Review Article

Double hit diffuse large B-cell lymphomas: diagnostic and therapeutic challenges

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Abstract: Although diffuse large B-cell lymphoma (DLBCL) is curable with standard chemoimmunotherapy, over 30% of patients with advanced stage disease experience refractory disease or progression. Recent studies suggest that rearrangement of the myc oncogene occurs in approximately 10% of patients with DLBCL, and confers a very poor prognosis, particularly when there is concomitant rearrangement of bcl-2, a condition referred to as "double hit DLBCL". Using immunohistochemistry, up to 30% of patients have evidence of increased expression of myc, which occurs in both activated B-cell and germinal center type DLBCL. When bcl-2 is also positive by immunohistochemistry, prognosis is also poor. There are no randomized studies guiding treatment for patients with double hit DLBCL, but new datasets are emerging suggesting a possible role for dose-adjusted EPOCH infusional chemotherapy with rituximab. This review will conclude with a survey of novel agents which may be rationally incorporated into chemotherapy platforms for this high risk subset of DLBCL.

Keywords: Large cell lymphoma; Bcl-2; Myc; treatment

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoma in the United States, and over the past two decades, significant improvements in overall survival for a substantial subset of patients have resulted from the incorporation of rituximab into the CHOP chemotherapy regimen. For example, data from a population-wide database indicated that the 2-year progression-free survival of newly diagnosed DLBCL improved from 51% to 69% after R-CHOP became standard therapy (1). Clinical prognostic scoring systems may be utilized to determine prognosis of patients newly diagnosed with DLBCL, and these remain robust in the rituximab era. The international prognostic index (2) (IPI: age >60, elevated LDH, performance status >1, stage >2 and extranodal sites >1) predicts a 59% overall survival for highest risk group at 3 years in a modern dataset (3). Efforts at refining this prognostic index include the NCCN IPI, which incorporates specific sites of disease involvement. Compared with the IPI, the NCCN-IPI better discriminated low- and high-risk subgroups (5-year overall survival: 96% *vs.* 33%) in two large retrospective datasets (4).

However, these clinical prognostic features are clearly surrogates for differential biology within DLBCL. Gene expression studies have indicated that DLBCL is a heterogeneous disease entity, as cell-of-origin studies reveal at least three distinct subtypes: primary mediastinal, activated B-cell, and germinal center B-cell types (5). These subtypes also predict for outcomes at diagnosis even when adjusted for clinical features, with inferior outcomes observed with activated B-cell type disease (6). Alternative strategies of organizing gene expression data emphasize this heterogeneity of DLBCL, with subsets characterized by signatures of host response, oxidative phosphorylation, and B-cell receptor pathway elements (7).

Rearrangement of the myc oncogene, resulting in constitutive overexpression, is necessary for the diagnosis of

Burkitt lymphoma (8). The incidence of myc rearrangement, measured with FISH, in patients with DLBCL is variable between series, but appears to be in the range of of 6-16% (9). Given the relative frequency of these diseases, there are more patients diagnosed with myc-positive DLBCL than with Burkitt lymphoma each year in the United States. Over the past three years, the impact of this abnormality on outcome in DLBCL has become clear, and indeed it may be the most powerful biological predictor of negative outcome for DLBCL in the rituximab era (10). This review will detail the prognostic power of myc positivity measured by both FISH and immunohistochemistry, correlate this information with gene expression information and the importance of associated bcl-2 rearrangements, and summarize data regarding optimal therapeutic strategies for patients with this abnormality.

Impact of myc rearrangement on outcome in DLBCL, and importance of double-hit

Several groups have correlated the presence of myc positivity with outcome in DLBCL. For example, Barrans and colleagues reviewed 303 patients with previously untreated, de novo DLBCL, treated with standard R-CHOP therapy (11). The median age of these patients was 71, and the majority patients had at least 4 years of follow-up. Myc rearrangements were demonstrated in 35 patients (14%). The overall survival was worse for patients with myc rearrangement, with 35% of patients alive at 2 years compared with 61% alive at 2 years in the non-rearranged group.

Similarly, the British Columbia Cancer Agency evaluated 135 patients with DLBCL treated with R-CHOP (12). Myc positive cases were more likely to have higher proliferation rate, and 67% had bcl-2 positivity by immunohistochemistry. The 5-year overall survival was significantly worse in myc rearranged cases (33%) compared with non-rearranged cases (72%). The incidence of CNS relapse was also higher in the myc rearranged cases, even in the presence of early stage disease.

In the Barrans series, 74% of the patients with myc rearrangement also had evidence of a t(14;18) using FISH. However, in the aforementioned BCCA experience, only 3 cases (25%) had a concurrent t (14;18). The incidence of bcl-2 abnormalities therefore varies significantly between series (13-15). The presence of concomitant bcl-2 rearrangement significantly impacts outcome in myc positive disease (16). The British Columbia Cancer Agency subsequently identified 54 cases that had concurrent bcl-2 and myc translocations ("double hit") (17). Seventeen of these cases were diagnosed as DLBCL; 36 were B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma ("unclassifiable"). Outcome of these patients was universally poor, however, patients with DLBCL histology had slightly better outcomes than the unclassifiable histology.

MD Anderson has also reported outcomes of patients with both myc rearrangements and t(14;18) (18). Of 60 patients, 23 had DLBCL; the remainder was either unclassifiable or follicular lymphoma. The median overall survival was only 18 months, and morphology did not impact outcome. A group from Denmark has also reported on a group of DLBCL and B-cell lymphoma unclassifiable cases, and found that 11% were double hit including myc and bcl-2; constituting 7% of primary DLBCL, and 21% of transformed cases (19). There were no clinical characteristics which correlated with double hit histology, and outcome was very poor.

Cases with a Myc breakpoint and bcl-2 rearrangement are the most common of the "double hit" lymphomas defined as a myc abnormality with another abnormality (20). In a recently published comprehensive analysis of the Mitelman database, 62% of double hit lymphomas involve bcl-2; 18% involved bcl-6, the remaining cases were triple hit lymphomas (9). When interpreting the literature in myc positive lymphomas, it is critically important to understand the frequency of additional abnormalities, particularly bcl-2 (16), given the impact on outcome.

Use of immunohistochemistry to define myc positive disease

All of the aforementioned series utilized FISH to determine the presence of a myc rearrangement. FISH is expensive, time-consuming, and may not be available for rapid routine use in all laboratories. In addition, certain DLBCLs without evidence of myc rearrangement on FISH exhibit features of molecular Burkitt lymphoma by gene expression profiling, suggesting that FISH only captures a subset of patients with myc-driven DLBCL (21). Two years ago, the first experiences using immunohistochemical approach to assess myc protein expression in formalin-fixed paraffin-embedded tissue were published (22). In a series from Harvard, of 77 cases of DLBCL, 15 had high myc protein as defined by nuclear staining in greater than 50% of tumor cells. All myc rearranged cases had increased myc protein expression using this immunohistochemical assay; there were four additional

cases that were negative on FISH but had increased protein expression. These cases had confirmed increased myc transcriptional activity by gene set enrichment analysis, suggesting alternative mechanisms for myc deregulation in these cases. Importantly, these cases had similar poor outcome, inferior to patients without this abnormality, as those cased detected by FISH.

Two groups independently validated these immunohistochemistry results, to define a group of "double hit" DLBCL which may be diagnosed with routine immunohistochemical methods in 2012. The group from Denmark evaluated 193 cases of DLBCL uniformly treated with R-CHOP therapy, and performed routine staining for myc, bcl-2 as well as markers allowing for cell of origin classification (23). In addition, FISH was performed for detection of myc rearrangement and for t(14;18). Eleven percent of cases had evidence of myc rearrangement by FISH, and six percent of cases were double hit by FISH. Poor outcome was only observed in the double hit cases. Moreover, 29% of cases had high expression of myc and bcl-2 on immunohistochemistry evaluation. These cases had similar inferior overall survival on multivariate analysis, controlled for clinical and molecular prognostic factors, specifically germinal center genotype *vs*. non germinal center genotype. These results were confirmed in a validation set.

Johnson and colleagues from British Columbia used a similar platform to evaluate prospective cases of DLBCL with immunohistochemical stains for bcl-2 and myc (24). In the training cohort, concurrent expression of myc (defined as 40% or more of tumor cells staining positive) and bcl-2 was found in 21% of cases. Increased myc was only predictive of outcome if increased bcl-2 was also present, and these results were also validated in an independent cohort after adjusting for clinical and molecular high risk features.

Subsequently, the R-CHOP consortium group performed a comprehensive gene expression analysis of 893 patients DLBCL treated with R-CHOP (25). Double hit DLBCL defined either by FISH or immunohistochemistry occurred in both GCB and ABC types of DLBCL, and conferred a similar poor prognosis. Interestingly, there was no difference in gene expression signatures between the GCB and ABC subptypes in the absence of MYC/BCL2 coexpression, suggesting that the poor prognosis of ABC subtype is largely driven by double hit status. Tumors with double hit status had downregulation of genes encoding extracellular matrix proteins, those involving matrix deposition/remodeling and cell adhesion, and upregulation of proliferation-associated genes. The authors concluded that MYC/BCL2 co-expression, rather than cell-of-origin classification, is the best predictor of prognosis in patients with DLBCL treated with R-CHOP.

In summary, the poor outcome in DLBCL observed with myc positive disease is largely due to "double hit" biology and it is the concurrent expression of bcl-2 and c-myc that is important for outcome. Concurrent overexpression of myc and bcl-2 is present in both germinal center and activated B-cell DLBCL suggesting heterogeneous molecular pathways may be responsible for myc deregulation, but the impact of these pathways results in a universally poor outcome with conventional therapy.

Treatment approaches to double hit DLBCL

Although the prognosis of double hit lymphoma, defined either by FISH or immunohistochemistry, is clearly poor with R-CHOP, there is very limited data evaluating alternative therapy, and no published prospective data focused on this patient population. Double hit biology DLBCL represents the largest unmet clinical need in DLBCL, and given the frequency of this abnormality, the majority of treatment failures after R-CHOP are in this category (10). It is clear from the aforementioned studies that R-CHOP is not sufficient induction therapy for this group of patients, as the majority of patients will experience disease progression after standard treatment. As myc positivity is present in Burkitt lymphoma, and Burkitt lymphoma has superior outcomes with more aggressive chemotherapy regimens (8,26), several have advocated for a more aggressive approach to patients with double hit DLBCL. Whether or not this will impact patients in a favorable way is not yet clear from limited published series.

Four patients with DLBCL that had t(14;18) and a myc rearrangement by FISH were included in a prospective study of modified CODOX-M/IVAC, a pediatric regimen developed for Burkitt lymphoma (27); all four patients were dead less than 5 months from the start of treatment (28). A subset analysis of the SWOG 9704 study (29), which randomized patients to either 8 cycles of R-CHOP or 6 cycles of R-CHOP followed by high dose therapy and autologous stem cell transplant (ASCT) was recently published. Of 198 cases available for immunohistochemistry, 27 (14%) were positive for MYC, and these cases were morphologically and phenotypically heterogenous and were associated with poor progression-free and overall survival in multivariate analysis (30). We have subsequently identified a subset of

these patients with double hit histology. Patients who were able to receive ASCT appeared to have superior outcome, but early progression and refractory disease limited the efficacy of this approach.

Similarly, in the setting of relapsed DLBCL, the outcomes of salvage chemotherapy and ASCT outcomes were poor for patients with myc-positive disease in the BIO CORAL study, the majority of whom had double hit disease defined by FISH (31). The authors concluded that ASCT outcomes were so poor and novel treatments were indicated for this group of relapsed/refractory patients.

In the Vancouver and Denmark series, the median age of patients with double hit DLBCL by IHC exceeded 65 years, making dose escalation a challenge for the majority of patients with this high risk feature. Currently, the United States Intergroup is evaluating dose adjusted R-EPOCH therapy for myc driven DLBCL, including patients with double hit biology. This regimen has activity in standard DLBCL, Burkitt lymphoma, and in myc-only (but not double hit) DLBCL (32). Additionally, this regimen is tolerable in older patients as compared to CODOX-M IVAC or ASCT-containing regimens. Preliminary results of the myc positive DLBCL group suggest a high overall response rate (K. Dunleavy, personal communication), but the frequency of patients with double hit disease is very low, and follow-up to date is short. Longer follow-up of this trial and additional prospective experience is needed before DA-R-EPOCH therapy may be considered the standard chemoimmunotherapy backbone for patients with double hit DLBCL.

Recently, a large group of investigators pooled data for a multicenter retrospective analysis addressing the impact of induction regimen on stem cell transplantation on outcomes in double hit DLBCL (33). Patients were coded as having either standard R-CHOP or "intensive" induction therapy, which included the dose adjusted R-EPOCH regimen, Hyper CVAD alternating with methotrexate and cytarabine, or CODOX-M and IVAC. Response rates were highest for dose adjusted R-EPOCH. Intensive induction was associated with improved progression-free survival, and ASCT was not associated with improved overall survival. When the authors tried to adjust for clinical risk factors, intensive induction appeared to be associated with improved overall survival. A small subset of patients (less than 10%) was identified who did not have leukocytosis, CNS involvement LDH >3 times normal or advanced stage disease and had excellent outcomes despite double hit biology (33).

Novel approaches and future directions

Novel agents with particular promise in these patients with double hit DLBCL may include small molecule inhibitors of bcl-2. Using cell lines with t(14:18) and t(8;14), ABT-263, a bcl-2 inhibitor, sensitized these double hit cells to conventional therapeutic agents (34). ABT-199, a more specific and safer bcl-2 inhibitor is currently in clinical trials (35). This agent has been shown to have *in vivo* efficacy against aggressive Myc-driven mouse lymphomas (36). Combinations of standard chemoimmunotherapy and ABT-199 are currently in clinical trials, and it may be of particular interest to study patients with double hit DLBCL.

Another approach of interest results from the fact that myc induces aurora A kinase, and blocking aurora A kinase activity in a murine model system triggers apoptosis of myc-driven DLBCL (37). Alisertib, a specific inhibitor of aurora A kinase, is currently under clinical development in DLBCL, and preliminary results suggest significant anti-tumor activity (38). Again, murine studies suggest that the interaction between alisertib plus with standard treatments like vincristine and rituximab is synergistic and synthetic lethal in Myc and Bcl-2 co-expressing DLBCL (39).

Bortezomib, a proteasome inhibitor approved for treatment of mantle cell lymphoma, has limited single agent activity in DLBCL, but is under evaluation in combination with R-CHOP for patients with non-germinal center type DLBCL (40). An alternative function of myc is apoptosis, and preclinical studies have demonstrated that bortezomib may increases MYC protein levels and that endogenous MYC is necessary for the induction of apoptosis in the setting of bortezomib. This kind of MYC-induced cell death is mediated by enhanced expression of the pro-apoptotic BCL2 family members, suggesting combinations of bortezomib with chemotherapy or bcl-2 inhibitors could have activity in double hit DLBCL (41).

Bromodomains are conserved protein regions that recognize specific histone modifications. Bromodomain inhibition reduces tumor growth in lymphomas, and it is felt this may be largely through the disruption of transcriptional networks driven by oncogenic MYC (42). The small molecule JQ1 suppresses c-MYC expression through inhibition of the bromodomain and extra-terminal family of bromodomain proteins. The expression of c-MYC was suppressed in vitro as a result of JQ1 treatment, and JQ1 treatment significantly suppressed growth of DLBCL cells engrafted in mice and improved survival of engrafted mice (43). Similar results have been demonstrated in

primary effusion lymphomas, suggesting that bromodomain inhibitor activity may not be limited to translocations involving MYC and they may have activity where c-Myc protein is deregulated at the post-translational level, such as FISH negative, IHC positive double hit DLBCL (44).

Conclusions

Double hit biology represents the greatest unmet need in DLBCL. The mechanisms leading to poor outcome in double hit DLBCL are unclear, but involve more than myc dysregulation, since Burkitt lymphoma, also involving myc, has a superior prognosis. The synergistic action of myc and bcl-2, and other molecular features such as genetic complexity both contribute to poor outcome in patients with double hit DLBCL (45,46). The existing literature is not adequate to answer the question of optimal therapy for double hit biology DLBCL. It is clear that R-CHOP needs to be replaced for this group of patients; however, there are no prospective trials suggesting alternatives. Age and frailty of this population of patients will limit the role of dose-escalated or intensified therapy. It is likely that rational combinations of novel targeted agents with standard chemoimmunotherapy platforms will ultimately provide the highest impact for double hit, and other molecularly defined subsets of DLBCL (47).

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