Current treatment of double hit and double expressor lymphoma

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A 60-year-old female presented with abdominal pain and distension. Following computed tomography scans of the abdomen and pelvis, she was taken urgently to the operating room, with the belief that she had appendicitis with perforation. At laparotomy, the findings were consistent with an ovarian carcinoma; there was extensive infiltration of the ovary, bowel, and omental deposits. Cytoreductive surgery was performed including total abdominal hysterectomy and bilateral salpingo-oophorectomy. The final pathology, however, revealed infiltration with medium-sized atypical lymphoid cells positive for CD20, CD10, MYC, BLC2, and BCL6 by immunohistochemistry. *MYC* and *BCL2* translocations were identified by fluorescence in situ hybridization consistent with a diagnosis of high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2*. With the current data available, what is the optimal treatment of this patient?

Learning Objectives

- Understand induction and transplant for double hit lymphomas
- Understand high risk of central nervous system involvement with double hit lymphomas

Introduction

Diffuse large B-cell lymphoma (DLBCL) is heterogeneous in pathologic characteristics, biology, and clinical behavior. Despite the heterogeneity of DLBCL, the standard treatment of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemoimmunotherapy has remained uniform across these varied subtypes. Aberrations of *MYC*, particularly concomitant genetic rearrangements of *MYC*, *BCL2*, and or *BCL6,* are associated with poor outcomes in the rituximab era.[1] These lymphomas have been referred to as double hit lymphomas (DHLs), and, in recognition of their unique biology and clinical behavior, the 2016 revision of the World Health Organization classification of lymphoid neoplasms has included a new category of high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*. It is important to differentiate these DHLs from double expressor lymphomas (DELs). DELs are defined as DLBCL with increased expression of MYC and BCL2 proteins by immunohistochemistry, in the absence of detectable translocation by fluorescence in situ hybridization (FISH). They do not form a distinct clinicopathological entity in the revised World Health Organization classification, but serve as markers for poor outcomes in DLBCL in the rituximab era. The magnitude of this association appears to be less than that with DHL. Additionally, the tumor biology is different with more DEL that have gene expression profiles that are consistent with the activated B-cell subtype, whereas those with translocations are of the germinal center B-cell subtype.[2]

These differences are relevant to the future planning of studies and the approach to the patient in the clinic. Currently, there is a lack of mature, prospective data guiding the treatment of DHL, and the current literature consists of retrospective series.

The identification of an effective, safe induction regimen is an unmet need in our field. Outcomes with various induction regimens such as R-CHOP, as well as intensive induction regimens including rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine (R-HyperCVAD/MA); rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide cytarabine (R-CODOX-M/IVAC); and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA EPOCH-R) have been reported in retrospective series (Table 1).[3-5] A multicenter study conducted by Petrich et al reported on a group of patients who received various induction regimens, including each of the regimens listed here. The intensive induction regimens had a higher rate of complete response (CR) and were associated with improved progression-free survival (PFS), although not overall survival (OS).[3] Similarly, a single-center experience reported by Oki et al demonstrated higher rates of CR in patients who received DA EPOCH-R or R-HyperCVAD compared with R-CHOP. Despite the improved CR rates in both intensive therapy groups, only the DA EPOCH-R group had an improved event free-survival and OS when compared with R-CHOP.[4]

A recently published multicenter analysis of patients who achieved CR also revealed that intensive induction regimens were associated with improved relapse-free survival and OS when compared with R-CHOP.[5] In a meta-analysis of multiple retrospective reports, a decrease in the risk of progression was associated with treatment with DA EPOCH-R when compared with R-CHOP; however, there was no difference in

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Table 1. Review of regimens for the treatment of DLBCL and high-grade B-celllymphoma

Study	Design	Sample size by treatment	Outcome
Petrich et al[3]	Retrospective, multicenter	R-CHOP (n = 100) R-HyperCVAD (n = 65) DA EPOCH-R (n = 64) R-CODOX-M/IVAC (n = 42) Other (n = 40)	Median PFS: R-CHOP: 7.8 mo Intensive regimens including R-HyperCVAD, DA EPOCH-R, and CODOX-M/IVAC: 21.6 mo; $P = .0463$ Median OS: No difference between regimens
Oki et al[4]	Retrospective, single center	R-CHOP (n = 57) R-HyperCVAD/MA (n = 34) DA EPOCH-R (n = 28) R-CODOX-M (n = 2) Other (n = 8)	CR: R-CHOP 40%; R-EPOCH 68%; R-HyperCVAD/MA 68% EFS: R-EPOCH vs R-CHOP HR of 0.37 (0.18-0.77; $P = ..008$) R-HyperCVAD/MA vs R-CHOP HR 0.61 (0.36-1.05; $P = .074$) OS: R-EPOCH vs R-CHOP HR of 0.47 (0.19-1.14; $P = .96$) R-HyperCVAD/MA vs R-CHOP HR of 0.67 (0.37-1.21; $P = .187$)
Howlett et al[6]	Meta-analysis	R-CHOP (n = 180) DA EPOCH-R (n = 91) Dose-intensive treatment including R-HyperCVAD/MA and R-CODOX-M/IVAC (n = 123)	Median PFS: R-CHOP 12.1 mo DA EPOCH-R 22.2 mo Dose intensive 18.9 mo Relative risk reduction for progression of 34% for DA EPOCH-R compared with R-CHOP ($P = .032$) Insignificant relative risk reduction of 26% for dose intensive treatments vs R-CHOP ($P = .088$)

CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, and etoposide cytarabine; EFS, event free-survival.

OS.[6] The currently available literature suggests that intensive induction regimens have been associated with a higher rate of CR and in some instances with improved PFS and OS. Although there is consistency between various large cohorts of patients in the literature, the retrospective nature of the data is problematic. A major concern with the data is that confounding factors such as patient fitness, age, and comorbidities cannot be addressed through randomization. The Cancer and Leukemia Group B/Alliance Group phase 3 study comparing DA-EPOCH-R to R-CHOP[7] reported no difference in overall and CR rates between arms. There was no difference in the primary end point of event-free survival (hazard ratio [HR] = 1.14 [0.82-1.61], $P = .4386$) at a median follow-up of 5 years and OS was not significantly different (HR = 1.18 [0.79-1.77], $P = .42$) between regimens (R-CHOP 85% vs DA-EPOCH-R 85% at 3 years). However no biomarker data have been presented to date, so these prospective findings may not apply to those patients with DHL or DEL. For the DEL population, there are no results from interventional studies focused on this population as yet, but it is a high priority for clinical investigation.

Consolidation with either autologous or allogeneic stem cell transplant following induction treatment is of interest given the highly aggressive nature of DHL and improved outcomes associated with intensive chemoimmunotherapy regimens. In the multicenter, retrospective series by Petrich et al, there was no OS benefit in those who received a transplant after induction chemoimmunotherapy.[3] In the cohort of patients who achieved CR to induction, there was not an appreciable benefit to a consolidative treatment either.[5] Patients treated with R-CHOP and consolidated with high-dose chemotherapy autologous stem cell rescue, however, had a similar outcome to those treated with intensified regimens. Given the lower rates of remission induction with R-CHOP, this does not present the optimal path to best outcomes.

Consolidation with transplant after salvage chemoimmunotherapy is the current practice in patients with relapsed and refractory DHL; however, the literature suggests that relapsed and refractory DHL patients derive very little benefit from this standard of care.[8,9] Analysis on the impact of *MYC*, *BCL2*, and *BCL6* rearrangements was performed on a subgroup of subjects enrolled onto the Cardiovascular Outcomes in Renal Atherosclerotic Lesions study who had tissue available to study. The subjects with *MYC* rearrangement alone, as well as those with *BCL2* and/or *BCL6* rearrangements, did very poorly with a 4-year PFS of $<20\%$.[8] A recent retrospective series detailing the outcomes of patients with patients with relapsed DLBCL undergoing autologous stem cell transplant was reported by Herrera et al. DHL represented the minority of cases in this series, with only 10% of the cases. In the group of patients who retained sensitivity to chemotherapy, the 4-year OS of DHL patients was 28% compared with 57% in patients who did not have DHL.[9] These studies highlight how ineffective standard salvage and consolidation with transplant is in DHL. An important point is that a substantial fraction of DHL patients are refractory to chemoimmunotherapy and are not eligible for a consolidative transplant.

One adverse clinical feature of particular concern DHL is the high rate of central nervous system (CNS) involvement. Patients can present with concomitant systemic and CNS involvement with DHL, or develop CNS involvement at the time of relapse. Various studies have reported on the rates of CNS involvement; these have varied from 7% to 10% at diagnosis in those who were screened for CNS involvement.[3,4] Because CNS screening was left to the discretion of the investigator, these may be underestimates. The development of CNS involvement, whether at the time of initial presentation or at relapse, has been associated with a poor prognosis.[3,4] The CNS international prognostic index (IPI) is a useful clinical tool to predict the risk for CNS relapse in patients with aggressive lymphomas. This is based on retrospective analysis of large datasets that identified the components of the traditional IPI score as well as kidney or adrenal involvement as factors associated with the development of CNS

relapse. In the high-risk group, the rate of CNS relapse at 2 years is approximately 10%.[10] Although *MYC*, *BCL2*, and *BCL6* translocation status was not included as part of this analysis, based on retrospective series, many of the DHL patients would be considered high risk based on traditional IPI risk factors.[3-5] The dose, route, and duration of prophylaxis for CNS disease are not well defined, nor is the treatment of patients with active CNS disease. Intensive induction incorporating high-dose methotrexate and cytarabine followed by consolidation with thiotepa-based high-dose chemotherapy with autologous stem cell support is a reasonable consideration in this high-risk group based on a prospective study of aggressive lymphomas with secondary CNS involvement. Limitations of this approach include that only one-half of the registered patients made it to transplantation and that the rate of DHL in the study is unknown.[11] The benefit of transplant in this situation remains unknown. R-HyperCVAD/MA is another reasonable induction strategy based on its activity in DHL and the CNS penetration of methotrexate and cytarabine.[3-5] Research efforts are needed to explore optimal prophylaxis and treatment strategies for these patients.

Given the prognostic value and potential need for a change in therapeutic approach, FISH analysis for *MYC* should be performed on all patients with DLBCL.[12] If a *MYC* translocation is identified, FISH should be used to identify the immunoglobulin partner and the presence of *BCL2* and *BCL6* rearrangements. Although acknowledging the relatively weak, retrospective evidence base, we do strongly recommend treatment with a dose-intensive chemoimmunotherapy regimen in patients who are eligible for this approach (grade IC recommendation). We typically treat fit patients with DA EPOCH-R and do not offer consolidative transplantation in first remission. Of note, however, many patients with DHL may be older and unfit for intensified regimens. We do routinely screen for CNS involvement with lumbar puncture and provide patients with no evidence of CNS disease with intrathecal methotrexate prophylaxis. The management of patients with relapsed and refractory disease is quite challenging given the aggressive clinical behavior of DHL. Novel, effective treatments are a research priority in relapsed and refractory DHL, and clinical trials should be considered. Optimizing induction is also a priority for this group of patients and requires further study. It is our opinion that patients would be best served through treatment on well-designed, prospective trials that incorporate rational, targeted therapies into dose-intensive chemoimmunotherapy backbones.

Our patient was treated with 6 cycles of DA EPOCH-R. She was successfully escalated to dose level 3 and received CNS prophylaxis with intrathecal methotrexate. An end of treatment, positron emission tomography computed tomography scans were consistent with a complete metabolic response to therapy. She was not offered consolidation with stem cell transplant and will be observed.

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