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Polatuzumab Vedotin for Diffuse Large B-Cell Lymphoma: Innovation's Allure versus a Time-Honored Tradition

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Abstract

Chemotherapy with R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone) is the standard of care for patients with diffuse large B-cell lymphoma as the first-line therapy. The recent approval of polatuzumab as the first-line therapy after demonstration of its efficacy in the Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma (POLARIX) trial is the first significant change in this treatment regimen over two decades. This concise appraisal of trial evidence and clinical context highlights the limited potential for a clinically significant benefit with the addition of polatuzumab to the first-line therapy for this common hematologic malignancy.

Keywords

- hematology
- internal medicine
- pharmacology

Introduction

Approval of rituximab as a part of the first-line combination therapy for diffuse large B-cell lymphoma (DLBCL) in 2006 was an important milestone. It was the first monoclonal antibody approved for cancer that substantially improved the overall response rates and progression-free survival (PFS) compared with conventional chemotherapy alone.[1,2] Since then, the R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone) drugs have continued to be a part of the first-line therapy for CD20-positive lymphomas. Additionally, no newer agents have shown a similar magnitude of benefit in addition to this chemotherapy backbone.[3] This paradigm was challenged in 2022 when polatuzumab vedotin (antibody–drug conjugate targeting CD79b) was proven effective in newly diagnosed patients with DLBCL in the randomized phase 3 POLARIX trial. This trial randomized 879 newly diagnosed patients to R-CHOP or Polatuzumab- Rituximab - Cyclophosphamide - Adriamycin- Prednisolone (Pola-R-CHP). After a median follow-up period of 28.2 months, PFS was higher in the polatuzumab group (76.7 vs. 70.2%), with no difference in response rates or overall survival (OS) at 2 years.[4] Based on these findings, polatuzumab received Food and Drug Administration (FDA) approval as the first-line therapy for DLBCL in 2023—a major change in upfront therapy for DLBCL for the first time in 20 years. However, the finer details of this clinical trial must be carefully reviewed in the context of real-world practice before effecting a change in a regimen that already has extensive and durable data on its safety and efficacy.

The magnitude of benefit noted with polatuzumab is much lower than that noted with the addition of rituximab to conventional chemotherapy. The addition of rituximab to CHOP was associated with added overall response rates of approximately 10 to 15%, with a notable augmentation of PFS and OS, which is not seen with polatuzumab vedotin.[2] The potential impact of polatuzumab vedotin on an OS benefit may be blunted by an already high efficacy of R-CHOP as the first-line therapy for most patients with DLBCL. In the POLARIX trial, overall response rates of 83.8% were noted in the control arm compared with 85.5% in the intervention arm, With this efficacy, the effect size of the addition of any new drug to the control arm required to detect a statistically significant difference between the two options may be

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substantial, and may not be detected in a trial setting.[5] The OS benefit may be further masked by the availability of effective second-line therapies including salvage chemotherapy, autologous stem cell transplant, and chimeric antigen receptor (CAR) T-cell therapy.

Moreover, achieving a complete response (CR) is important for an aggressive disease like DLBCL, where a majority of patients (>80%) achieving CR are functionally "cured" with less than 20% risk of relapse after 5 years.[6] Similar rates of CR in both arms may further diminish any observable OS benefit in this trial.

Powering this study for OS would considerably prolong the trial duration to greater than 5 years and delay the approval of potentially effective therapy. Several drugs for hematological cancers have recently been approved after assessing surrogate endpoints to reduce the time to regulatory approval.[7] PFS has been espoused as a valid surrogate endpoint by industry-sponsored reviews, lending credence to selecting this as a primary endpoint.[8] Older trials leading to rituximab approval also considered PFS as the primary endpoint. However, the quantitative effect of adding rituximab to chemotherapy on PFS and OS made it a viable first-line therapeutic option.[9] Using endpoints other than OS may enable the achievement of favorable but clinically less relevant endpoints for regulatory approval in the trial setting.

From a policy perspective, the absolute risk reduction for progression from the POLARIX trial is 0.06, indicating a number needed to treat (NNT) of 16.7. At present, the addition of a second drug likely to be priced higher than rituximab may not be viable in India due to the small PFS benefit and high NNT as noted earlier.

R-CHOP therapy's efficacy appears to have plateaued for a subset of patients; hence, introducing a second drug may not enhance treatment outcomes for standard-risk patients. However, specific subgroups of high-risk diseases including double-/triple-hit lymphomas still present an unmet need, and may benefit from a second drug.[10,11] There is a mismatch between double-/triple-hit lymphomas, implying that most "high-risk lymphomas" in this trial are ABC: Activated B Cell Lymphoma (ABC) lymphomas and not true double-/triple-hit lymphomas (highlighted by Dr. Advani, Lymphoma CME on May 5, 2023). A preferential benefit on ABC lymphoma subtypes has been recently highlighted, making it possible that this drug may show greater efficacy when evaluated on this specific patient subset.[12] Similar findings were noted in the POLARIX trial, with no clear benefit in patients younger than 60 years or those with low international prognostic index scores or germinal center subtypes, further limiting the target population for this new drug.

A substantial proportion of patients with high-risk DLBCL subtypes are of advanced age. The development of newer non-chemotherapy-based treatment options is necessary in this subset. Until then, R-CHOP appears to be the best option for most patients with DLBCL. Furthermore, polatuzumab is likely a better option as the second-line therapy till better efficacy than R-CHOP can be documented. The allure of innovation may entice, but older and dependable ways may hold greater value in certain scenarios.

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Conflict of Interest
None declared.

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