Heterogeneity among diffuse large B-cell lymphoma: new entities in WHO classification, a first step in personalized therapy

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Abstract
Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma, being part of mature B-cell neoplasm according to the 2016 World Health Organization (WHO) Classification of lymphoid tumors. This type of non-Hodgkin’s lymphoma (NHL) can develop in the lymph nodes in most cases, or in extranodal sites (the most frequent involvement being the digestive tract, but also the thyroid, central nervous system, testes, etc.). Despite being an aggressive lymphoma, DLBCL benefits of potentially curable therapy. The addition of monoclonal antibodies to standard chemotherapy in the therapeutic approach of DLBCL leads to some net superior results to those obtained by chemotherapy alone. Despite the fact that the aggressive therapy is very efficient, 10% of patients remain refractory to it, 30–40% of them after obtaining a complete response (CR) will relapse, and 90% of refractory DLBCL have poor survival rates. Based on these findings, an explanation for the differences in clinical outcome and therapy response was attempted. The important progresses made in the understanding of DLBCL heterogeneity were based on molecular biology studies and showed differences in chromosomal alterations and in signaling pathways activation. These findings have paved the way for new therapeutic targets in order to improve therapy response. The large heterogeneity of DLBCL is acknowledged by the 2016 WHO Classification of lymphoid neoplasms, with 17 DLBCL subtypes, some of them as new varieties, compared to the 2008 Classification, and others introduced as provisional entities.

Keywords: diffuse large B-cell lymphoma, cell of origin, heterogeneity.

Introduction
Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma, consisting of about 30% of B-cell lymphoid neoplasms, potentially curable in a proportion of 50–60% by aggressive chemotherapy [1]. In medical practice, there were differences in clinical aggressiveness and response to standard immunochemotherapy using Rituximab, Cyclophosphamide, Adriamycin, Vincristine and Dexamethasone (R-CHOP) regimen. For DLBCL – an aggressive lymphoma in which chemotherapy has a curative intent – the total remission rate may reach 60% [2, 3] but there are cases of aggressive clinical progression in which only 30% of patients achieve complete remission and 10–15% of patients experience refractory or progressive disease, showing primary resistance to therapy [4]. These were included in the 2008 World Health Organization (WHO) Classification of lymphoid neoplasms in the DLBCL category with an intermediate phenotype between DLBCL and Burkitt lymphoma (BL), which included cases that had histopathological (HP) appearance of DLBCL but with aggressive clinical evolution.

Information of the proliferating cell origin, cell activation pathways, cytogenetic and molecular abnormalities involved in DLBCL pathogenesis were provided by cytogenetic examination and molecular biology techniques. Cytogenetic examination and molecular biology techniques have been able to provide information of proliferating cell origin, the signaling pathways activation, and the cytogenetic and molecular abnormalities involved in DLBCL pathogenesis, showing distinct clinical and biological characteristic of the same HP entity. Also, understanding biology and proving DLBCL heterogeneity have created the premises for different therapeutic approaches and customized new targeted therapies of great interest in modern medicine. However, their inclusion in the current treatment guidelines remains a goal to be fulfilled. Concerning the new molecular biology techniques, the advantages of gene expression profiling studies is the analysis of hundreds of genes with fast and accurate results. The level of gene expression can be determined by microarray tests due to the ability of the messenger ribonucleic acid (mRNA) to bind each gene in the network.

Therefore, the mRNA reflects for each gene in a tumor cell its biological characteristics, highlighting the unique genetic disorders. Gene expression profile provides an overview of the cellular function and useful information...
for the diagnosis, prognosis and to identify new therapeutic targets in DLBCL [5].

The DLBCL heterogeneity is recognized in the latest WHO Classification of lymphoid neoplasms, which contains a wide variety of entities other than DLBCL [6]. Some of these are kept from the 2008 Classification, but a number of new entities appear, some provisional and others associated with genetic rearrangements (Table 1).

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| HBCL, NOS                             | HHV-8 Epstein–Barr virus 1; NOS: Not otherwise specified; HBCL: High-grade B-cell lymphoma; BCL2/BCL6: B-cell lymphoma leukemia 2/6; HHV-8: Human herpes virus-8; CNS: Central nervous system; ALK1: Anaplastic lymphoma kinase 1. |}

**Histopathology**

HP appearance of the lymph node describes a diffuse tumor proliferation that may be associated with secondary sclerosis [7]. The tumor cells are large in size, with prominent nuclei and relatively abundant cytoplasm (Figure 1, a and b) [8]. Histologically, the ganglion architecture is completely disorganized due to lymphoid neoplastic proliferation, with numerous mitoses. Based on tumor cytormorphology, germinal center cells (large cleaved and uncleaved cells), immunoblasts and cells found in the anaplastic subtype can be encountered [5]. The large cleaved cells exhibit a low eosinophilic cytoplasm, a small, cleaved or irregular edges nucleus and invisible nucleoli. Generally, their size ranges between 15 and 30 μm, and their presence in extranodal sites is associated with local sclerosis [7]. Large uncleaved cells have a diameter between 20–30 μm, abundant cytoplasm and round-oval nucleus with 2–3 well-visible nucleoli. The largest neoplastic lymphoid cell identifiable in DLBCL is the tumor immunoblast, containing abundant cytoplasm with eccentric, volumetric, polymorph nucleus (oval or vesicular) with central nucleoli [5].

![Figure 1 – Histopathological exam in DLBCL: (a) DLBCL lymph node histology – diffuse lymphoid proliferation with large cells, round nucleus, with prominent nucleoli; (b) Monomorphic proliferation with large round cells, with one or two nucleoli. HE staining: (a) ×200; (b) ×400. DLBCL: Diffuse large B-cell lymphoma; HE: Hematoxylin–Eosin.](image)

In certain cases, HP examination reveals fibrosis and the presence of an intermediate or large lymphoid cell infiltrate. Collagen-type fibrosis separates proliferating malignant cells into compartments. The cell nuclei may be round, regular or irregular, sometimes multilobular, surrounded by clear cytoplasm. In some cases, neoplastic cells are characterized by the presence of pleomorphic nuclei with large, visible nucleoli, similar to Reed–Sternberg cells. Some of these cells may exhibit abundant cytoplasm, being similar to lacunar cells in classical Hodgkin’s lymphoma (HL) with nodular sclerosis [9]. This HP aspect is distinctive in primary mediastinal (thymic) large B-cell lymphoma (PMLBCL). Some of PMLBCLs that resemble morphologically, immunophenotypically and molecularly with classical HL, nodular sclerosis subtype, are part of the non-classified B-cell lymphomas with intermediate characteristics between DLBCL and HL, according to the WHO Classification. This category is also maintained in the updated 2016 WHO Classification [6].

**Cell of origin. Cell activation pathways**

A study of gene expression profiling by Alizadeh et al., in 2000, identified three DLBCL subtypes with different
cell origin: germinal center B-cell-like (GCB) DLBCL, coming from dark zone centroblast, activated B-cell type (ABC) DLBCL, in which B-cell lymphocytes are in course of transformation into plasmablast and PMLBCL. These three groups are characterized by clinical evolution, prognosis, cell activation pathways involved and response to treatment [10–12].

In DLBCL with GCB phenotype, the cell of origin is thought to be germinal center B-lymphocyte, expressing the following surface markers: cluster of differentiation (CD)10+, B-cell lymphoma/leukemia (BCL)6+, CD5+/−, CD23+/−, BCL2+/−, multiple myeloma oncogene 1 (MUM1)+, cyclin D1−[13]. The pathway of cellular activation in GCB DLBCL involves disruption of the B-lymphocyte antigen receptor. Thirty to forty percent of cases are associating with overexpression of BCL2, anti-apoptotic gene, 30% c-rel amplification, a member of the nuclear factor-kappa B (NF-xB) transcription factor family, 20% histone methyl transferase (EHZip) mutations (implicated in histone methylation and ultimately interfering with transcriptional mechanisms) and 10% phosphatase and tensin homolog (PTEN) deletion, tumor suppressor gene encoding phosphatidylinositol triphosphate. These abnormalities are not found in ABC DLBCL. Activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway may occur on several ways may be found in a wide variety of lymphomas, besides the GCB DLBCL. In GCB DLBCL, the activation is accomplished by the deletions of PTEN, among others, that these mutations are identified in 10% of cases and the loss of PTEN immunophenotypic expression is found in 55% of cases [14].

Histone transferase mutations and BCL6 abnormalities are inducers of the malignant transformation process in GCB DLBCL. Only point mutations of EZH2 can cause increased histone 3 mutation with inhibitory effect on genes that regulate transcriptional mechanisms, thereby producing lymphomagenesis [15]. Overexpression of BCL2 protein in GCB DLBCL is due to the present of t(14;18) [16]. There are ongoing clinical trials that test the effectiveness of BCL2 inhibitors (Venetoclax) in combination with chemo-immunotherapy (R-CHOP or Obinutuzumab-CHOP) [17]. The main signaling pathways are shown in Figure 2a.

In ABC DLBCL, it is considered that the cell of origin is post-germinal center B-lymphocyte in plasmablastic stage, thus expressing on the surface, specific mature plasma cell markers. Their immunohistochemical profile includes: CD20+, CD79α+, CD10−, BCL6+/−, CD5+/−, CD23+/−, BCL2+/−, MUM1+, cyclin D1−[18,19]. Proliferation, inhibition of apoptosis and ultimately cell survival are determined by activation of NF-xB signaling pathway [20]. This can be accomplished by involving the CBM complex formed by caspase recruitment domain family member 11 (CARD11), BCL10 and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1), activated but transient in normal lymphocytes after antigenic stimulation. The CBM complex may be activated either by CARD11 mutations found in 10% of cases, through continuous activation of the B-lymphocyte receptor by CD79A or CD79B mutations, or by the decrease of tyrosine kinase activity that involved spleen tyrosine kinase (SYK), PI3K, Bruton tyrosine kinase (BTK), and protein kinase Cb (PKCb) [21]. In ABC DLBCL, the myeloid differentiation primary response 88 (MYD88) mutation, which is positive in 30% of cases, also causes cellular activation both via the NF-xB mediated pathway and via the tyrosine kinases involved in transcription and translational mechanisms [22,23]. The main signaling pathways are shown in Figure 2b. Response to standard R-CHOP therapy in ABC DLBCL is inferior to GCB DLBCL with 40% vs. 75% progression-free survival (RFS) [24]. The involvement of BTK in ABC DLBCL cellular activation has led to the use of Ibrutinib (Bruton tyrosine kinase inhibitor) associated with chemotherapy [25]. Lenalidomide, an immunomodulator that acts by increasing harmful action of interferon-beta (IFN-β) overproduction, through the inhibition of IFN regulatory factor 4 (IRF4), known as MUM1, has shown superiority in recurrent/refractory ABC DLBCL as monotherapy by improving RFS [2,26].

PMLBCL – a subtype that originates from medullary thymic B-cells – is more common in young patients around the age of 30–40 years old, especially in the female population, representing about 10% of DLBCL. This subtype is characterized by large mediastinal tumor masses with intrathoracic extension, local compressive phenomena with superior vena cava syndrome or upper airway obstruction with respiratory failure. Immuno-histochemistry (IHC) – neoplastic cells are positive for B-line markers, including CD20 and CD79α. MUM1 is positive in 75% of cases, BCL2 in 78%, and BCL6 in 48% of cases. The positivity for CD10 is variable, while CD15 is negative [27]. CD30 is positive in most cases (80%), but with variable intensity [9].

Cellular activation pathway in PMLBCL involves the deregulation of Janus kinase/signal transducer and activator of transcription (JAK/STAT) protein pathways, determined by mutations of suppressor of cytokine signaling 1 (SOCS1) (a gene encoding cytokine receptor inhibitory proteins), activating negative feedback, protein tyrosine phosphatase non-receptor type 1 (PTPN1) and STAT6 or JAK2 expression amplification [28,29]. In PMLBCL, as in Epstein–Barr virus 1 (EBV1) large B-cell lymphomas and T-cell-rich large B-cell lymphoma, there is a programmed cell death-ligand 1 (PD-L1) increased expression. The interaction of PD-1 on T-cell surface with the PD-L1 leads to the evasion of these cancer cells from the immune system by impeding the activation of additional cytotoxic T-cells in the lymph nodes and consequent tumor recruitment. This mechanism for neoplastic cells survival could be targeted by the use of PD-1-blocking drugs, such as Nivolumab, a monoclonal antibody approved and already used in the treatment of lung cancer [30].

Since the gene expression analysis is an expensive and unavailable investigation in many laboratories, the medical practice has attempted to find correlations between gene expression and the immunophenotypic profile in order to categorize the cases in one of the two categories: germinal center DLBCL phenotype or activated DLBCL phenotype. Thus, several algorithms have been developed and used in the current practice, the most widely used being the Hans algorithm (Figure 3).
Figure 2 – The main signaling pathways in diffuse large B-cell lymphoma (DLBCL): (a) Germinal center B-cell like phenotype (GCB DLBCL) – deletions of phosphatase and tensin homolog (PTEN) induce activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway; B-cell lymphoma/leukemia 2 (BCL2) overexpression, c-rel amplification and histone methyltransferase (EZH2) point mutation induce proliferation, apoptosis and alteration of differentiation; (b) Activated B-cell type (ABC DLBCL) – activation of nuclear factor-kappa B (NF-κB) signaling pathway by the myeloid differentiation primary response 88 (MYD88) mutation, and also by the CBM complex, composed of caspase recruitment domain family member 11 (CARD11), BCL10 and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1). Also, involved interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene 1 (MUM1) overexpression. Their consequences being cell survival through proliferation, apoptosis and alteration of differentiation.

Figure 3 – Hans algorithm for the diagnosis of DLBCL [31]. DLBCL: Diffuse large B-cell lymphoma; CD10: Cluster of differentiation 10; GCB: Germinal center B-cell-like; Bcl-6: B-cell lymphoma/leukemia-6; MUM1: Multiple myeloma oncogene 1.

This algorithm correlates with an 80% accuracy to gene expression analysis [31], differentiating the GCB DLBCL from the activated phenotype using three immunohistochemical markers: CD10 (GCB marker), MUM1 and polyclonal BCL6. The cut-off for positivity is 30%. The germinal center types are CD10+ and MUM1+, and those with activated phenotype are MUM1+ and BCL6+ in more than 30% of malignant cells [13]. There are also exceptions, such as the cases of large B-cell lymphomas with no positive expression of any of the three markers [32]. By using germinal center B-cell-expressed transcript 1 (GCET1), CD10, BCL6, MUM1 and forkhead box protein P1 (FOXP1), a 90% match with the gene expression profile can be obtained [33, 34]. FOXP1 and MUM1 are post-germinal center markers, thus associated with the activated phenotype [35]. The use of the different IHC algorithms is not sufficient since it only differentiates the GCB DLBCL from ABC DLBCL, failing to clarify the non-classifiable DLBCL cases.

However, due to its widespread accessibility in most laboratories, it is an accepted and recognized method in the 2016 WHO Classification of lymphoid neoplasia, which introduced GCB DLBCL and ABC DLBCL as distinct entities.

IHC positivity for C-MYC protein is counting for approximately 25–30% of cases, which shows an increased expression compared to the C-MYC genetic rearrangement, accounting for 5–10% of cases. This suggests that there are other mechanisms involved in activating C-MYC expression, such as microRNA amplifications or mutations. Co-expression of C-MYC (more than 40% of positive tumor cells) and BCL2 (>50% of positive tumor cells) are negative prognostic markers in non-Hodgkin’s lymphoma (NHL) with double expression [36, 37]. C-MYC protein expression by IHC is considered positive if more than 40% of tumor cells are positive [38]. The association of IHC expression of MYC and BCL2 proteins defines double expressor lymphoma, which accounts for about 30% of DLBCL cases [38]. Double IHC expression is of prognostic importance but does not define a separate category of DLBCL. Most double expressor forms belong to ABC DLBCL, the ratio between ABC DLBCL and GCB DLBCL double expressor being 2/1. There is a poor prognosis in the double expressor lymphoma, with rates of up to 39% in three-year PFS and 43% of overall survival (OS). When it is compared to double-hit lymphoma, there is a better prognosis [39]. The C-MYC and BCL2 IHC positivity (double-expression lymphoma) does not correlate with molecular C-MYC and BCL2 presence, being more likely to have a prognostic significance rather than a diagnostic one for double-hit lymphoma [40]. Double-expression DLBCL should not be confused with double-hit NHL. The double-hit term refers to C-MYC and BCL2 and/or BCL6 rearrangement cases and this will be discussed in the molecular abnormalities section.
Cytogenetic and molecular abnormalities in DLBCL

Antigen-dependent B-lymphocyte maturation, as well as the somatic mutations of the hypervariable region of the antigen receptor, is carried out in the germinal center of the lymphatic follicle, in order to increase the antigen recognition specificity. In this process, several important factors with regulatory function are involved, such as BCL6 and IRF4/MUM1. BCL6 is expressed in B-lymphocytes of the germlinal center, having a role in its formation [41], while IRF4/MUM1 is involved in the switch phenomenon, favoring differentiation of B-lymphocytes that cross the germinai center into plasma cells [42]. BCL6 and IRF4/ MUM1 anomalies, which interfere with the two important reactions in the germinai center, somatic mutations and isotype switching, lead to the development of B-lymphoproliferative diseases, most of them having the germinal center or post-germinai center B-lymphocyte cell of origin [43].

Approximately 50% of DLBCL show aberrant mutations of the surface immunoglobulin hypervariable region. They interfere with many proto-oncogenes including proto-oncogene serine/threonine-protein kinase Pim-1 (PIM1), MYC, paired box gene 5 (PAX5). Genetic abnormalities such as point mutations, deletions, or gene amplifications have been highlighted in DLBCL, averaging between 30 and 100 anomalies for each case [44].

C-MYC oncogene is a critically important transcription factor, adjusting the proliferation, growth and cell apoptosis mechanisms. C-MYC abnormalities are involved in many lymphoproliferative disorders and may be structured as primary abnormalities, as in BL, or secondary as in DLBCL, mantle cell lymphoma or plasmablastic lymphoma. C-MYC rearrangement can be found in 10% of DLBCL cases, while in 5% of cases it is associated with BCL2 and/or BCL6 rearrangements with a poor prognosis and an eight-month median survival [45, 46]. The C-MYC rearrangement is associated with a lower rate of PFS and OS for patients receiving standard R-CHOP chemotherapy [47, 48]. Regarding DLBCL with C-MYC rearrangement, there is an increased risk of relapse to the central nervous system, independently of other risk factors [48].

NHLs with C-MYC, BCL2 or BCL6 rearrangement are called double-hit lymphomas, while the triple-hit term is used for cases with triple simultaneous gene translocations/disruptions. Typically, this type of lymphomas is displaying an aggressive behavior, with a high cell proliferation index. However, there are double-hit lymphomas with less aggressive evolution that could be explained by the impact of the partner gene of MYC [22]. The vast majority (93%) of the double-hit lymphoma originate in the germinal center. However, lymphomas with C-MYC and BCL6 are often CD10−, IRF4/MUM1+ and BCL2 rarely positive [49]. Because a very high expression of C-MYC to the IHC correlates with the presence of the C-MYC rearrangement, the GCB DLBCL with a high overexpression of C-MYC at IHC is very likely to be a double-hit type. Therefore, in these cases, molecular confirmation by fluorescence in situ hybridization (FISH) is required [50]. From a molecular perspective, double-hit lymphomas have features between DLBCL and BL and have been recognized as a distinct entity in the 2008 WHO Classification [B-cell lymphoma, unclassifiable with feature intermediate between DLBCL, not otherwise specified (NOS) and BL] [51, 52]. In the 2016 WHO Classification, this category was excluded, as it was recognized as a distinct entity called “high grade B-cell lymphoma with MYC and/or BCL2 and/or BCL6 translocation”. Therefore, all B-cells with MYC and BCL2 and/or BCL6, excluding lymphoblastic lymphoma and follicular lymphoma, are included in the new category of high-grade B-cell lymphoma (HBCL) with MYC and/or BCL2 and/or BCL6 translocation. Aggressive DLBCL cases which are histologically characterized by the proliferation of large CD10+ blastoid-like cells with high proliferation index but without C-MYC, BCL2 and/or BCL6 rearrangement are included in the HBCL NOS, which is also a new entity introduced in the WHO Classification updated in 2016 (Figure 4) [6].

T(14;18) that characterizes follicular lymphoma can also be found in about one third of DLBCL cases. The gene encoding the surface immunoglobulin heavy chain – the B-lymphocyte antigen receptor – is located on the chromosome 14, while the BCL2 gene with an anti-apoptotic role is located on the chromosome 18. The presence of T(14;18) indicates either that DLBCL originates from the transformation of a follicular lymphoma or that it occurs de novo and is reasonably suggestive of a DLBCL with germinai center phenotype, demonstrating that the cell of origin is in the germinal center. BCL2 overexpression associated with P53 mutations demonstrates that DLBCL originates from a transformed follicular lymphoma. Moreover, BCL2 gene is responsible for the development and differentiation of B-cells and it inhibits the apoptosis, thus giving the neoplastic cells with BCL2 overexpression a survival advantage and an increased resistance to the chemotherapy regimens [53]. BCL2 oncogene with an antiapoptotic effect may be overexpressed in both GCB DLBCL and ABC DLBCL by different mechanisms. In the former subgroup, BCL2 overexpression is primarily due to t(14;18), while in ABC DLBCL it is predominantly produced by transcriptional abnormalities or gene amplification [54]. The BCL2 rearrangement is present in 80–90% of double- or triple-hit DLBCL cases [55]. The BCL6 gene encodes a transcriptional repressor that is required during B-cell differentiation, controlling the germinal center formation and the antigen dependent T-cell response.

BCL6 rearrangement is found in 5% of double or triple-hit DLBCL cases [55]. This mutation is more common in DLBCL NHL associated with immunodeficiency (40%) and human immunodeficiency virus (HIV) infection (20%). BCL6 overexpression results from a juxtaposition process between the promoters and the coding domain of BCL6, which results from reciprocal translocation between 3q27 and the chromosomes that host the genes coding for the heavy and light chains of the surface immunoglobulin – chromosomes 14, 2, and 22, respectively. BCL6 is expressed in B-cells of the germinal center, but not in plasma cells, which is the final stage of lymphoid B-cell differentiation. A disbalance in the BCL6 expression may lead to a failure in the differentiation of B-cells into plasmocytes and memory B-lymphocytes that are responsible for the secondary immune response.

New deoxyribonucleic (DNA) sequencing techniques have identified recurrent single nucleotide variants (SNV)
in some DLBCL subtypes [56]. The analysis of the profile of these mutations identified the occurrence of cytidine deaminase-induced abnormalities of the activation process (AID), which are usually involved in the germinal center somatic and switching mutations, as a possible triggering mechanism of SNV [57].

Despite several cytogenetic and molecular anomalies as well as different cellular activation in GCB and ABC DLBCL, some oncogene anomalies or tumor suppressor genes provide prognostic information that are independent of the tumoral subtype. Two typical examples of such anomalies are the overexpression of MYC and cyclin-dependent kinase inhibitor (CDKN) 1B, that encode p27 protein, which in turn is involved in cell growth and differentiation, and the loss of tumor protein P53 and CDKN2A expression, that encodes two proteins with tumor suppressor action [58]. Next-generation sequencing studies also revealed other common somatic mutations for all DLBCL subgroups, such as the inactivation of genes involved in immune surveillance (the CD58 gene encoding a CD2 activation ligand expressed on T-lymphocytes) or the activation of BCL6 oncogene.

Conclusions

The advances in genetic, molecular and DNA sequencing techniques during the last 20 years have succeeded in a better understanding of the origin of proliferating cells and cell activation pathways, managing to explain, even if only partially, the differences in evolution and response to standard R-CHOP therapy, within the same condition: DLBCL. Although the gold standard in establishing the DLBCL subtype is represented by gene expression study, due to its high costs and low accessibility, the Hans algorithm with an 80% concordance with gene expression profile is still recommended for separating the GCB DLBCL from ABC DLBCL. The DLBCL heterogeneity is recognized in the latest 2016 WHO Classification of lymphoproliferative malignancies, which introduced several new and interim entities, as the first step in the selection of a personalized therapy – a fundamental desideratum for the 21st century medicine. There are several ongoing trials evaluating new, targeted therapies, adapted to molecular profile whose results are to be validated and included in the therapeutic guidelines.

Conflict of interests

The authors declare that they have no conflict of interests.

References

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