ABC, GCB, and Double-Hit Diffuse Large B-Cell Lymphoma: Does Subtype Make a Difference in Therapy Selection?

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OVERVIEW

Personalized therapy for the treatment of patients with cancer is rapidly approaching and is an achievable goal in the near future. A substantial number of novel targets have been developed into therapeutic agents. There is a substantial variability to antitumor activity by novel therapeutics because of the unique heterogeneity and biology that exists both between and within lymphoma subtypes. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). Approximately 40% of patients have refractory disease or disease that will relapse after an initial response, and the majority of patients with relapsed DLBCL will succumb to the disease. There are two major biologically distinct molecular subtypes of DLBCL: germinal center B-cell (GCB) and activated B-cell (ABC). ABC DLBCL is associated with substantially worse outcomes when treated with standard chemoimmunotherapy. In addition to GCB and ABC subtypes, double-hit lymphomas (approximately 5% to 10% of patients) and double-expressor lymphomas, which overexpress MYC and BCL2 protein, are aggressive DLBCLs and are also associated with a poor prognosis. Double-hit lymphomas have concurrent chromosomal rearrangements of MYC plus BCL2 (or less likely, BCL6). Advances in molecular characterization techniques and the development of novel agents targeting specific subtypes of DLBCL have provided a foundation for personalized therapy of DLBCL based on molecular subtype. A number of early clinical trials evaluating combinations of novel targeted agents with standard chemotherapy (R-CHOP) have been completed and have demonstrated the feasibility of this approach with encouraging efficacy. As such, molecular classification of DLBCL is not only important for prognostication, but moves to center stage for personalization of therapy for DLBCL.

The addition of the anti-CD20 monoclonal antibody rituximab (R) to the standard CHOP regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was a major breakthrough in the front-line treatment for patients with DLBCL, resulting in dramatic improvements in progression-free survival (PFS) and overall survival (OS). However, despite these improvements approximately 40% of patients with DLBCL who are treated with R-CHOP or R-CHOP-like chemotherapy will relapse or develop refractory disease, and the majority of patients with relapsed or refractory DLBCL will succumb to the disease. Various strategies have been implemented to improve the outcome of DLBCL, including intensification of chemotherapy and use of maintenance therapy. Regardless of molecular subtype, standard front-line treatment for DLBCL is a combination of R-CHOP or CHOEP-like chemotherapy. Additional regimens and immunochemotherapy combinations are under investigation as alternatives to front-line R-CHOP, including dose-dense R-CHOP14, dose-adjusted R-EPOCH (rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), and R-CEOP90 (rituximab, cyclophosphamide, etoposide, vincristine, prednisone). In a phase III trial including 1,080 patients with previously untreated DLBCL, no additional clinical benefit was observed in patients treated with R-CHOP every 14 days (R-CHOP14) versus every 21 days (R-CHOP21). Although evaluation of some of these intensification strategies is still ongoing, recent insight into the biology of DLBCL allowed the development of strategies based on the addition of novel agents (X) to R-CHOP in so-called XR-CHOP combinations that target specific oncogenic pathways (Fig. 1). In the development of these strategies, molecular characterization of DLBCL and the development of biomarkers is a critical step to identify patients who might benefit from the addition of novel agent(s). Indeed, because of the molecular heterogeneity of DLBCL, addition of a novel agent may benefit only a subgroup of patients with DLBCL. In this regard, preclinical and clinical studies of novel agents as monotherapies in relapsed and refractory DLBCL often provide important initial indications regarding the subtype of DLBCL that might benefit from specific targeted therapy.

Gene expression profiling (GEP) of DLBCL resulted in the identification of two major and clinically distinct subtypes that are classified based on cell of origin (COO) and are as-
associated with differences in clinical outcome: GCB and non-GCB, which is further comprised of ABC and primary mediastinal B-cell types.\textsuperscript{10,11} DLBCL subtypes have striking differences in clinical outcome, with the ABC DLBCL subtype being associated with poor outcome. Until recently, COO classification of DLBCL had little influence on clinical practice. However, COO classifications have become more clinically relevant as a result of two major factors: (1) the development of new real-time COO assessment methods, including immunohistochemistry (IHC) and Nanostrings technology and (2) the identification of novel agents with activity in a specific DLBCL subtype (particularly ABC DLBCL).

**CLASSES OF AGENTS WITH MOLECULAR SUBTYPE-SPECIFIC ACTIVITY CURRENTLY IN DEVELOPMENT FOR THE TREATMENT OF DLBCL**

**Agents Predominantly Active in Non-GCB (ABC) DLBCL**

The majority of novel agents in development as front-line treatment for DLBCL appear to specifically target the ABC subtype of DLBCL, through either the B-cell receptor (BCR) pathway or pathway(s) downstream of the BCR pathway. This review will include only agents that are already in advanced clinical trials.

**Proteasome inhibitors.** Proteasome inhibitors play a key role in suppression of the transcription factor nuclear factor kappa B (NFkB), a critical pathway downstream of the BCR pathway that is constitutively activated in ABC DLBCL.\textsuperscript{12} Use of the first-generation proteasome inhibitor bortezomib as monotherapy generated no responses in patients with relapsed/refractory DLBCL despite good preclinical evidence of possible activity. Bortezomib combined with DA-EPOCH (dose-adjusted etoposide, vincristine, doxorubicin, with cyclophosphamide and prednisone) chemotherapy yielded a complete response (CR) of 18% and a partial response (PR) of 16%,\textsuperscript{13} and demonstrated a significantly higher response (83% vs. 13%; \( p < 0.001 \)) and median OS (10.8 vs. 3.4 months; \( p = 0.003 \)) in ABC DLBCL compared to GCB DLBCL, respectively.

**Immunomodulatory agents.** Immunomodulatory drugs (IMiDs) are structural and functional analogs of thalidomide that have immunomodulatory, antiangiogenic, and antitumor functions.\textsuperscript{14} Preclinical studies show that IMiDs modulate antibody synthesis; regulate the production of certain subsets of T cells (T-helper cells); inhibit the production of cytokines, including tumor necrosis factor alpha (TNF\( \alpha \)); induce G\( \text{G}_0/G_1 \) cell cycle arrest; and decrease angiogenesis through the suppression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).\textsuperscript{15} In vivo and in vitro experiments have shown that the IMiD lenalidomide functions in DLBCL through multiple mechanisms, for example by enhancing antibody-dependent cell-mediated cytotoxicity (ADCC), inhibiting the production of proinflammatory cytokines such as TNF\( \alpha \), decreasing NFkB activity, and arresting DNA synthesis.\textsuperscript{16,17} The effect of single-agent lenalidomide was investigated in 217 patients with aggressive relapsed/refractory NHL as part of an international phase II study. Median PFS and response duration in the DLBCL subpopulation were 2.7 months and 4.6 months, respectively.\textsuperscript{18} In a retrospective analysis of two phase II trials (NHL-002 and NHL-003), patients with aggressive relapsed/refractory NHL who received single-agent lenalidomide and prior autologous stem cell transplantation (ASCT) were compared with those who did not receive ASCT. Thirty-four patients (39%) with relapsed or refractory NHL and prior ASCT therapy responded to lenalidomide (objective response rate [ORR] 39%), including patients with DLBCL (ORR 29%).\textsuperscript{20} In an ongoing, randomized, phase II/III clinical trial, the safety and efficacy of lenalidomide in relapsed/refractory DLBCL is being compared to the Investigator’s choice (gemcitabine, oxaliplatin, rituximab, or etoposide) (NCT01197560).\textsuperscript{21}

**B-cell receptor signaling pathway inhibitors.** The BCR complex and associated protein tyrosine kinases are important for normal B-cell function and antibody production. Constitutively activated BCR signaling is linked to the initiation and maintenance of B-cell malignancies, including involvement in the pathogenesis of the ABC subtype of DLBCL.\textsuperscript{22} The BTK inhibitor ibrutinib was investigated in 70 patients with relapsed/refractory DLBCL as part of a multicenter, open-label, phase II trial. Among 60 patients who were evaluable for response, the ORR was 22% (5% CR) and PFS was 1.6 months.\textsuperscript{23} In a phase II study, 23 patients treated with the
spleen tyrosine kinase (SYK) inhibitor fostamatinib demonstrated a median PFS of 2.7 months and achieved an ORR of 22%.24

AGENTS WITH POTENTIAL ACTIVITY IN GCB DLBCL

Although patients with GCB DLBCL have better outcomes than patients with the ABC subtype, approximately 20% of patients with the GCB subtype of DLBCL relapse following R-CHOP or R-CHOP–like chemotherapy and DLBCL relapse is associated with poor outcomes regardless of molecular subtype. Several agents show potential activity in the GCB subtype of DLBCL, among which BCL2 inhibitors are the best studied to date. Importantly, DLBCL with concurrent MYC and BCL2 or BCL6 translocation, known as double-hit DLBCL,25 is associated with very poor outcomes and is usually the GCB subtype by molecular profiling. Double-hit DLBCL represents approximately 5% of de novo cases of DLBCL, and is responsible for approximately a quarter of all relapses in GCB DLBCL. Treatment of this particularly high-risk lymphoma is discussed later.

BCL2 inhibitors. Prevention of apoptosis is one mechanism through which cancer cells continue to survive. Unlike most oncogenes that promote proliferation, members of the anti-apoptotic B-cell lymphoma-2 (BCL-2) family of proteins (BCL-2, BCL-XL, BCL-w, MCL-1, BFL1/A-1, and BCL-B) suppress apoptosis through interaction with, and inactivation of, proapoptotic proteins such as BH3.26 In contrast to most agents active in ABC DLBCL, which appear to have low activity in the GCB subtype, BCL2 inhibitors might be active in both ABC and GCB DLBCL. Whereas in the GCB subtype BCL2 is often overexpressed as a result of translocation, some patients with the ABC subtype appear to overexpress BCL2 at the protein level.27 ABT-737 and its oral equivalent ABT-263 target multiple antiapoptotic members of the BCL-2 family, including BCL-2, BCL-XL, and BCL-w, whereas ABT-199 potently and selectively inhibits BCL-2, thereby sequestering the proapoptotic proteins and facilitating death of malignant cells.26,28,29

FRONT-LINE TREATMENT: XR-CHOP

A combination of the proteasome inhibitor bortezomib and R-CHOP (VR-CHOP or Bor-RCHOP) was evaluated in patients with previously untreated DLBCL or mantle cell lymphoma. The evaluable ORR was 100%; 86% of patients exhibited CR or CR unconfirmed (CRu). In the intent-to-treat (ITT) population of 40 patients, ORR was 88%, and 75% had CR/CRu. The 2-year PFS was 64% and 2-year OS was 70%.30 A current randomized phase II trial is designed to compare the effect of VR-CHOP versus R-CHOP on PFS (NCT00931918),31 and an ongoing randomized phase III
trial is investigating the efficacy of CHOP versus RV-CHOP in patients with DLBCL (REMoDL-B; NCT01324596).  

**R2-CHOP**

Patients treated with the immunomodulatory agent lenalidomide (R) in combination with R-CHOP (R2-CHOP) achieved ORRs and CRs of 90% to 100% and 77% to 86%, respectively, in phase I and phase II trials. In one phase II trial, the most frequent grade 3/4 hematologic adverse events (AEs) included neutropenia (31%), leukocytopenia (28%), and thrombocytopenia (13%); no grade 4 nonhematologic AEs were reported. Response to R2-CHOP in patients with GCB versus non-GCB DLBCL was similar in a phase II trial (32 tissue samples available), and the 2-year PFS was 71% and 81%, respectively. Interestingly, in a separate phase II trial involving patients with newly diagnosed DLBCL who were treated with R2-CHOP, the 2-year OS was 75% for patients with GCB DLBCL compared with 83% for non-GCB subtypes. In patients treated with R-CHOP alone, a 2-year OS of 78% and 46% was achieved in GCB and non-GCB subgroups, respectively, suggesting that the addition of lenalidomide can improve the poor prognosis usually reported in the non-GCB population in response to standard R-CHOP therapy (Fig. 2). A randomized phase II trial designed to evaluate the effect of R-CHOP versus R2-CHOP in patients with newly diagnosed DLBCL (NCT01856192) is ongoing. A separate phase III study (ROBUST) evaluating R2-CHOP versus R-CHOP in patients with ABC DLBCL as defined by GEP is currently open. Real-time GEP with a turnaround time of 5 business days or less is used to assess patient eligibility for this trial.

**IR-CHOP**

The Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib has been investigated in combination with R-CHOP (IR-CHOP) in a phase Ib, nonrandomized, open-label trial in 33 patients with newly diagnosed DLBCL, mantle cell lymphoma, or follicular lymphoma. At the interim evaluation, the ORR was 100% (CR 64% and PR 36%) in 22 patients with DLBCL. The most common all-grade AEs reported in all patients were neutropenia (67%), nausea (67%), thrombocytopenia (61%), vomiting (48%), and anemia (36%). Additionally, a randomized, double-blind, phase III study is currently comparing event-free survival in patients treated with IR-CHOP versus R-CHOP (NCT01855750).

**TREATMENT FOR RELAPSED/REFRACTORY DLBCL**

In the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, 396 patients with relapsed/refractory CD20⁺ DLBCL were randomly selected to receive either rituximab, ifosfamide, etoposide, and carboplatin (R-ICE),...
or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). Patients whose disease relapsed early (<1 year) following front-line rituximab chemotherapy had a very poor prognosis, with a 3-year PFS of 20% compared with 45% for patients whose disease relapsed after 1 year.40

**MYC-POSITIVE AND DOUBLE-HIT DLBCL**

MYC is a transcription factor associated with a number of cellular functions (e.g., cell growth and proliferation, angiogenesis, protein synthesis, metabolism, and DNA replication) with a strong oncopgenic potential.42 In human B-cell neoplasms, MYC rearrangements involving the (t(8;14)) is a hallmark in Burkitt lymphoma and present in the majority of cases. Typically, it is a primary genetic event and presents as a simple karyotype and the sole chromosomal abnormality in this aggressive subtype of B-cell lymphoma. MYC gene rearrangements have also been identified in other lymphoid neoplasms, including: DLBCL (7% to 14%), unclassifiable B-cell lymphoma (35%), plasmablastic lymphoma (50%), plasma cell myeloma (15% to 50%), and mantle cell lymphoma (26 patients). Of interest, in non-Burkitt lymphoma histologies, MYC rearrangements are found as part of a complex karyotype and typically represent secondary genetic events.42-43 MYC gene activation in DLBCL can occur via translocation (5% to 14%), copy gain (19% to 38%), amplification (2%), or mutation (32%).44-47 In general, MYC rearrangement predicts an inferior outcome in DLBCL, but it is not clear whether it is because of MYC rearrangement itself or because 58% to 83% of MYC-translocated DLBCL also have concurrent dual or triple translocation with BCL2 and/or BCL6 (less likely) identified as double-hit or triple-hit DLBCL.48-49 These patients often have 12 months or less OS when treated with R-CHOP.50

Of note, high MYC-protein expression (28% to 41%) of DLBCL without MYC gene abnormalities has been identified (suggesting alternate mechanisms of MYC induction). Patients with DLBCL with a high percentage of both MYC and BCL2 protein (20% to 44%) expression by IHC staining carry a poor prognosis; treatment with standard R-CHOP or CHOP-like immunotherapy results in inferior PFS and OS on retrospective analyses.51-54 Many studies have defined these patients as having double-expressor DLBCL, and most studies require that tumor cells express at least 40% MYC and at least 50% to 70% BCL2 positivity. Although patients with double-expressor DLBCL (DEL) have a worse prognosis than those without double expression of MYC plus BCL2, it should be noted that different studies utilize variable cutoff points to define positivity. Unlike the reproducibility of the fluorescent in situ hybridization (FISH) technique, the IHC technique is less robust and has more variability associated with it. Interestingly, the majority of double-hit DLBCL (DHL) (defined here as having MYC + BCL2 rearrangements) is primarily GCB-like, whereas DEL is primarily ABC-like. This unique observation leads us to question whether a successful therapeutic approach in DHL will be equally successful in DEL based on differences inherent within the COO and likely differences in cellular/molecular pathways, genetics, and variable-resistance pathways. Only large prospective clinical trials utilizing central path review of FISH, as well as IHC, and well-defined inclusion definitions of positivity will be able to answer this question.

**CURRENT TREATMENT APPROACH: OVERVIEW**

As mentioned previously, R-CHOP is an inadequate induction therapy for DHL (i.e., most patients die within 2 years of diagnosis). The malignant DHL neoplastic cell attains an amazing survival advantage. Concurrent MYC + BCL2 translocations confer increased cell growth, cell cycle transit, and metabolism and angiogenesis via MYC, but at the same time increased apoptosis (i.e., drug resistance) via BCL2. In general, DHL patients often present with several poor prognostic characteristics: median age in the seventh decade (many unable to tolerate dose-intensive therapeutic approaches); stage III/IV disease; high-intermediate/high (HI/H) IPI; elevated LDH; high frequency of extranodal sites (including the central nervous system).55-56 Various multidrug therapy regimens with or without rituximab have been utilized to treat DHL, including dose-intensive therapies that have curative potential in BL, although published data from retrospective reviews do not indicate any single optimal induction therapy approach (Table 2). Patients achieving a
complete remission with regimens more intensive than R-CHOP had better PFS, but consolidative SCT did not seem to improve OS in these patients. Of the regimens utilized, R-EPOCH: (1) has curative potential in BL, (2) is better tolerated than more dose-intensive (DI) regimens, and (3) appears to have at least similar efficacy compared to DI therapies. In addition to the data from Oki et al (Table 2), a meta-analysis of 401 DHL patients by Howlett et al57 presented at the 2014 American Society of Hematology (ASH) Annual Meeting demonstrated R-EPOCH (and more DI regimens) were associated with improvement in PFS (but not OS) compared to R-CHOP. Another presentation at ASH 2014 by Dunleavy et al58 utilizing R-EPOCH in a multicenter phase II study, which included DHL, demonstrated a promising early PFS (87% at 14 months).

Currently consolidative autologous SCT in chemotherapy-sensitive patients (especially CRs) does not appear to

**TABLE 2. DHL Induction Therapy and Outcome**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Outcome (Median)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrich et al50</td>
<td>311</td>
<td>R-CHOP (32%)</td>
<td>PFS: 10.9; OS: 21.9 mo</td>
<td>Median follow-up: 23 mo</td>
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<tr>
<td></td>
<td></td>
<td>R-Hyper CVAD/MA (21%)</td>
<td>PFS (R-CHOP): 7.8 mo versus 26.6 mo (for any “intensive” regimen; p = 0.001)</td>
<td>No difference between intensive regimens</td>
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<td></td>
<td></td>
<td>R-EPOCH (21%)</td>
<td>R-Hyper CVAD/MA: 32%</td>
<td></td>
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<td></td>
<td></td>
<td>R-CoDox-M/IVAC (14%)</td>
<td>R-EPOCH: 67%</td>
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<td></td>
<td></td>
<td>R-CHOP: 25%</td>
<td>CR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>R-Hyper CVAD/MA: 32%</td>
<td>R-CHOP: 20%</td>
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<td></td>
<td></td>
<td>R-EPOCH: 68%</td>
<td>R-EPOCH: 68%</td>
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<tr>
<td>Oki et al60</td>
<td>129 (93 with both MYC and BCL2 translocation)</td>
<td>R-CHOP</td>
<td>2-yr EFS</td>
<td>Increased OS with R-EPOCH c/w R-CHOP (p = 0.057)*</td>
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<td></td>
<td></td>
<td>R-Hyper CVAD/MA</td>
<td>Overall: 33% (overall)</td>
<td>CNS involvement: 13% at 3 yrs</td>
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<td></td>
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<td>R-EPOCH</td>
<td>R-CHOP: 65%</td>
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<td>R-CHOP: 25%</td>
<td>R-Hyper CVAD/MA: 70%</td>
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<td>R-EPOCH: 65%</td>
<td>R-EPOCH: 68%</td>
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<td>R-CoDox-M/IVAC (14%)</td>
<td>R-CoDox-M/IVAC (14%)</td>
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<tr>
<td>Johnson et al61</td>
<td>54</td>
<td>CHOP-like (43%)</td>
<td>OS</td>
<td>BCL2 protein-negative cases (more favorable)</td>
</tr>
<tr>
<td></td>
<td>BCL-U (36 patients)</td>
<td>R-CHOP (20%)</td>
<td>R-CHOP: 1.4 yr</td>
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<td>DLBCL (17 patients)</td>
<td>HDT (17%)</td>
<td>CHOP: 5 mo</td>
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<td></td>
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<td>Palliative (26%)</td>
<td>Palliative (26%)</td>
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<tr>
<td>Li et al62</td>
<td>BCL-U (33 patients)</td>
<td>R-CHOP (39%)</td>
<td>OS: 18.6 mo</td>
<td>Median age: 55</td>
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<td></td>
<td>DLBCL (23 patients)</td>
<td>R-Hyper CVAD/MA (57%)</td>
<td>R-Hyper CVAD/MA (57%)</td>
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**TABLE 3. Novel Future Therapeutic Considerations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>ABT-199</td>
<td>Platelet-sparing BCL2 inhibitor (BH3-mimetic)</td>
<td>28, 63</td>
</tr>
<tr>
<td>BET bromodomain inhibitors (JQ1, I-BET 151, OTX015)</td>
<td>Down-regulation of MYC-associated transcription: Decreased cell proliferation and inhibition of MYC-driven neoplasms</td>
<td>64–66</td>
</tr>
<tr>
<td>CAR-T cells</td>
<td>Autologous T-cell-mediated killing of CD19-positive lymphoid neoplasms</td>
<td>67, 68</td>
</tr>
<tr>
<td>Aurora kinase inhibitors (alisertib)</td>
<td>Aurora kinase function is required for tumor maintenance of MYC-driven lymphoma</td>
<td>69, 70</td>
</tr>
<tr>
<td>mTor inhibition</td>
<td>mTOR may plan an important role in tumor maintenance by MYC in B lymphocytes</td>
<td>71, 72</td>
</tr>
<tr>
<td>MLN9708/Ixazomib (second generation proteasome inhibitor)</td>
<td>Preclinical model: Degraded MYC and can induce lymphoma cell death at nanomolar concentrations</td>
<td>73</td>
</tr>
<tr>
<td>PI3K inhibition</td>
<td>High percent GCB-DLBCL cases: loss of PTEN → activation of PI3K/AKT pathway → MYC upregulation</td>
<td>74</td>
</tr>
<tr>
<td>Inhibition of human mitochondrial peptide deformylase</td>
<td>Causes apoptosis in MYC-overexpressing hematopoietic neoplasms</td>
<td>75</td>
</tr>
<tr>
<td>SIRT4 protein</td>
<td>Suppresses tumor formation in MYC-induced B-cell lymphoma models</td>
<td>76</td>
</tr>
</tbody>
</table>

Abbreviations: BCL-U, B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; Hyper CVAD/MA, hyper-fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone/methotrexate, cytarabine; EPOCH, etoposide, prednisone, doxorubicin, cyclophosphamide, doxorubicin; CoDox-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; PFS, progression-free survival; OS, overall survival; SCT, stem cell transplant.

*Consolidative SCT in 50% R-EPOCH versus 4% R-CHOP group.

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Currently consolidative autologous SCT in chemotherapy-sensitive patients (especially CRs) does not appear to signifi-
cantly change clinical outcomes. This may likely be a result of the inherent rapid tumor cell growth and inherent drug-resistant DHL cells that remain after induction therapy (i.e., minimal residual disease) that would likely not be cured with a high-dose, chemotherapy-based conditioning regimen typically utilized during autologous stem cell transplantation. Of interest, review of the literature identified two abstracts, which included a total of approximately 50 patients, that concluded that patients with DHL who undergo allogeneic SCT following dose-intensive induction therapy have prolonged OS.57,59 Unfortunately, several reasons make it unlikely that allogeneic SCT will make a major effect in the future treatment of a significant percentage of DHL patients: (1) limited data from a small number of selected patients, (2) the risk of relapsed disease while awaiting graft-versus-lymphoma to occur, (3) the need for a suitable HLA-compatible donor, and (4) the risk of chronic graft-versus-host disease.

The future holds promise that novel targeted agents, which either directly or indirectly inhibit MYC and BCL2, will lead to improved overall survival in patients with DHL (Table 3). Many agents have demonstrated in vitro and in vivo antitumor activity, and a limited number are in early human clinical trials. It is quite likely that DHL will require a rational combination of MYC/BCL2 inhibitors in combination with effective chemotherapeutic agents (e.g., BH₁ mimetics to sensitize cells to drug toxicity, etc.) to optimize the killing of these highly resistant lymphoma cells and change DHL from one of the worst subtypes of DLBCL into a therapeutically responsive subtype (with a significant improvement in clinical outcomes). Based on the information provided above, all newly diagnosed DLBCL tumor biopsies should undergo FISH and IHC evaluation to identify DHL and DEL, respectively. These patients, whenever possible, should be referred to participation on clinical trials. Off study, the use of R-EPOCH induction (including central nervous system prophylaxis) is a reasonable approach while we await further testing and validation of effective novel targeted agents to be added to our current therapeutic armamentarium against DHL.

Disclosures of Potential Conflicts of Interest

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66. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large


