Current Concepts in Double-Hit Lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL) in North America, with an estimated annual incidence of 25,000.[1] While most patients achieve durable remissions, a substantial minority experience primary refractory or relapsed disease. Improved understanding of the genetic and proteomic basis of large-cell lymphoma has led to the recognition of its heterogeneity and to efforts to refine classification and more accurately identify aggressive variants based on molecular features

In recent years, several retrospective studies have observed that rearrangement (RA) of the *c-Myc* oncogene, classically found in Burkitt lymphoma,[2] occurs in 7% to 15% of cases of DLBCL and may confer an inferior prognosis in these cases.[3-6] Gene expression suggests distinct pathobiology of cases of DLBCL with *c-Myc* RA compared with those lacking *c-Myc* RA.[7] It is now recognized that among cases of DLBCL with *c-Myc* RA, patterns of particularly aggressive disease, with high rates of resistance to chemotherapy, are driven primarily by the coexistence of a partner RA in either B-cell lymphoma 2 (*BCL2*) or *BCL6* (or sometimes both).[8-10] B-cell lymphoma with *c-Myc* has provisionally been termed double-hit lymphoma or triple-hit lymphoma (THL) in cases harboring all three mutations (*c-Myc*, *BCL2*, and *BCL6*).

Double-hit lymphoma makes up approximately 12% of cases of DLBCL4; however, there is limited retrospective data and no prospective data to inform choices of treatment for these patients. After the publication of smaller studies, larger multi-institutional retrospective analyses have corroborated the poor prognosis and attenuated rates of response to rituximab-based chemoimmunotherapy.[11] Currently, there are no consensus guidelines for treatment, and this disease remains challenging to treat.

This review summarizes the available literature on DHL, including an overview of biology and pathogenesis, induction therapy regimens, role of consolidative stem cell transplantation, treatment of relapsed/refractory disease, and, finally, ongoing clinical trials and the prospects of novel therapy.

Key words: diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, heterogeneity, pathogenesis, stem cell transplantation, relapsed/refractory disease, novel therapy, rituximab, chemoimmunotherapy

Histology and Molecular Pathogenesis

Recognizing the need for distinct histologic definitions for the variations of aggressive B-cell lymphomas, the World Health Organization modified the 2008 categories to include B-cell lymphoma unclassifiable (BCLU) with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL).[12] Because double-hit lymphoma (DHL) is genotypically defined, it is not bound to any specific histology. Most DHL tumors are medium to large in size, with aggressive-appearing cells, with a high proliferative index (as measured by Ki67), and a mature B-cell immunophenotype.[13] In the largest multi-institutional analysis to date, cases of DHL were distributed evenly among DLBCL and BCLU (with a very small minority of follicular lymphoma [FL]), and neither histology nor the partner rearrangement (RA) (B-cell lymphoma 2 [*BCL2*] vs *BCL6* vs both) significantly affected either progression-free survival (PFS) or overall survival (OS).[11,14]

Approximately 84% to 87% of cases of DHL have *BCL2* as the partner RA, and 93% are of germinal center origin.[11,14,15] Because B cells harboring a *BCL2* RA with t(14;18) are found circulating in healthy individuals[16] and this RA alone is insufficient for lymphogenesis even in FL,[17] it is speculated that this precedes *c-Myc* RA. Furthermore, because the RA of *c-Myc* is thought to be mediated by activation-induced cytosine deaminase in the germinal center,[18] it is suspected that cells harboring a *BCL2* RA acquire a secondary *c-Myc* RA in the permissive environment of the germinal center during somatic hypermutation. As evidence, analysis of FL in transformation demonstrates 2 clones, one harboring a *BCL2* RA and one harboring a *BCL2* and *c-Myc* RA, suggesting that BCL2 RA preceded the acquisition of the *c-Myc* RA.[19] Less is understood about the timing of RA in DHL with a *BCL6* RA or THL.

At the proteomic level, the dual RA of *c-Myc* and *BCL2* results in overexpression of the respective proteins. However, non-RA aberrations can result in overexpression of both proteins and impart a similarly aggressive phenotype. These 'double express-

er' (DRL) lymphomas have been increasingly recognized, and several studies suggest a similar clinical course.[20] There do not appear to be any morphologic or histologic differences with the dual RA genotype, and although experience is limited, they are approached similarly to those cases with dual RA.

Induction Therapy, Consolidation Stem Cell Transplantation, and Central Nervous System Prophylaxis

A phase III intergroup study established CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) as standard induction therapy for aggressive non-Hodgkin's lymphoma (NHL) given its comparable efficacy and favorable toxicity compared with more intensive regimens.[21] Addition of the anti-CD20 antibody rituximab to CHOP (R-CHOP) led to clear improvement in response rates, PFS, and OS.[22,23] Subsequently, R-CHOP has remained the standard treatment option for most cases of large cell lymphoma for the last 15 years. However, retrospective series have suggested significantly inferior outcomes for patients with DHL compared with those with DLBCL lacking the DHL phenotype when treated with R-CHOP.[4,8] For example, in an analysis by the British Columbia Cancer Agency of 54 patients with DHL, those treated with CHOP or R-CHOP had a PFS of 11% at a median follow-up of 5.6 years.

In an effort to improve these poor outcomes, escalated induction (EI) has been employed, mostly reported at small, single-center clinics. These regimens include R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, and methotrexate alternating with ifosfamide, etoposide, and cytarabine),[24] R-Hyper-CVAD (rituximab, doxorubicin, vincristine, and hyperfractionated cyclophosphamide alternating with high-dose methotrexate and cytarabine),[25] and dose-adjusted (DA) EPOCH-R (etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide, rituximab). Likewise, intensification of treatment by way of consolidative high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) has been shown prospectively to improve outcomes for those with high-risk, aggressive NHL,[26] suggesting that there may be a role for HDT-ASCT in those with DHL who achieve first remission.

To more effectively compare various induction regimens for DHL, and to help define the role of HDT-ASCT, we conducted a multi-institutional, retrospective analysis of 311 patients.[11] In this cohort, 32% were treated with R-CHOP compared with 56% treated with EI (21% with R-Hyper-CVAD, 21% with DA-EPOCH-R, and 14% with R-CODOX-M/IVAC). At a median follow-up of 23 months, the use of EIs was associated with improved PFS ($P = .0016$) compared with R-CHOP, but not with improved OS ($P = .119$). Additionally, there was no significant difference in PFS or OS associated with any of the 3 EI when compared with one other. However, DA-EPOCH-R did achieve a higher rate of complete response compared to other regimens. Use of HDT-ASCT or allogeneic SCT in first remission was associated with a nonsignificant trend toward improved OS.

Oki and colleagues evaluated similar questions in their large single-center report on patients with DHL.[14] Allowing for surrogate similarity between PFS and event-free survival (EFS), there was a striking similarity in the Kaplan-Meier survival curves between this study and ours, with respect to OS and EFS/PFS. Also similar to our analysis, Oki et al observed a nonsignificant association between SCT in first remission and improved OS. However, the most notable difference between the two studies was that Oki and colleagues observed that DA-EPOCH-R was associated with significantly improved EFS and OS, both compared with other EIs as used in their experience and compared with that reported by our group (eg, 60% vs 42%, respectively and EFS at 24 months). Also potentially bolstering a role for EPOCH, Dunleavy and colleagues recently presented outcomes for a subset of 14 patients with DHL treated with DA-EPOCH-R as part of a large prospective study of patients with *c-Myc* RA aggressive NHL.[27] They reported a PFS of 87%, but at a median follow-up of only 14 months.

The potential importance of central nervous system (CNS) prophylaxis was highlighted by our observation that the use of either intrathecal or high-dose CNS-directed therapy—when incorporated into frontline induction therapy—was associated with improved OS, and the observation by Oki and colleagues that CNS prophylaxis was associated with decreased rates of secondary CNS relapse/progression.[11,14] By comparison, rates of CNS relapse in DLBCL appear to be 3% to 9%, with poor PFS and presence of extranodal disease as the possible risk factors.[28,29] The optimal strategy and regimen for CNS prophylaxis remain undefined and can include incorporation of high-dose cytarabine, high-dose methotrexate, or either agent administered intrathecally.

Relapsed/Refractory Disease

Our experience suggests that patients with relapsed or refractory DHL face a dismal prognosis, such that salvage chemotherapy was not associated with improved OS compared with palliation alone, with median survivals of 6 months or less from time of relapse.[11] Although the role of HDT-ASCT for relapsed/refractory aggressive NHL may be fairly well established,[30] our estimation is that very few patients with relapsed/refractory DHL experience adequate disease control for salvage HDT-ASCT to even be an option.

An ad hoc analysis of patients enrolled in the CORAL trial[31] suggests that patients harboring a *c-Myc* RA face significantly inferior outcomes compared with those patients without a *c-Myc* RA.[32] However, it is unclear how many of those patients harbored *c-Myc* RA at time of original NHL diagnosis, and unclear how many had DHL.

Future Directions

The last several years have witnessed important advancements in the understanding of the molecular pathogenesis of B-cell lymphoid malignancies, leading to mounting clinical data supporting the use of novel agents targeting critical, aberrantly activated pathways. These include inhibitors of the B-cell receptor signaling complex,[33] the phosphoinositide 3-kinase pathway,[34] BCL2 antiapoptotic proteins,[35] NF-κB complex,[36] and nuclear export pathways,[37] among others. There are several FDA-approved agents (eg, ibrutinib, idelalisib) along with many others that are being investigated as part of induction therapy for DLBCL, potentially increasing the available agents for DHL as well.

Conclusions

Although collective data suggest that about 40% of patients with DHL may be cured,[11,14] our opinion is that those with relapsed/refractory DHL are essentially incurable with current therapies, including those offered as part of clinical trials. For this reason, the most meaningful strategies for improving outcomes are likely to be the addition of novel drugs to aggressive chemoimmunotherapy backbones and/or the addition of maintenance therapy after achievement of remission, with or without HDT-ASCT.[38] That said, there are multiple trials under way that specifically include patients with relapsed/refractory DHL,[39,40] and the sponsors and clinicians conducting such studies should be applauded for their willingness to address this unmet need in a patient population with an extremely aggressive course and poor overall prognosis.

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