Practical Hematologist

Frontline Treatment of DLBCL: Practice Implications

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In the last article of **this series**, Dr. Zelenetz addresses frontline treatment of patients with the most common lymphoma, diffuse large B-cell lymphoma (DLBCL). This discussion includes key data from recent publications and conferences, and emerging frontline approaches for the treatment of DLBCL, as well as current and possible future practice implications.

TAKE-HOME MESSAGES

- R-CHOP is the international standard of care in the first line treatment of DLBCL
- Substitution of polatuzumab-vedotin for vincristine improves progression-free survival by 6%
    - With follow-up to date, there is no impact on overall survival
    - In the subset analyses, it appears that the benefit is restricted to the activated B-cell DLBCL
- Though the Phoenix trial was negative, younger patients had superior overall survival
    - Addition of ibrutinib to R-CHOP was not well tolerated in older patients
    - Several trials are underway to determine whether there is a subset of activated B-cell DLBCL that should be treated with Bruton tyrosine kinase inhibitors (BTKis)

Classification

The WHO classification of lymphoid neoplasms was last updated in 2016 but is currently under revision and will be similar to the International Consensus Classification that was recently published.[1,2]There have been several changes, including the reclassification of lymphocyte-predominant Hodgkin lymphoma as nodular lymphocyte-predominant B-cell lymphoma because it appears to have no relationship to classical Hodgkin lymphoma.

Early-stage disease

According to Dr. Zelenetz, the early-stage algorithm is pretty straightforward. If it is a primary mediastinal B-cell lymphoma (PMBL), the treatment is dose-adjusted EPOCH. He mentioned that at Sloan Kettering, a sequential regimen of R-CHOP, followed by ICE or R-ICE, is used with similar outcomes.

If a patient presents with DLBCL, stage-modified IPI 0 without bulky disease treatment with short course R-CHOP without radiation therapy is appropriate in cases with a PET negative complete response. If the PET scan demonstrates a partial response, involved site radiation is indicated. Patients with stage-modified IPI 1 (age > 60, elevated LDH, Stage II disease, or a performance status of ≥2), are treated with 4 cycles of R-CHOP, followed by a PET scan, then 2 more cycles of R-CHOP. If the PET scan at cycle 4 is positive, consolidation with radiation is needed, but this can be avoided if the PET scan is negative.[3] Patients with bulky disease should be treated similar to patients with advanced-stage disease and should receive involved site radiation therapy.[3]

Advanced stage disease: Standard therapy

Standard of care for advanced disease, is, as per NCCN guidelines, R-CHOP.[3] This is based on the original GELA study, confirmed in multiple randomized studies, and with very long-term follow-up.[4,5] R-CHOP provides superior progression-free survival (PFS) and a long-term overall survival (OS) advantage, even many years after the completion of therapy. This is the international standard of care, and results in a cure for close to 60% of patients with advanced stage large cell lymphoma. However, 40% of patients are not cured by this approach.

Improving on R-CHOP-21: Alternative Dosing and Regimens

Adding etoposide to CHOP unfortunately did not improve either PFS or OS. An alternative chemotherapy schedule, with rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP), followed by sequential consolidation therapy with 2 courses of high dose methotrexate, 4 courses of etoposide and ifosfamide, and 2 courses of cytosine-arabinoside subcutaneously, is, according to Dr. Zelenetz, one of the most ignored results since there was not only an advantage in PFS, but also OS.[6] However, there is a major caveat. Only young patients (18 to 59 years old) and patients with an international prognostic score of 1 were included. In addition, the protocol included vindesine, but most patients, even in France, receive vincristine when treated with this regimen.

R-CHOP-14 was an attempt to improve outcomes by giving more of the same. Unfortunately, two separate studies were negative for both PFS and OS.[7,8] The next attempt was to give obinutuzumab rather than rituximab, with negative results as well.[9] And finally, dose-adjusted EPOCH, same results.[10]

Improving on R-CHOP-21: Maintenance After Induction with R-CHOP-like Therapy

Several different approaches have been explored. Adding rituximab to maintenance did not result in a survival benefit. Enzastaurin, lenalidomide, and everolimus have all been tried without consistent benefits for both PFS and OS. A meta-analysis compared all these trials and did not show an overall survival benefit.[11]

Improving on R-CHOP-21: R-CHOP + X

The next idea was to add another drug to R-CHOP-21 (R-CHOP given every 21 days). Bortezomib, based on molecular studies, should have been superior for patients with activated B-cell tumors (ABC). Thus, patients received one cycle of R-CHOP while their tumors were tested, and if they were found to have ABC tumors, were randomized to receive bortezomib or not. Unfortunately, there was no difference in PFS or OS when initially presented; however, the 5-year update presented at ASH 2022 demonstrated an OS benefit (HR 0.58) for the patients treated with RB-CHOP.[12]

The PHOENIX trial of R-CHOP plus ibrutinib was also negative for both PFS and OS, but there was a clear OS advantage for patients under the age of 60. The failure to see benefit in older patients was likely related to the toxicity rather than a different biology. [13] Lenalidomide was supposed to be preferentially active for non-germinal center (NGC) tumors, but a large randomized study showed no difference in PFS or OS. ECOG performed a phase II randomized study which showed a small advantage in PFS but not for OS.[14]

A phase I/II study in which venetoclax was added to R-CHOP, done as a matched case control to historical data, showed an OS advantage in BCL2-expressing tumors, but this needs to be confirmed in a prospective randomized study.[15,16]

Recently, the addition of polatuzumab to CHOP has been studied. Polatuzumab vedotin is an antibody-drug conjugate that targets the B cell protein CD79B. It delivers auristatin, or MMAE, to the tumor. After binding to CD79B it is endocytosed and the drug is released from the antibody, creating a very potent microtubular disruption. A study in relapsed/refractory disease using bendamustine or rituximab with or without polatuzumab, showed both a PFS and OS advantage, and this led to the approval of polatuzumab for the relapsed/refractory setting.[17] The subsequent first-line trial (POLARIX) of R-CHOP compared with R-CHP + polatuzumab, was a large study of almost 900 patients with a median follow-up of 28 months, and it showed a 6% improvement in PFS but so far no difference in OS.[18]

Applied Biology: Bruton Tyrosine Kinase Inhibitors (BTKi) in DLBCL

In an initial multi-center study, ibrutinib was beneficial for people with activated B-cell tumors, and in particular, people who had mutations of CD79D or MYD88.[19] Interestingly, some DLBCLs are "hyper-addicted" to the BTK-driven pathway, representing about 10% of nodal-activated B-cell lymphomas, but about 37% of primary central nervous system lymphomas, and a large proportion of testicular and extranodal leg lymphomas.

The primary endpoint in the PHOENIX trial mentioned above was PFS, and overall, there was no difference in patients with NGC tumors between ibrutinib and placebo. However, there was an unplanned subset analysis which showed a big difference in PFS as well as OS for younger patients (<60 years old).[13] Analysis of biopsies revealed 3 previously characterized genetic subtypes of DLBCL: MCD (a genetic subset of ABC-DLBCL with gain-of-function mutations in both MYD88 and CD79B), BN2 (based on BCL6 fusions and NOTCH2 mutations), and N1 (based on NOTCH1 mutations).[20,21] There appears to be an age difference in types of tumors, with older patients more likely to have MCD tumors, less likely to have N1 or BN2 tumors.[19] The 3-year event-free survival of younger patients (age≤60) treated with ibrutinib plus R-CHOP was 100% in the MCD and N1 subtypes, and the outcome with R-CHOP alone was significantly inferior (42.9% and 50%, respectively). But, as Dr. Zelenetz pointed out,

> **Both of these groups, MCD and N1 are more frequent in older patients, but when we do the same analysis for older patients, we actually see a poor outcome for ibrutinib in the MCD patients. I think it's toxicity, not biology. We have to figure out how to make these treatments safer to derive the benefit for older patients.**

The question of how to integrate BTK inhibitors is currently the topic of several trials, most of them looking at combinations of R-CHOP and acalabrutinib.

Discussion

Should new subgroups be taken into account outside of a clinical trial when deciding about treatment options for a patient with newly diagnosed DLBC? Dr. Zelenetz answered that although there clearly was a benefit in the post hoc analysis of PHOENIX, this has not yet been incorporated into the clinical routine, partly because it still takes too long to determine these subgroups. Although tempted to offer this to a younger patient with a non-GCB tumor, the insurance company would most likely not give approval due to the overall negative results of the trial.

The next question was whether there were any subgroups other than people with a mediastinal tumor or a tumor with a Burkitt-like proliferative factor, where R-EPOCH would be a consideration? Dr. Zelenetz said that in the case of high-grade lymphomas with translocation of *myc* and *BCL2*, or *myc* and *BCL6*, he would treat with dose-adjusted R-EPOCH, although there are no randomized data and no universal consensus.

The one group that I treat a little differently, based on data that has been reported and that you will see in publication hopefully soon, is our regimen of R-CHOP x 4 cycles followed by RICE for 3 cycles, which has been particularly effective for non-GCB DLBCL. In fact, our outcomes in the non-GCB patients are superior with that regimen compared to germinal center tumors.

The R-CHOP treatment can be done as an outpatient with an inpatient admission for the first day of ICE because the infusional ifosfamide can be difficult to administer as an outpatient.

What about the timing and usefulness of interim PET scans? As per Dr. Zelenetz, there is no evidence that changing treatment based on interim PET results is necessary. A positive interim PET does not really predict outcome, and the end-of-therapy PET scan is sufficient, except for patients who have largely osseous- disease invisible by CT, where it can be helpful to make sure they are responding to treatment.

The final question asked was whether, apart from CNS, mediastinal, and testicular disease, an alternative approach should be considered for any other primary sites? Dr. Zelenetz responded that the leg type of DLBCL has a poor outcome with a high risk of CNS involvement. Like testicular and CNS tumors, these are hyper-addicted to the BTK pathway, frequently with MYD88 and CD79 mutations. In these patients he would consider using dose-adjusted EPOCH and possibly enroll them in the ESCALADE trial, a trial that is trying to answer the question of the role of BTK inhibitors in large cell lymphoma.

Summary

In conclusion, R-CHOP is the international standard of care in the first line. Substitution of polatuzumab-vedotin for vincristine improved PFS by 6%, although there was no impact on OS, and the benefit appeared to be restricted to the ABC DLBCL. Although the overall results from the PHOENIX trial were negative, younger patients had superior OS, possibly because the addition of ibrutinib to R-CHOP was not tolerable in older patients. Several trials are currently underway to determine whether a subset of ABC DLBCL should be treated with a BTK inhibitor.

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Provided by MediCom Worldwide, Inc.

This activity is supported by educational grants from Bristol Myers Squibb and Genentech, a member of the Roche Group.

