How I treat double-hit lymphoma

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The 2016 revision of the World Health Organization (WHO) classification for lymphoma 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 <10% of cases of diffuse large B-cell lymphoma, have been referred to as double-hit lymphomas (or triple-hit lymphomas if all 3 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, by using variable cutoff percentages to define positivity. Patients with 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 the transformation of the underlying indolent lymphoma. There are no published prospective trials in double-hit lymphoma, however retrospective studies strongly suggest that aggressive induction regimens may confer a superior outcome. In this article, 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. (*Blood*. 2017; 130(5):590-596)

Case presentation 1

A 53-year-old man presents with a 2-month history of left hip pain. He did not respond to initial conservative management, including rest and physical therapy. Magnetic resonance imaging (MRI) of the left hip was eventually performed and showed a destructive, enhancing lesion involving the left iliac wing, acetabulum, and pubic ramus, measuring 8 × 7 × 7 cm. Computed tomographic (CT) scan of the 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 finding was consistent with diffuse large B-cell lymphoma (DLBCL), stage IVA. Clinical risk factors included high-stage, high-LDH, and extranodal disease; performance status was normal, making this high intermediate-risk disease based on 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; the 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, fluorescence in situ hybridization (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 that 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*. Positron emission tomography (PET)/CT demonstrated a large hypermetabolic mass in the 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 Eastern Cooperative Oncology Group 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 R-EPOCH therapy (rituximab, etoposide, prednisone, vincrstine, cyclophosphamide, and doxorubicin), and tolerated 2 cycles well. A lumbar puncture for planned prophylaxis with intrathecal methotrexate was performed as part of cycle 3, and the results of cerebrospinal fluid (CSF) analysis revealed the presence of large lymphoid forms with a high nuclear/cytoplasmic ratio, fine chromatin, and vacuoles, which were confirmed as clonal on flow cytometry, consistent with central nervous system (CNS) involvement by high-grade B-cell lymphoma with *myc* and *bcl-2* rearrangements.

Introduction: Myc-associated lymphoma

c-Myc 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,

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gene amplification, and chromosomal translocation.[3] The *c-myc* gene translocation with an immunoglobulin gene is the genetic hallmark of Burkitt lymphoma (BL) and is required to make this diagnosis.[4,5]

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 utilize 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.[6,7] These clinical factors largely represent surrogates for genetic and molecular factors within the tumor. Cell-of-origin studies have revealed at least 3 major subtypes of DLBCL: activated B-cell (ABC), germinal center B-cell (GCB) and primary mediastinal B-cell; these subtypes not only constitute unique molecular entities, but also have differential clinical outcomes using modern therapy.[8] 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.[9]

c-MYC protein expression is increased in up to one-third of cases of DLBCL, suggesting that changes in myc may be an important secondary transforming event. By 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 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) therapy.[10] Twenty-nine percent of cases had high expression of MYC and BCL-2 (an antiapoptotic 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.[11] In the training cohort, concurrent expression of MYC (defined as ≥40% 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 DLBCL patients treated with R-CHOP.[12] 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 the ABC subtype was largely driven by the 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 2 recent German prospective randomized trials in DLBCL, cell-of-origin determination failed to identify prognostic subgroups, whereas dual expression of MYC and BCL2 was highly predictive of poor survival.[13]

A lower number of patients present with DLBCL with an underlying translocation of *c-myc*. Patients with such a translocation have demonstrated particularly poor outcomes in several retrospective series. Barrans and colleagues[14] reviewed 303 patients with previously untreated, de novo DLBCL, treated with standard R-CHOP therapy. The overall survival was worse for the 14% of patients with the *myc* rearrangement, with a 2-year overall survival rate of 35% for those with a translocation compared with 61% for those in the non-rearranged group. Similarly, the British Columbia Cancer Agency evaluated 135 patients with DLBCL treated with R-CHOP.[15] The 5-year overall survival rate 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,[16] conferring a particularly poor outcome when these 2 translocations occur simultaneously.[17,18] Similarly, in a German trial of a more aggressive chemotherapy platform incorporating etoposide (R-MegaCHOEP [rituximab, high dose cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone]), 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.[19] Simultaneous translocations involving both *myc* and *bcl-6* also appear to confer poor prognosis in patients treated with R-CHOP.[20]

Table 1. Terminology of myc-associated disease

Double-hit	High-grade lymphoma with rearrangements of *myc* and *bcl-2* or *myc* and *bcl-6*; 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*; must be diagnosed with FISH or more advanced genomic techniques.
Double-expressor	Protein expression of MYC and BCL-2 and/or BCL-6; measured by using an immunohistochemistry cutoff for the percentage of positive cells.

In recognition of these data, the 2016 revision of the WHO classification for lymphoma has included a new category of lymphoma, separate from DLBCL, termed high-grade B-cell lymphoma with translocations involving *myc* and *bcl-2* or *bcl-6*.[21] These cases have been more often referred to as double-hit lymphoma (when *myc* translocation is present with either the *bcl-2* or *bcl-6* translocation) or triple-hit lymphoma (when all 3 translocations are present), as noted in Figure 1 and Table 1.[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, and the remaining cases are triple-hit lymphomas.[23] Finally, the specific translocation partner of myc impacts outcome, with immunoglobulin gene translocations conferring the shortest survival time.[24]

In this article, I 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 article focuses on double-hit lymphomas (requiring translocations of myc and either *bcl-2* or *bcl-6* detected usually by FISH) and 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 is 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 that suggest limiting FISH testing include restricting the testing to those lymphomas that are of the 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 the MYC protein by immunohistochemistry.[25]

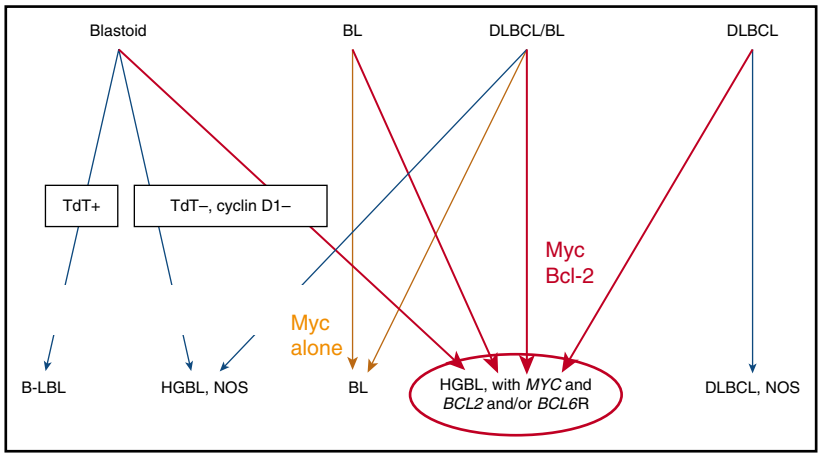

Figure 1. New WHO classification of lymphoma. Regardless of morphology, if *myc* and *bcl-2* rearrangements are present, they are now categorized as high-grade B-cell lymphoma with *myc* and *bcl-2* and/or *bcl-6* rearrangements. HGBL, high-grade B-cell lymphoma; NOS, not otherwise specified. Adapted from Swerdlow et al.[21]

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.[25] Importantly, the cell of origin was determined by using the Lymph2Cx assay[26] in this analysis rather than an immunohistochemistry algorithm, which is most commonly used in the clinic.[8] Given the 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 the cell of origin.

There are similar limitations to using the 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 that were double-hit lymphomas. MYC-positive DLBCL showed higher median Ki-67 fraction (>90%) and CD10 positivity (as a surrogate for GCB) as compared with MYC-negative cases.[27] The authors recommended a cutoff value of ≥30% for MYC by immunohistochemistry; however, this has not been validated, and there are reports of cases of *myc*-rearranged lymphoma that are below that threshold for protein 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.[28] 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 of the GCB subtype (Figure 2) and express MYC on immunohistochemistry, so limiting testing to this group is an acceptable, but inferior alternative.[29]

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.[30] In a retrospective series, 21% of transformed follicular lymphomas were double-hit lymphomas,[31] 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.[32] Patients with *myc*-rearranged lymphoma have a statistically significant increased risk of CNS involvement or relapse in the CNS compared with other patients with DLBCL, even when adjusted for other clinical risk factors of CNS invovlement.[15] In an analysis from the British Columbia database, ~10% of patients with double-expressor lymphoma (including a subset with double-hit lymphoma) subsequently relapsed in the CNS.[33] 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 always be analyzed with flow cytometry, given its substantially increased sensitivity as compared with routine cytological analysis.[34] 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.

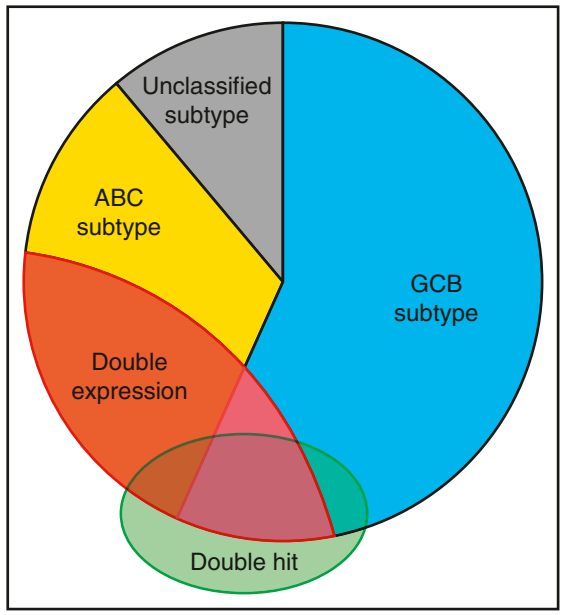

Figure 2. Myc and DLBCL. Approximately one-third of DLBCLs are positive for myc and bcl-2 by immunohistochemistry (double expressor); most of these occur in ABC DLBCL. The new WHO category of high-grade B-cell lymphoma with *myc* and *bcl-2* and/or *bcl-6* rearrangements (double hit) usually, but not always, falls in the double-expressor group, but in the GCB subtype. Additionally, morphology of this group may include Burkitt-like lymphoma.

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 DLBCL according to a recent clinical trials planning meeting from the National Cancer Institute 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.[35] Until such trials are completed, it is clear that R-CHOP is not sufficient induction therapy for this group of patients, because the majority of patients will experience disease progression after standard treatment. Because myc rearrangements are present in BL, and BL has superior outcomes with more aggressive chemotherapy regimens,[4,36] several study groups have advocated for a more aggressive "Burkitt-like" approach to patients with double-hit DLBCL.

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine) is an aggressive pediatric regimen developed for BL.[37] In an early prospective trial of a modified CODOX-M/IVAC regimen, there were no long-term responses in 4 patients with double-hit lymphoma.[38] 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 outcomes over historical controls, only 44% of patients who started the regimen remained in remission at 2 years, with early progressions precluding ASCT in 41% of patients.[39] Similarly, in a subset analysis of the SWOG 9704 study,[40] which randomized patients to undergo 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.[41] All patients with double-hit lymphoma died whether or not they received ASCT.[42] Finally, in a series of 163 patients treated at 17 US academic medical centers, patients with double-hit lymphoma who achieved complete remission with induction therapy did not appear to benefit from consolidation with high-dose therapy and ASCT.[43] However, for a subset of patients who received induction with R-CHOP (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/MA fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, 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.[44] The 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 rates in patients who received R-CHOP, R-EPOCH, and R-HyperCVAD/MA were 25%, 67%, and 32%, respectively.[45]

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 US Intergroup has completed a prospective single-arm study of dose-adjusted R-EPOCH therapy in 52 patients with *myc* rearranged aggressive B-cell lymphomas, of whom 44% had double-hit lymphoma. This regimen is better tolerated in older patients as compared with 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 and equivalent outcomes in single- or double-hit MYC-rearranged DLBCL. (Kieron Dunleavy, George Washington University, e-mail, 19 June 2017, with written permission).[46] Additional prospective and ideally randomized trials are needed to definitively conclude that R-EPOCH is superior to R-CHOP for double-hit lymphoma, particularly in light of the randomized trial in advanced stage DLBCL presented at the 58th annual meeting of the American Society of Hematology demonstrating no differences between the 2 regimens.[47] 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 R-CHOP. 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 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone every 14 days), which, similar to R-EPOCH, intensifies the treatment interval and incorporates etoposide into the regimen.[48]

Despite the limitations of these data, I currently approach most patients with double-hit lymphoma by using the dose-adjusted R-EPOCH regimen. I favor this regimen because it is tolerated well in patients $<$80 years old[49] and has demonstrated improved outcomes compared with historical controls in several retrospective and 1 small prospective study. I consider adding 4 cycles of intrathecal methotrexate as CNS prophylaxis, particularly in patients with extranodal disease, high LDH, or other CNS risk factors.[50] Others have advocated for an even more aggressive approach to CNS prophylaxis based on retrospective analyses.[51] For patients with documented CNS involvement, I place an Ommaya reservoir for more intensive intrathecal therapy and use more ag-gressive systemic therapy incorporating high-dose methotrexate and high-dose cytarabine, alternating this with R-CHOP. 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 $>$80 years old, frail patients, or those with cardiac dysfunction that precludes anthracycline use. For these patients, I use an individualized approach, generally the miniRCHOP regimen[52] or RCGOP (rituximab, cyclophosphamide, gemcitabine, vincristine, prednisone).[53] 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 R-CHOP followed by radiation therapy consolidation as published by SWOG,[54] given the favorable prognosis and limited data supporting this approach.[55]

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 the Alliance, Eastern Cooperative Oncology Group, 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 the 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 the 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.[30] In several studies of transformed lymphoma, ASCT consolidation appears to provide benefit even in the rituximab era.[56-58] 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 the 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.[59] 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 (rituximab, dexamethasone, high dose cytarabine, cisplatin) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) salvage therapy and ASCT.[60] 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 progression-free survival, 0%).[61] These results emphasize the importance of dedicated trials, including double-hit patients in the relapsed setting.[62] Based on these results, if a patient with double-hit lymphoma were treated with intensive induction and still experienced progressive disease, I would refer them to a clinical trial involving novel agents rather than try conventional 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 complete remission 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[63] and has been studied in patients with relapsed lymphoma with limited activity in aggressive histologies.[64] 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.[65] The small molecule JQ1 suppresses c-*MYC* expression through inhibition of the bromodomain and extraterminal family of bromodomain proteins. JQ1 treatment significantly suppressed growth of DLBCL cells engrafted in mice, including myc-rearranged DLBCL,[66] and several bromodomain inhibitors are currently under study in myc-associated lymphomas. Synergy has been demonstrated when venetoclax is combined with JQ1 in vitro.[67] Finally, anti–CD19 chimeric antigen receptor T cells have been demonstrated to have significant clinical activity in patients with highly refractory DLBCL[68-70] and have promise in patients with refractory double-hit lymphoma. At present, I consider a trial of chimeric antigen receptor 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 on R-EPOCH.[71] I would sample the CSF and plan prophylaxis with intrathecal methotrexate for 4 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.[72] Finally, I would consider radiation therapy[73] 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, his CNS risk score was high given the renal involvement and high-risk International Prognostic Index score.[50] There is now evidence of leptomeningeal involvement given the 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 an MRI of the brain and spinal cord. I would place an Ommaya reservoir to facilitate frequent intrathecal therapy with methotrexate, with the 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 the management of this uncommon, high-risk scenario. A recently published phase 2 study demonstrated the efficacy of high-dose methotrexate and cytarabine, followed by intensification, high-dose therapy, and ASCT for secondary CNS lymphoma.[74] Thirty-eight patients were enrolled; only 20 were able to proceed to ASCT, but the 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.[75] Based on 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.[74]

Authorship

Contribution: J.W.F. analyzed the literature and wrote the manuscript.

Conflict-of-interest disclosure: J.W.F. declares no competing financial interests.

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