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Double Hit Lymphoma: a New Category of Lymphoma without a Standard of Care Treatment

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Abstract

The 2016 revision of the WHO classification for lymphoma has included a new category of lymphoma, termed high-grade B-cell lymphoma with translocations involving MYC and BCL-2 or BCL-6. These lymphomas have been referred to as DHL when MYC translocation is present with either the BCL-2 or BCL-6 translocation or THL if all 3 rearrangements are present.

Abbreviations: WHO: World Health Organization; MYC: Myelocytomatosis Oncogene; BCL-2: B-Cell Lymphoma-2; LDH: Lactate Dehydrogenase; IPI: International Prognostic Index; DHL: Double Hit lymphoma; THL: Triple Hit Lymphoma; DLBCL: Diffuse Large B-cell Lymphoma

Introduction

The majority of DHLs originate from germinal centre cells [1]. DHL occurs de novo and in <10% of cases of DLBCL [2]. DHL occurs also in the setting of transformation of underlying indolent lymphoma, particularly follicular lymphoma, when this t(14;18) lymphoma acquires a MYC translocation [2]. Double-hit follicular lymphomas tended to be high-grade histology, high MYC protein expression, high MYC /IGH fusion, and minimal common region of gain at 2p16.1 [3]. A rare case of Waldenstrom macroglobulinemia presents with MYC and BCL-2 positive mutations making it a case of double hit B cell lymphoplasmacytic lymphoma with plasmacytic differentiation without morphological transformation to aggressive histology like DLBCL [4].

It is important to differentiate DHL from the larger group of double-expresser lymphomas, which have increased expression of MYC and BCL-2 and/or BCL-6 by immunohistochemistry, using variable cutoff percentages to define positivity [2]. Deregulation of MYC is an important driver of oncogenic transformation [1]. MYC rearrangement alone is usually associated with a poor outcome for DLBCL patients with some exceptions [1]. MYC is up regulated by translocation or other mechanisms, such as gene gain or amplification, mRNA over expression, aberrant somatic mutation, or microRNA deregulation. MYC enhances cell proliferation, growth, angiogenesis, genomic instability, cellular metabolism, and inhibits cell differentiation [1]. Single-hit lymphomas (which contain MYC rearrangements only) and DHLs are not different in MYC translocation partner, genomic complexity and MYC expression [1]. All MYC-translocated lymphomas have similar gene expression profiles to single hit lymphomas and DHLs, and share several gene expression patterns with lymphomas with immunoglobulin–MYC translocations [1].

Clinically

Most high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements are aggressive B-cell lymphomas [3]. DHL patients do not have a specific clinical presentation that is distinct from other DLBCLs or aggressive non-Hodgkin lymphoma. However, higher frequency of bone marrow involvement, extra nodal disease including CNS involvement, stage III/IV disease, higher IPI score and abnormal serum LDH elevation have been reported in DHL than in other lymphoma types [1]. Patients with MYC-rearranged lymphoma have a statistically significant increased risk of CNS involvement or CNS relapse compared with other DLBCL patients, even when adjusted for other clinical risk factors of CNS involvement. Ten percent of patients with double-expresser lymphoma (including a subset with DHL) subsequently relapsed in the CNS [2].

Double-hit follicular lymphomas seemed to be a different disease from high-grade B-cell lymphomas with MYC and

BCL-2 and/or BCL-6 rearrangements as they have an indolent clinical behavior similar to follicular lymphomas without MYC rearrangement [3]. A novel prognostic index specifically for DHL has been created. It classified patients as either low-, intermediate- and high-risk, depending on number of common factors known to cause poorer survival outcomes for DHL [5].

How to evaluate double-hit lymphoma patients?

DHL patients typically have the histological feature of DLBCL, Burkitt Lymphoma or high grade B cell lymphoma [6]. Pathologically, most cases of BCL2–MYC DHL are of germinal centre origin (CD10+, BCL6+, MUM1–) and are highly proliferative. By contrast, BCL6–MYC DHL is more frequently of activated B-cell origin, more likely to be immunoblastic, infrequently expresses BCL2, and is cytogenetically less complex than BCL2–MYC DHL [1]. DHL patients should undergo routine staging procedures, including baseline PET/CT scans, bone marrow aspirate and biopsy, as well as testing for serum LDH, liver and kidney function, HIV and hepatitis B, and cardiac function evaluation [2].

Baseline lumbar puncture and CSF sampling is recommended in most DHL [2]. Exceptions include early-stage disease, where CSF involvement is much less common and frail elderly patients, where treatment with curative intent is contraindicated. CSF should always be analyzed with flow cytometry. Brain imaging is performed in DHL patients if neurological symptoms are present or CSF is positive for malignant cells [2].

N.B.

i. The expression of TdT in B cell lymphoma with mature features or the expression of surface light chain in a case otherwise suggestive of B lymphoblastic leukemia/lymphoma should prompt the expedited evaluation for DHL/THL [7].

ii. It is important to incorporate FISH testing for MYC rearrangement into the diagnostic algorithm for transformed follicular lymphomas since 21% of transformed follicular lymphomas were reported to be DHL [2].

Prognosis

The MYC translocation partner is an important prognostic factor in MYC translocation lymphoma. When immunoglobulin was the MYC partner, the patient demonstrated a poorer prognosis than in the MYC/non-immunoglobulin situation [3]. BCL-2 or BCL-6 rearrangements did not affect progression-free survival or overall survival [1]. The overall survival was significantly better for double expresser lymphoma than for DHL and both groups had worse outcomes than patients lacking these alterations [8]. High-grade B-cell lymphomas with MYC and BCL-2 and/or BCL-6 rearrangements show poorer prognosis than standard DLBCL. They frequently exhibit median survival duration of less than 1 year [3].

Clinical factor variables of THL were similar with high-grade B-cell lymphomas with MYC and BCL-2 and/or BCL-6 rearrangements without BCL-6 translocation, but the median survival duration of THL patients was shorter [3]. Patients with DHL treated with standard chemo immunotherapy have a poor prognosis and have increased risk of central nervous system involvement and progression [2]. Preventing relapse is very critical since patients relapse after initial therapy is associated with very poor outcome [8].

What is the Best Induction Regimen?

High-grade B-cell lymphomas with MYC and BCL-2 and/or BCL-6 rearrangements are resistant to conventional chemotherapy [3]. R-CHOP alone is not adequate treatment, as it is unlikely to achieve long term remission [8].

Intensive Treatment Strategies

Intensive treatment strategies such as DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone) demonstrated an improved likelihood of achieving a complete remission, and longer progression-free survival [5]. Compared with DA-EPOCH-R, the R-hyper CVAD regimen resulted in higher complete response rates (68%) but shorter progression-free survival (32% at 2 and 3 years) and overall survival (44% at 2 years and 40% at 3 years) [1].

Does Patients still need Transplant after Intensive Chemotherapy?

There was no difference in survival rate between patients who underwent a stem cell transplant during their first remission and those who did not undergo any treatment during this period [5]. However, in a study of 16 patients given CODOX-M/IVAC-R followed by autologous transplant, 13 (82%) achieved 2-year overall survival [1]. This data suggests that the key predictive factor of a positive outcome in DHL is whether a patient is able to achieve a complete remission with induction therapy of any type [5]. Transplant may be considered in patients with DHL who had several IPI risk factors [8].

Novel agents with particular promise in double-hit DLBCL patients may include small molecule inhibitors of BCL-2, such as venetoclax, which has demonstrated in vivo efficacy against aggressive MYC-driven mouse lymphomas. The small molecule JQ1 suppresses c-MYC expression through inhibition of the bromodomain and extra terminal family of bromodomain proteins. Bromodomains are conserved protein regions that recognize specific histone modifications. JQ1 treatment significantly suppressed growth of MYC-rearranged DLBCL cells engrafted in mice. Synergy has been demonstrated when venetoclax is combined with JQ1 in vitro [2]. Anti–CD19 chimeric antigen receptor T cells have shown promise in refractory DHL patients. A trial of chimeric antigen receptor T cells is a preferred option for fit patients with refractory DHL [9].

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Conclusion

Further study of DA-EPOCH-R and other intensive therapies versus R-CHOP in DHL patients is needed.

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