The Spectrum of Double Hit Lymphomas

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KEYWORDS

• Double-hit lymphomas • Double-expressing lymphomas
• High grade B-cell lymphoma • MYC • BCL2

KEY POINTS

- Double-hit lymphomas (DHLs) constitute a unique high-risk biologic and clinical subset of aggressive B-cell non-Hodgkin lymphomas characterized by translocations of MYC in addition to BCL2, BCL6, or both.
- DHLs typically present in older adults with high-risk clinical features including advanced stage, extranodal involvement, elevated lactate dehydrogenase (LDH), and often with involvement of bone marrow, peripheral blood, and the central nervous system.
- Prognosis of DHL is overall far inferior to typical diffuse large B-cell lymphoma (DLBCL), but selected low-risk patients can be identified with a favorable prognosis including limited stage, LDH less than 3 times upper limit of normal, and absence of central nervous system (CNS), bone marrow, and leukemic disease.
- Intensive treatment strategies such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) appear associated with an improved outcome compared with R-CHOP (rituximab, cyclophophamide, doxorubicin, vincristine, prednisone).
- Double-expressing lymphomas are a subset of DLBCL with dual immunohistochemical expression of BCL-2 and MYC, but without chromosomal translocations, and also constitute a high-risk subset of DLBCL, though more favorable than DHL.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) in United States and worldwide, and approximately two-thirds of newly diagnosed patients can be expected to be cured using modern therapies. Over the last decade, a particularly high-risk entity within DLBCL has been identified, characterized molecularly by carrying translocations of the MYC proto-oncogene along with BCL2, or less commonly BCL6, or both. Presence of a MYC translocation in concert with either BCL2 or BCL6 is now known as a double-hit lymphoma (DHL), or as a triple-hit lymphoma (THL) if all 3 rearrangements are present. More recently, an

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adverse prognosis in DLBCL has also been attributed to dual immunohistochemical expression of both MYC and BCL2. Such cases of dual expression of MYC/BCL2 in the absence of dual genomic translocations should not be considered cases of DHL, but rather double-expressing lymphomas (DELs), which constitute a distinct phenotypic entity and have unique considerations in terms of prognosis and therapy. DHL and THL follow a highly aggressive natural history with disappointing responses to standard chemoimmunotherapy platforms, and a poor overall prognosis. The literature guiding understanding of these high-grade lymphomas is almost entirely retrospective in nature, and therefore limited by the biases inherent in such analyses. That said, recent large retrospective series have contributed to the current prognostication and therapeutic selection.

DIAGNOSIS OF DOUBLE-HIT LYMPHOMA

DHLs constitute an uncommon but high-risk subset within DLBCL. It is estimated that approximately 5% to 10% of DLBCLs will be characterized by double-hit cytogenetics.[1,2] In addition to MYC, the most common additional translocation is BCL2 in approximately 85% of DHL cases, with a minority having a BCL6 translocation, or both (THL). It is important to recognize that karyotyping shows that these discrete chromosomal rearrangements occur in the broader context of a complex karyotype in virtually all cases, speaking to overall genomic instability.[1,3,4] The majority of DHLs presents as a de novo DLBCL, while others will have their disease transform out of a low-grade follicular lymphoma.[5–9] In 2008, the World Health Organization (WHO) created a provisional diagnostic category known as B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BCLu).[10] Cases in this category may have more aggressive morphologic features than a typical case of DLBCL, such as a high proliferation index and starry sky appearance, but are lacking in strict features diagnostic of Burkitt lymphoma such as having more pleomorphic morphology, immunohistochemical expression of BCL2, or presence of a complex karyotype. Though DHLs represent a distinct minority of DLBCLs as a whole, both retrospective and prospective cohorts suggest that DHL constitutes 50% to 75% of cases classified within the BCLu category.[6,11,12] Increasingly, the identification of double-hit cytogenetics within a case of DLBCL has prompted hematopathologists to sign out these cases as BCLu rather than grouping them in with traditional DLBCLs, leading to a migration of DHLs out of the traditional DLBCL diagnostic category and into the provisional diagnosis of BCLu. Most recently, however, the WHO has issued a revision of the classification of lymphoid tumors and has eliminated the BCLu category.[13] In recognition of the unique characteristics of DHL, these cases now have a distinct classification known as high-grade B-cell lymphoma (HGBCL), with MYC and BCL2 and/or BCL6 translocations. DEL will still largely be included in the traditional DLBCL, not otherwise specified (NOS) category, although cases with blastoid morphology or other highly aggressive histologic features will be included in a new category of HGBCL, NOS.

DLBCL is commonly subclassified based on cell of origin (COO) as either germinal center B-cell like (GCB) or activated B-cell like (ABC). Though this classification is defined by gene expression profiling (GEP), immunohistochemical correlates are commonly employed as imperfect surrogates for GEP, which can classify cases as either GCB or non-GCB.[14] Nearly all true DHLs will be classified as GCB DLBCL,[3,7,9,15–18] making them a particularly high-risk subset within the DLBCL COO category typically associated with the more favorable prognosis. Similarly, nearly all cases of DHL will also have immunohistochemical expression of MYC and BCL-2 at the protein level, most commonly defined as MYC expression of at least 40% of cells,