoma
- 10) Monomorphic epitheliotropic intestinal T-cell lymphoma*
- 11) Indolent T-cell lymphoproliferative disorder of the GI tract*
- 12) Hepatosplenic T-cell lymphoma
- 13) Subcutaneous panniculitis-like T-cell lymphoma
- 14) Mycosis fungoides
- 15) Sezary syndrome
- 16) Primary cutaneous CD301 T-cell lymphoproliferative disorders

Hodgkin lymphoma

- 1) Nodular lymphocyte predominant Hodgkin lymphoma
- 2) Classical Hodgkin lymphoma
- 3) Nodular sclerosis classical Hodgkin lymphoma
- 4) Lymphocyte-rich classical Hodgkin lymphoma
- 5) Mixed cellularity classical Hodgkin lymphoma
- 6) Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)

- 1) Plasmacytic hyperplasia PTLD
- 2) Infectious mononucleosis PTLD
- 3) Florid follicular hyperplasia PTLD*
- 4) Polymorphic PTLD
- 5) Monomorphic PTLD (B- and T-/NK-cell types)
- 6) Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

- 1) Histiocytic sarcoma
- 2) Langerhans cell histiocytosis
- 3) Langerhans cell sarcoma
- 4) Indeterminate dendritic cell tumor
- 5) Interdigitating dendritic cell sarcoma
- 6) Follicular dendritic cell sarcoma
- 7) Fibroblastic reticular cell tumor
- 8) Disseminated juvenile xanthogranuloma
- 9) Erdheim-Chester disease*

Conclusion

Diffuse large beta cell lymphoma is the most common subtype of NHL and is a cancer of B-lymphocytes (essential component of immune system of body). In recent years, DLBCL has turned out to be an emerging epidemic in Pakistan. In order to evaluate a patient's risk profile, clinical parameters are used presently in combination form and these predictable variables are considered to be alternative for the basic cellular and molecular discrepancies within DLBCL. This review not only focused on characteristics subtypes but also WHO classification of DLBCL.

References

- Vail DM. Lymphoma. Schalm's veterinary hematology. 5th ed. Philadelphia: Lippincott, 2000. 620-625.
- Gatter K, Pezzella F. Diffuse large B-cell lymphoma. Diagnostic Histopathology. 2010; 16: 69-81.
- Rizvi MA, Evens AM, Tallman MS, Nelson BP, Rosen ST. T-cell non-Hodgkin lymphoma. Blood. 2006; 107: 1255-1264.
- LeBien TW, Tedder TF. B lymphocytes: how they develop and function. Blood. 2008; 112: 1570-1580.
- Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003; 198: 851-862.
- Naz E, Mirza T, Danish F. Clinicopathologic evaluation of subgroups of diffuse large B cell lymphoma by immunohistochemistry. Asian Pac J Cancer Prev. 2011; 12: 3335-3339.
- Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009; 523-531.
- Bea S, Zettl A, Wright G, Salaverria I, Jehn P, Moreno V, et al. Diffuse large B-cell lymphoma subgroups have distinct genetic profiles that influence tumor biology and improve gene-expression-based survival prediction. Blood. 2005; 106: 3183-3190.
- Lenz G, Wright GW, Emre NT, Kohlhammer H, Dave SS, Davis RE, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A. 2008; 105: 13520-13525.
- Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A, et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J Clin Oncol. 2006; 24: 961-968.
- Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403: 503-511.
- Wolf BB, Green DR. Suicidal tendencies: apoptotic cell death by caspase family proteinases. J Biol Chem. 1999; 274: 20049-20052.
- Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A. 2003; 100: 9991-9996.
- Iqbal J, Joshi S, Patel KN, Javed SI, Kucuk C, Aabida A, et al. Clinical implication of genome-wide profiling in diffuse large B-cell lymphoma and other subtypes of B-cell lymphoma. Indian J Cancer. 2007; 44: 72-86.
- Hollenhorst PC, Jones DA, Graves BJ. Expression profiles frame the promoter specificity dilemma of the ETS family of transcription factors. Nucleic acids research. 2004; 32: 5693-5702.
- Calvo KR, Traverse-Glehen A, Pittaluga S, Jaffe ES. Molecular profiling provides evidence of primary mediastinal large B-cell lymphoma as a distinct entity related to classic Hodgkin lymphoma: implications for mediastinal gray zone lymphomas as an intermediate form of B-cell lymphoma. Adv Anat Pathol. 2004; 11: 227-238.
- Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature. 2009; 459: 717-721.
- Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med. 2001; 194: 1861-1874.
- Pileri SA, Dimhofer S, Went P, Ascani S, Sabattini E, Marafioti T, et al. Diffuse large B-cell lymphoma: one or more entities? Present controversies and possible tools for its subclassification. Histopathology. 2002; 41: 482-509.
- Boyd SD, Natkunam Y, Allen JR, Warnke RA. Selective immunophenotyping for diagnosis of B-cell neoplasms: immunohistochemistry and flow cytometry strategies and results. Appl Immunohistochem Mol Morphol. 2013; 21: 116-131.
- El-Galaly T, Sheah C, Villa D, Hansen J, Poulsen MØ, Rady K, et al. Validation of the German high-grade non-hodkin lymphoma study group (DSHNHL) prognostic model for CNS relapse in a large cohort of PET/CT staged patients. 13-ICML. 2015; 33:171-172.
- Pinkerton R. Continuing challenges in childhood non-Hodgkin's lymphoma. Br J Haematol. 2005; 130: 480-488.
- Savage KJ, Gaulard P. Primary mediastinal (thymic) large B-cell lymphoma. Extranodal lymphomas pathology and management. Ed Cavalli F, Stein H, Zucca E, Inborma UK. 2008: 196-211.
- Rodríguez J, Gutiérrez A, Piris M. Primary mediastinal B-cell lymphoma: treatment and therapeutic targets. Leuk Lymphoma. 2008; 49: 1050-1061.
- Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M, Pileri SA. Diffuse large B-cell lymphoma. Crit Rev Oncol Hematol. 2013; 87: 146-171.
- Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127: 2375-2390.