How I treat “Double Hit” Lymphoma

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Abstract

The 2016 revision of the WHO classification for lymphoma classification has included a new category of lymphoma, separate from diffuse large B-cell lymphoma termed *High grade B-cell lymphoma with translocations involving myc and bcl-2 or bcl-6*. These lymphomas, which occur in less than 10% of cases of diffuse large B-cell lymphoma, have been referred to as "double hit" lymphomas (or triple hit lymphomas if all three rearrangements are present). It is important to differentiate these lymphomas from the larger group of "double expressor" lymphomas which have increased expression of MYC and BCL-2 and/or BCL-6 by immunohistochemistry, using variable cut-off percentages to define positivity. Double hit lymphomas have a poor prognosis when treated with standard chemoimmunotherapy, and have increased risk of central nervous system involvement and progression. Double hit lymphomas may arise as a consequence of transformation of underlying indolent lymphoma. There are no published prospective trials in double hit lymphoma, however retrospective studies strongly suggest that “aggressive” induction regimens may confer superior outcome. In this manuscript, I review my approach to the evaluation and treatment of double hit lymphoma, with an eye toward future clinical trials incorporating rational targeted agents into the therapeutic armamentarium.
Case Presentation 1

A 53 year old man presents with a two month history of left hip pain. He did not respond to initial conservative management, including rest and physical therapy. MRI of the left hip was eventually performed, which showed a destructive, enhancing lesion involving the left iliac wing, acetabulum and pubic ramus, measuring 8x7x7 cm. Computed tomographic scan of chest, abdomen and pelvis was then performed, demonstrating enlarged left supraclavicular and right hilar lymph nodes. The soft tissue component of the dominant mass contacted the prostate gland and displaced the urinary bladder. A lucency was also seen in the left T11 pedicle. A biopsy of the bone lesion was performed, revealing a poorly differentiated and pleomorphic infiltrate of large malignant cells, with extensive areas of necrosis. Immunohistochemical stains demonstrated that the infiltrate was CD20 and CD79a positive. This was consistent with diffuse large B-cell lymphoma, stage IVA. Clinical risk factors included high stage, high LDH, and extranodal disease; performance status was normal, making this high intermediate risk disease based upon the international prognostic index, and the age adjusted international prognostic index. \(^1\) Subsequent immunohistochemical stains revealed the lymphoma to be positive for BCL-6, BCL-2 and MYC, and negative for CD10, CD30, MUM1 and EBER; Ki-67 fraction was 50%. This suggests the tumor is of germinal center origin (using the Hans algorithm\(^2\)) and a double expressor phenotype (MYC and BCL-2). The patient was started urgently on standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) therapy. One week later, FISH results returned demonstrating the presence of a myc rearrangement, a bcl-6 rearrangement, and evidence of the t(14;18) (bcl-2 rearrangement), consistent with a “triple hit” lymphoma.

Case Presentation 2

A 63 year old man presented with progressive fatigue and right shoulder pain. An MRI was performed which revealed an abnormal marrow signal suggesting an infiltrative process, which led to a biopsy and intramedullary nail placement for stabilization. Pathology evaluation revealed malignant-appearing lymphoid cells with extensive necrosis that were positive for CD20, CD10, MYC and BCL-2 on immunohistochemistry; FISH confirmed rearrangements of myc and bcl-2. PET/CT demonstrated a large hypermetabolic mass in right upper extremity with multiple other sites of osseous and muscle involvement, as well as suggestion of gastric and renal involvement by lymphoma. LDH was above normal and performance status was 1. This presentation was consistent with advanced stage high grade B-cell lymphoma with rearrangements of myc and bcl-2 (“double hit” lymphoma); with high risk disease per the
international prognostic index. The patient was started on dose-adjusted EPOCH therapy, and tolerated two cycles well. A lumbar puncture for planned prophylaxis with intrathecal methotrexate was performed as part of cycle 3, and results of CSF analysis revealed the presence of large lymphoid forms with high nuclear:cytoplasmic ratio, fine chromatin and vacuoles, which were confirmed as clonal on flow cytometry, consistent with CNS involvement by high grade B-cell lymphoma with myc and bcl-2 rearrangements.

**Introduction: Myc-associated lymphoma**

cMyc is an essential “global” transcription factor and has roles in proliferation and cellular growth. This gene, located on chromosome 8q24, is normally carefully regulated which results in low c-MYC protein levels, and has the ability to induce apoptosis under normal physiological conditions. The c-myc gene has long been recognized as a *bona fide* oncogene, and may transform cells via unregulated overexpression of intact c-MYC protein through insertional mutagenesis, gene amplification, and chromosomal translocation. The c-myc gene translocation with an immunoglobulin gene is the genetic hallmark of Burkitt lymphoma, and required to make this diagnosis.

Diffuse large B-cell lymphoma is the most common lymphoma diagnosed in the Western world, and is curable in approximately two thirds of cases with standard chemoimmunotherapy approaches. This disease exhibits significant clinical heterogeneity, and prognostic scoring systems utilizes clinical factors (for example age, stage, performance status, serum lactate dehydrogenase level, and number of extranodal sites involved) to successfully stratify outcomes in the modern era. These clinical factors largely represent surrogates for genetic and molecular factors within the tumor. Cell-of-origin studies have revealed at least three major subtypes of diffuse large B-cell lymphoma: activated B-cell (ABC), germinal center (GCB) and primary mediastinal; these subtypes not only constitute unique molecular entities, but also have differential clinical outcomes using modern therapy. 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.

c-MYC protein expression is increased in up to one third of cases of diffuse large B-cell lymphoma, suggesting that changes in myc may be an important secondary transforming event. Using an immunohistochemical approach to assess MYC protein expression in formalin-fixed paraffin-embedded tissue, a group from Denmark evaluated 193 cases of DLBCL uniformly treated with standard R-CHOP therapy. Twenty nine percent of cases had high expression of
MYC and BCL-2 (an anti-apoptotic oncogene) on immunohistochemistry evaluation, and had inferior overall survival on multivariate analysis, controlled for clinical and molecular prognostic factors, specifically germinal center genotype vs. non germinal center genotype. A group from British Columbia used a similar platform to evaluate prospective cases of DLBCL with immunohistochemical stains for BCL-2 and MYC. 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 expression was only predictive of poor 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. Taken together, protein positivity for MYC and BCL-2 (termed “double expressor” phenotype, see table 1) was demonstrated to confer an inferior outcome after standard therapy. The R-CHOP consortium group performed a comprehensive gene expression analysis of 893 patients DLBCL treated with R-CHOP. Double expressor DLBCL occurred in both GCB and ABC types of DLBCL, and conferred a similar poor prognosis. In this analysis, the poor prognosis of ABC subtype was largely driven by expression of MYC, resulting in downregulation of genes encoding extracellular matrix proteins, those involving matrix deposition/remodeling and cell adhesion, and upregulation of proliferation-associated genes. Finally, in two recent German prospective randomized trials in diffuse large B-cell lymphoma, cell of origin failed to identify prognostic subgroups, whereas dual expression of MYC and BCL2 was highly predictive of poor survival.

A lower number of patients present with diffuse large B-cell lymphoma with an underlying translocation of cmyc. Patients with such a translocation have demonstrated particularly poor outcome in several retrospective series. Barrans and colleagues reviewed 303 patients with previously untreated, de novo diffuse large B-cell lymphoma, treated with standard R-CHOP therapy. The overall survival was worse for the 14% of patients with myc rearrangement, with two year overall survival of 35% with a translocation compared to 61% in the non-rearranged group. Similarly, the British Columbia Cancer Agency evaluated 135 patients with DLBCL treated with R-CHOP. The 5 year overall survival was significantly worse in myc rearranged cases (33%) compared with non-rearranged cases (72%). Similar to what was observed with protein expression, the presence of concomitant bcl-2 rearrangement significantly impacts outcome in myc positive disease, conferring a particularly poor outcome when these two translocations occur simultaneously. Similarly, in a German trial of a more aggressive chemotherapy platform incorporating etoposide (R-MegaCHOEP), the adverse impact of myc rearrangements was confirmed, but the sole presence of bcl-2 rearrangements emerged as a novel prognostic marker associated with inferior overall survival.
Involving both myc and bcl-6 also appear to confer poor prognosis in patients treated with RCHOP.\textsuperscript{20}

In recognition of these data, the 2016 revision of the WHO classification for lymphoma classification has included a new category of lymphoma, separate from diffuse large B-cell lymphoma termed \textit{High grade B-cell lymphoma with translocations involving myc and bcl-2 or bcl-6}.\textsuperscript{21} These cases have been more often referred to as “double hit” lymphoma (when myc translocation is present with either bcl-2 or bcl-6 translocation) or “triple hit” lymphoma (when all three translocations are present), as noted in figure 1 and table 1.\textsuperscript{22} Data from the Mitelman database reveal that 62\% of these newly categorized myc-rearranged lymphomas involve bcl-2 translocations; 18\% involve bcl-6 translocations, the remaining cases were triple hit lymphomas.\textsuperscript{23} Finally, the specific translocation partner of myc impacts outcome, with immunoglobulin gene translocations conferring the shortest survival.\textsuperscript{24}

In this manuscript I will focus on the approach to double hit lymphomas involving myc and bcl-2 translocations. There is limited data to guide the therapeutic approach to myc-rearranged lymphomas involving bcl-6 translocations, and at present I would approach double hit lymphomas involving bcl-6 and triple hit lymphomas in the same manner as double hit lymphomas involving bcl-2 translocations. An important point to emphasize is that this manuscript focuses on double hit lymphomas (requiring translocations of myc and either bcl-2 or bcl-6 detected usually by FISH fluorescent in situ hybridization), not the larger subset of lymphomas that have increased expression of MYC measured by immunohistochemistry, as noted in figure 2.

**Which lymphomas should be evaluated for double hit status?**

At our institution, every newly diagnosed aggressive large B-cell lymphoma is referred for FISH testing with a myc break-apart probe, as well as for bcl-2 translocation, t(14;18). The WHO emphasizes that there no consensus on which large B-cell lymphomas should undergo this testing. Testing all cases clearly may increase diagnostic costs, and substantially increase the testing burden in FISH laboratories. Strategies suggested to limit FISH testing include restricting the testing to those lymphomas that are GCB subtype by immunohistochemistry, restricting the testing to highly proliferative lymphomas measured by Ki-67, and/or restricting the testing to those lymphomas that express MYC protein by immunohistochemistry.\textsuperscript{25}
In a recent analysis from British Columbia, the incidence of myc and bcl-2 genetic alterations and their clinical significance were largely dependent on cell-of-origin subtypes. In the setting of myc translocation, bcl-2 translocation association with poor outcome was limited to GCB lymphoma. Importantly, cell-of-origin was determined using the Lymph2Cx assay in this analysis rather than an immunohistochemistry algorithm, which is most commonly used in the clinic. Given known discrepancies between gene expression profiling with Lymph2Cx and immunohistochemistry algorithms in classifying DLBCL, I think it is premature to conclude that only GCB lymphomas should be tested for double hit status with FISH, unless Lymph2Cx or a similar platform is used to determine cell-of-origin.

There are similar limitations to using Ki-67 proliferation index or MYC expression on immunohistochemistry to determine which cases should be referred for FISH evaluation of translocations. A recently published analysis of 209 cases of aggressive lymphoma included 7.4% of the cases which were double hit. MYC-positive DLBCL showed higher median Ki-67 (>90%) and CD10 positivity (as a surrogate for GCB) as compared with MYC-negative cases. The authors recommended a cut-off value of >/=30% for MYC by IHC; however, this has not been validated, and there are reports of cases of myc rearranged lymphoma that are below that threshold for detection. For example, in a study from the University of Pennsylvania, double hit status could not be inferred by any baseline disease- or patient-related characteristics. In toto, I believe these findings support the practice of routine performance of FISH in large cell lymphoma to detect double hit status. If resources preclude this broad approach, the majority of double hit cases are GCB subtype (see figure 2) and express MYC on IHC, so limiting testing to this group is an acceptable, but inferior alternative.

In addition to de novo disease, double hit lymphoma occurs in the setting of transformation of underlying indolent lymphoma, particularly follicular lymphoma, when this t(14;18) lymphoma acquires a myc translocation. In one retrospective series, 21% of transformed follicular lymphomas were double hit lymphomas, emphasizing the importance of incorporating FISH testing for myc rearrangement into the diagnostic algorithm for this group of patients.

**How do I evaluate patients with double hit lymphoma?**

Patients with double hit lymphoma should undergo routine staging procedures including baseline functional and anatomic imaging with PET/CT scans, bone marrow aspirate and biopsy, as well as serum testing for LDH, liver and kidney function, HIV and Hepatitis B, and cardiac function evaluation. Patients with myc-rearranged lymphoma have a statistically
significant increased risk of CNS involvement or relapse in the CNS compared with other patients with diffuse large B-cell lymphoma, even when adjusted for other clinical risk factors of CNS involvement. In an analysis from the British Columbia database, almost 10% of patients with double expressor lymphoma (including a subset with double hit lymphoma) subsequently relapsed in the CNS. For these reasons, unlike the situation with routine DLBCL, I recommend baseline lumbar puncture and CSF sampling in most patients with double hit lymphoma. Exceptions include patients who present with early stage disease where CSF involvement is much less common, or frail elderly patients where treatment with curative intent is contraindicated. When performed, CSF should be always be analyzed with flow cytometry, given substantially increased sensitivity as compared to routine cytological analysis. I do not routinely perform imaging of the brain in patients with double hit lymphoma unless neurological symptoms are present or CSF is positive for malignant cells.

How do I treat patients with de novo double hit lymphoma?

As previously noted, the outcome of patients with double hit lymphoma treated with conventional RCHOP chemotherapy is poor. Unfortunately, there are no published prospective trials in the setting of double hit lymphoma. These patients represent the greatest unmet clinical need in diffuse large B-cell lymphoma according to a recent clinical trials planning meeting from the NCI National Clinical Trials Network, and prospective randomized trials are currently being developed for double hit lymphoma, as well as for the larger group of double expressor lymphoma. Until such trials are completed, it is clear 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 rearrangements are present in Burkitt lymphoma, and Burkitt lymphoma has superior outcomes with more aggressive chemotherapy regimens, several have advocated for a more aggressive “Burkitt-like” approach to patients with double hit DLBCL.

CODOX-M/IVAC is an aggressive pediatric regimen developed for Burkitt lymphoma. In an early prospective trial of a modified CODOX-M/IVAC regimen, there were no long-term responses in four patients with double hit lymphoma. In a larger retrospective series from British Columbia, patients with double hit lymphoma were treated with CODOX-M/IVAC and then considered for consolidation with high dose therapy and autologous stem cell transplantation (ASCT). Although patients who completed the regimen appeared to have favorable outcome over historical controls, only 44% of patients who started remained in remission at 2 years, with early progressions precluding ASCT in 41% of patients.
a subset analysis of the SWOG 9704 study,\textsuperscript{41} which randomized patients to either 8 cycles of R-CHOP or 6 cycles of R-CHOP followed by ASCT, lymphomas with MYC expression were morphologically and phenotypically heterogeneous and were associated with poor progression-free and overall survival in multivariate analysis.\textsuperscript{42} All patients with double hit lymphoma died whether or not they received ASCT.\textsuperscript{43} Finally, in a series of 163 patients treated at 17 United States academic medical centers, patients with double hit lymphoma who achieve complete remission with induction therapy do not appear to benefit from consolidation with high dose therapy and ASCT.\textsuperscript{44} However, for a subset of patients who received induction with RCHOP (rather than a more aggressive regimen) ASCT appeared to prolong progression-free survival.

In another analysis of pooled data from a multicenter retrospective analysis, patients with double hit lymphoma were treated with R-CHOP or “intensive” induction therapy, which included the dose adjusted R-EPOCH regimen, HyperCVAD alternating with methotrexate and cytarabine, or CODOX-M/IVAC. Response rates in this nonrandomized retrospective study were highest for dose-adjusted R-EPOCH. Intensive induction was associated with improved progression-free survival, and improved overall survival on multivariable analysis. A small subset of patients with low LDH and early stage disease had excellent outcomes.\textsuperscript{45} MD Anderson Cancer Center published a similar retrospective study involving 129 patients from their institution. In this study, CNS involvement occurred in 13% of patients. Patients with bone marrow involvement and poor performance status had the worst prognosis. Two-year event-free survival (EFS) rates in patients who received R-CHOP, R-EPOCH, and R-HyperCVAD/MA were 25%, 67% and 32%, respectively.\textsuperscript{46}

Double hit lymphoma is associated with advanced age in many of these retrospective experiences. Therefore, regimens such as CODOX-M/IVAC and HyperCVAD/MA, which are poorly tolerated in elderly patients, are not appropriate for the majority of these patients. The United States Intergroup has completed a prospective single arm study of dose adjusted R-EPOCH therapy for myc driven lymphomas, which included 29 patients with double hit lymphoma. This regimen is better tolerated in older patients as compared to CODOX-M IVAC or ASCT-containing regimens. Preliminary results of the myc rearranged DLBCL group suggest a high overall response rate with few late relapses (Dunleavy, personal communication),\textsuperscript{47} however only 21 patients had double hit lymphoma. Further prospective and ideally randomized trials are needed to definitively conclude that R-EPOCH is superior to RCHOP for double hit lymphoma, particularly in light of the randomized trial in advanced stage DLBCL presented at
ASH demonstrating no differences between the two regimens. Although subset analyses from that trial are ongoing, it is unlikely that there will be a sufficient number of patients with double hit disease on that trial to make definitive conclusions about whether R-EPOCH is truly better than RCHOP. Further support of the R-EPOCH regimen is provided by results from a German randomized trial in younger patients with high-risk aggressive B-cell lymphoma demonstrating high event-free survival with the R-CHOEP-14 regimen, which, similar to R-EPOCH, intensifies treatment interval and incorporates etoposide into the regimen.

Despite the limitations to these data, I currently approach most patients with double hit lymphoma using the dose-adjusted R-EPOCH regimen. I favor this regimen as it is tolerated well in patients under age 80 and has demonstrated improved outcomes compared to historical controls in several retrospective and one small prospective study. I consider adding four cycles of intrathecal methotrexate as CNS prophylaxis, particularly in patients with extranodal disease, high LDH, or other CNS risk factors. Others have advocated for an even more aggressive approach to CNS prophylaxis based upon retrospective analyses. For patients with documented CNS involvement, I place an Ommaya reservoir for more intensive intrathecal therapy, and use more aggressive systemic therapy incorporating high dose methotrexate and high dose cytarabine, alternating this with RCHOP. Should these patients with CNS involvement obtain a remission, I consider consolidation with high dose therapy and ASCT.

Exceptions to the use of dose-adjusted R-EPOCH include patients older than age 80, frail patients, or those with cardiac dysfunction that precludes anthracycline use. For these patients, I use an individualized approach, generally the miniRCHOP regimen, or RCGOP. Finally, for the small subset of patients with limited stage DLBCL who present with double hit lymphoma, but normal LDH, and no other clinical risk factors, I generally approach these patients with a combined modality regimen of RCHOP followed by radiation therapy consolidation as published by SWOG, given favorable prognosis and limited data supporting this approach.

The National Clinical Trials network is planning to conduct a randomized trial for patients with double expressor lymphoma, including double hit lymphoma. In this trial, dose-adjusted R-EPOCH will be the chemoimmunotherapy backbone, demonstrating a consensus across Alliance, ECOG and SWOG lymphoma committees that dose-adjusted R-EPOCH is an appropriate induction option for most patients with double hit lymphoma.
How do I treat patients with double hit lymphoma occurring in setting of transformed follicular lymphoma?

As previously noted, it is not uncommon for patients with follicular lymphoma who experience histologic transformation to acquire a myc translocation, resulting in a double hit lymphoma. There are no trials to guide management of these patients, who again are often elderly, and not infrequently extensively pretreated with various chemotherapy regimens for follicular lymphoma. In patients who have not had prior anthracycline, I generally consider dose-adjusted R-EPOCH as for de novo double hit lymphoma. For the majority of other patients who have had prior anthracycline, I consider a salvage lymphoma regimen followed by ASCT. In several studies of transformed lymphoma, ASCT consolidation appears to provide benefit even in the rituximab era. The benefit of ASCT on patients with double hit transformation has not been established in these studies, but no doubt a subset of patients included in these retrospective analyses of transformed lymphomas had double hit lymphoma at time of transformation.

Relapsed double hit lymphoma, and novel agents

The standard curative approach to the treatment of relapsed aggressive lymphoma in patients who are fit is to administer non cross resistant salvage chemotherapy followed by consolidation with high dose therapy and ASCT. Recent studies have suggested, not surprisingly, that outcomes of salvage chemotherapy and ASCT are poor for patients with myc-rearranged disease. For example, in the BIO CORAL study, patients with double hit disease defined by FISH had extremely poor outcomes with either R-DHAP or R-ICE salvage therapy and ASCT. In a recently published larger series of 117 patients examining the role of ASCT in double expressor and double hit lymphomas, the outcome of patients with double expressor and double hit lymphoma was dismal (4-year PFS, 0%). These results emphasize the importance of dedicated trials including double hit patients in the relapsed setting. Based upon these results, if a patient with double hit lymphoma were treated with intensive induction and still experienced progressive disease, I refer them to a clinical trial involving novel agents rather than try salvage therapy. For patients with relapsed/refractory double hit lymphoma who were treated with RCHOP induction, I consider an attempt at salvage therapy, with plans for clinical trial referral if CR is not obtained.

Novel agents with particular promise in patients with double hit DLBCL may include small molecule inhibitors of BCL-2 such as venetoclax, which has demonstrated in vivo efficacy.
against aggressive myc-driven mouse lymphomas\textsuperscript{64} and has been studied in patients with relapsed lymphoma with limited activity in aggressive histologies.\textsuperscript{65} Bromodomains are conserved protein regions that recognize specific histone modifications. Bromodomain inhibition reduces tumor growth in lymphomas, in part through the disruption of myc-driven transcriptional networks.\textsuperscript{66} The small molecule JQ1 suppresses c-MYC expression through inhibition of the bromodomain and extra-terminal family of bromodomain proteins. JQ1 treatment significantly suppressed growth of DLBCL cells engrafted in mice including myc rearranged DLBCL,\textsuperscript{67} and several bromodomain inhibitors are currently under study in myc associated lymphomas. Synergy has been demonstrated when venetoclax is combined with JQ1 in vitro.\textsuperscript{68} Finally, anti CD-19 CAR-T cells have been demonstrated to have significant clinical activity in patients with highly refractory DLBCL\textsuperscript{69-71}, and have promise in patients with refractory double hit lymphoma. At present, I consider a trial of CAR-T cells a preferred option for fit patients with refractory double hit lymphoma.

**Conclusion: Decisions on Cases**

For the patient presented in the first case, given the triple hit status and retrospective studies suggesting a benefit to “aggressive” induction approaches, I would advise that the patient be switched to dose adjusted R-EPOCH for subsequent cycles. He should receive a total of 6 cycles of induction therapy, with appropriate dose-escalations as mandated in the original publications of R-EPOCH.\textsuperscript{72} I would sample the CSF and plan prophylaxis with intrathecal methotrexate for four cycles if CSF were negative. I would restage him with a PET/CT scan at completion of treatment, and, presuming he achieves a complete remission, follow him without consolidation or transplantation. Given the high risk nature of the bone destruction, I would immediately consult with an orthopedic surgical oncologist to ensure there is stability and no rod placement is indicated.\textsuperscript{73} Finally, I would consider radiation therapy\textsuperscript{74} as consolidation given the destructive bulky mass and morbidity associated with local recurrence.

For the patient in the second case, he was started on appropriate induction therapy for double hit lymphoma with dose adjusted R-EPOCH. At baseline, CNS risk score was high given renal involvement and high risk IPI.\textsuperscript{51} There is now evidence of leptomeningeal involvement given documented malignant cells in the CSF. As previously noted, this is a common site leading to treatment failure in double hit lymphoma, and unfortunately his expected outcome is poor. Given the positive CSF, I would fully stage the CNS with MRI of brain and spinal cord. I would place an Ommaya reservoir to facilitate frequent intrathecal therapy with methotrexate, with a goal of achieving a negative CSF as quickly as possible. Dose-adjusted R-EPOCH does not
adequately penetrate the CNS. There is inadequate data to guide management for this uncommon, high risk scenario. A recently published phase two study demonstrated efficacy of high dose methotrexate and cytarabine, followed by intensification and high dose therapy and ASCT for secondary CNS lymphoma.\textsuperscript{75} Thirty eight patients were enrolled; only 20 were able to proceed to ASCT, but outcome in this subgroup was favorable. Double hit status was not reported. These results are similar to another phase 2 trial incorporating thiotepa into ASCT after aggressive salvage therapy.\textsuperscript{76} Based upon these experiences, I would alternate the high dose methotrexate/cytarabine combination with the remaining cycles of dose-adjusted R-EPOCH, and then consider consolidation with high dose therapy and ASCT using thiotepa based conditioning.\textsuperscript{75}

**Authorship**

JWF analyzed the literature and wrote the manuscript.

The author declares no competing financial interests.
Table 1: Terminology of myc-associated disease

“**Double Hit**”: high grade lymphoma with rearrangements of myc and bcl-2 or myc and bcl-6. These must be diagnosed with FISH, or more advanced genomic techniques.

“**Triple Hit**”: high grade lymphoma with rearrangements of myc and bcl-2 and bcl-6. These must be diagnosed with FISH, or more advanced genomic techniques.

“**Double expressor**”: protein expression of myc and bcl-2 and/or bcl-6. These are measured using an immunohistochemistry cut-off for percentage of positive cells.
Figure legends

**Figure 1:** New WHO classification of lymphoma. Regardless of morphology, if myc and bcl-2 rearrangements are present, these are now categorized as high grade b-cell lymphoma with myc and bcl-2 and/or bcl-6 rearrangements.

**Figure 2:** Myc and Diffuse large B-cell lymphoma. Approximately one third of DLBCLs are positive for myc and bcl-2 by immunohistochemistry (double expressor); most of these occur in ABC DLBCL. The new WHO category of high grade B-cell lymphoma with myc and bcl2 and/or bcl-6 rearrangements (double hit) usually, but not always falls in the double expressor group, but in GCB subtype. Additionally, morphology of this group may include Burkitt-like.
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Figure 1:
BL=Burkitt lymphoma, DLBCL=diffuse large b-cell lymphoma, NOS=Not otherwise specified.
Adapted from Swerdlow et al, Blood 127:2375-90, 2016
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