Polatuzumab Vedotin for the Front-Line Treatment of Diffuse Large B-Cell Lymphoma: A New Standard of Care?

JAMES A. DAVIS, PharmD, BCOP, ABIGAIL SHOCKLEY, PharmD, AMANDA HERBST, PA-C, and LINDSEY HENDRICKSON, DNP, APRN, FNP-C

From Medical University of South Carolina, Charleston, South Carolina

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: James A. Davis, PharmD, BCOP, Medical University of South Carolina - Hollings Cancer Center, 86 Jonathan Lucas Street, Charleston, SC 29425
E-mail: davisjaa@musc.edu

https://doi.org/10.6004/jadpro.2023.14.1.6

Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma in the US. For nearly 2 decades, standard front-line treatment has consisted of chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Numerous trials have unsuccessfully attempted to achieve better outcomes in these patients. Recently, the results of the phase III POLARIX trial were published. This study randomized newly diagnosed DLBCL patients to receive polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) or standard-of-care R-CHOP. The POLARIX trial demonstrated 2-year progression-free survival of 76.7% for pola-R-CHP compared with 70.2% for R-CHOP with comparable safety profiles between the two arms. Based on these results, a new standard of care may be emerging in patients with DLBCL. This article provides a practical approach to managing a newly diagnosed patient with DLBCL.

CASE STUDY

Mr. D is a well-educated 71-year-old male who presents to clinic with complaints of an enlarging neck mass, general malaise, and fatigue. A core needle biopsy is performed that reveals a diagnosis of non-germinal center B-cell diffuse large B-cell lymphoma. A subsequent PET scan reveals extensive hypermetabolic cervical, thoracic, and abdominopelvic involvement with notable renal and adrenal lesions. A bone marrow biopsy is performed, which is negative for lymphoma involvement. Fluorescence in situ hybridization analysis reveals no chromosomal abnormalities. He is deemed to have stage 4 disease, and his International Prognostic Index score is determined to be 4, which is indicative of a high risk of relapse after front-line therapy. His risk for central nervous system involvement is also deemed high due to kidney and adrenal involvement.

J Adv Pract Oncol 2023;14(1):67–72

The treating hematologist recommends treatment with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with intrathecal chemotherapy. However, Mr. D states that he recently read an article stating a newer front-line treatment incorporating polatuzumab vedotin may provide him a better outcome.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell non-Hodgkin lymphoma in the world, with more than 18,000 people in the US diagnosed each year (Sehn & Salles, 2021; National Comprehensive Cancer Network, 2021; Lymphoma Research Foundation, 2021). It is a rapidly progressing cancer characterized by uncontrolled growth of mature B lymphocytes in the lymph nodes and/or other extranodal sites. The median age at diagnosis is 65 years, but 30% of patients are over the age of 75. Non-germinal center B-cell (GCB) subtype DLBCL has been associated with an unfavorable prognosis and increased disease burden (Nowakowski & Czuczman, 2015). For nearly 2 decades, the standard of care has consisted of front-line chemoimmunotherapy using rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with cure rates between 60% to 70% (Sehn & Salles, 2021; Lymphoma Research Foundation, 2021).

Because 30% to 40% of patients are not cured with front-line treatment, novel treatments are being investigated to improve outcomes. Over 15 clinical trials have unsuccessfully attempted to improve these outcomes (Sehn & Salles, 2021). Dose intensification of R-CHOP from 21-day to 14-day cycles also failed to yield statistically significant results (Cunningham et al., 2013). Separate trials adding etoposide, obinutuzumab, bortezomib (Gazyva), ibrutinib (Imbruvica), and lenalidomide (Revlimid) to R-CHOP also resulted in non-significant benefits (Schmitz et al., 2012; Sehn et al., 2019; Davies et al., 2019; Younes et al., 2019).

FDA APPROVAL

In June 2019, the US Food and Drug Administration (FDA) granted polatuzumab vedotin (Polivy) accelerated approval in combination with bendamustine and rituximab for patients with relapsed or refractory DLBCL after failure of two or more lines of therapy. Polatuzumab vedotin is an antibody-drug conjugate that targets CD79b, a cell surface marker expressed by B cells (Dornan et al., 2009; Genentech Inc., 2020). Accelerated approval was based on the phase II GO29365 study in 80 patients who received polatuzumab vedotin in combination with bendamustine and rituximab (PBR) or bendamustine and rituximab (BR) alone. GO29365 demonstrated complete response rates of 40% vs. 17.5% in the PBR and BR arms, respectively. Median progression-free survival (PFS) in the PBR arm was 9.5 months (hazard ratio [HR], 0.36, 95% confidence interval [CI] = 0.21–0.63) and median overall survival (OS) was 12.4 months (HR, 0.42; 95% CI = 0.24–0.75; Sehn et al., 2020).

PHARMACOLOGY

The CD79a/b dimer is a cell surface protein expressed exclusively on B cells in the very early stages of development and is maintained until the last stage of maturation before differentiation into plasma cells. When CD79a/b covalently assembles, it results in B-cell maturation and activation (Luger et al., 2013). The majority of DLBCL cells express CD79a/b and antibodies that bind specifically to CD79b are rapidly internalized, making it an ideal target for treatment (Dornan et al., 2009; Young et al., 2015).

Polatuzumab vedotin consists of a humanized IgG1 antibody linked to a cytotoxic payload made up of monomethyl auristatin E (MMAE), a potent microtubule inhibitor. The antibody portion of the conjugate binds CD79b on the B-cell surface, the receptor complex is internalized, and the toxic payload of MMAE causes microtubule inhibition and apoptosis of the B cell (Genentech Inc., 2020).

POLARIX TRIAL

On December 14, 2021, the results of the phase III POLARIX trial were published. POLARIX was an international, randomized, double-blind, placebo-controlled trial that included 879 patients with newly diagnosed DLBCL. Patients were randomized 1:1 to receive either polatuzumab vedotin in

combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) or standard-of-care R-CHOP every 21 days for six cycles followed by single-agent rituximab for two cycles (Tilly et al., 2022). Polatuzumab vedotin was dosed at 1.8 mg/kg on day 1 in combination with standard doses of R-CHP. The use of granulocyte colony-stimulating factor (G-CSF) was required for all patients during the first six cycles. For patients at risk of central nervous system (CNS) disease, prophylaxis with intrathecal chemotherapy was allowed, but high-dose chemotherapy for CNS prophylaxis was not permitted. PET/CT scans were required during the screening phase, after cycle four, and 6 to 8 weeks after the end of treatment (Tilly et al., 2022).

Four hundred forty patients in the pola-R-CHP arm received placebo in place of vincristine and 439 patients in the R-CHOP arm received placebo in place of polatuzumab vedotin. Patients were 18 to 80 years of age with a median age of 65. Eighty-eight percent of patients had stage III to IV disease. The trial included patients with an International Prognostic Index (IPI) score of 2 to 5, with 62% of those patients having a score of 3 to 5. Patients were also required to have adequate hematologic function, Eastern Cooperative Oncology Group performance status of 0 to 2, and left ventricular ejection fraction (LVEF) ≥ 50%. Patients were excluded if they had a history of indolent lymphoma, CNS lymphoma, or prior organ transplant (Tilly et al., 2022).

Data cutoff occurred at a median follow-up time of 28.2 months. The primary outcome of PFS favored the pola-R-CHP arm (HR, 0.73, $p < .02$). Two-year PFS was 76.7% (95% CI = 72.7%–80.8%) in the pola-R-CHP arm compared with 70.2% (95% CI = 65.8%–74.6%) in the R-CHOP arm. An exploratory subgroup analysis of patients under age 60, patients with GCB subtype, patients with bulky disease, and patients with IPI scores < 2 did not show a clear PFS benefit. At the time of data cutoff, OS was not statistically different (HR, 0.94, 95% CI = 0.65–1.37, $p = .75$), but 8% fewer patients in the pola-R-CHP arm had received subsequent therapy, including radiation, hematopoietic stem cell transplant (HSCT), and chimeric antigen receptor (CAR) T-cell therapy for progressive disease (Tilly et al., 2022).

SAFETY AND TOXICITY

The safety profiles were comparable for both arms. The most common grade ≥ 3 toxicities in the pola-R-CHP and R-CHOP arms were neutropenia (28.3% vs. 30.8%), febrile neutropenia (13.8% vs. 8%), and anemia (12% vs. 8.4%; Tilly et al., 2022). As previously stated, primary prophylaxis with G-CSF was required, with more than 90% of patients in each arm reporting use. The most common grade 1 to 2 toxicities were peripheral neuropathy, nausea, diarrhea, constipation, and fatigue. The frequency and severity of peripheral neuropathy were similar in both arms. Overall, 6% of patients in both arms required dose discontinuation due to an adverse event. There were 13 deaths in the pola-R-CHP arm and 10 in the R-CHOP arm, which were primarily due to infections (Tilly et al., 2022). A further breakdown of treatment-related adverse events is presented in Table 1.

CASE STUDY CONTINUED

The hematologist and Mr. D discuss the risks and benefits of receiving pola-R-CHP instead of R-CHOP with explicit emphasis placed on the increased risk of neutropenic fever and the lack of OS data at this time. Mr. D states his understanding and pola-R-CHP is agreed upon, pending insurance approval. The hematologist introduces the advanced practitioner (AP), and they obtain informed consent in order for Mr. D to receive treatment.

ROLE OF THE ADVANCED PRACTITIONER

Advanced practitioners play a large role in the management of patients with oncologic diseases through initiation of anticancer therapy, monitoring of response, management of toxicity, and more. They should be knowledgeable in regard to patient populations that may have better outcomes with pola-R-CHP over R-CHOP. Subgroups of patients over 60 years of age with IPI scores of 3 to 5, non-bulky disease, and non-GCB subtype trended toward improved outcomes with pola-R-CHP. These patient populations may benefit from pola-R-CHP over R-CHOP, and these disease characteristics should be carefully considered during therapy selection.

Advanced practitioners can manage a variety of potential issues for patients receiving pola-R-CHP.

Table 1. Treatment-Emergent Adverse Events From POLARIX

	pola-R-CHP		R-CHOP	
	All grade, *n* (%)	**Grade ≥ 3, *n* (%)**	**All grade, *n* (%)**	**Grade ≥ 3, *n* (%)**
Peripheral neuropathy	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.38)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0 (0.0)	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)

Note. pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Prior to treatment, it is important to obtain cardiac function via echocardiogram or multigated acquisition (MUGA) scan. Patients with LVEF below 50% may need to receive a regimen that excludes an anthracycline. Additionally, due to the aggressive nature of DLBCL, APs should also initiate tumor lysis syndrome prophylaxis with hydration and allopurinol at least 3 days prior to treatment initiation in at-risk patients. Patients also should be assessed for the need of a central line because doxorubicin is a vesicant.

In order to manage potential toxicity and ensure quality of life, patients should be educated to report developing peripheral neuropathy, and APs should be attuned to asking patients prior to each cycle. According to the package insert, polatuzumab vedotin should be held for patients who develop grade 2 to 3 neuropathy and only resumed when neuropathy improves to grade 1 or better. If recovery occurs before day 14 of the cycle, the dose should be reduced to 1.4 mg/kg for the remainder of treatment. Polatuzumab vedotin should be permanently discontinued for grade 4 neuropathy (Lexicomp, 2021).

The combination of polatuzumab vedotin and rituximab may cause infusion-related reactions (IRRs). It is pertinent to incorporate antihistamine and antipyretic premedications prior to initiating treatment. Patients who experience IRRs should be managed according to institutional protocol, which typically involves pausing the infusion, administering corticosteroids and supportive care, and allowing resolution of symptoms. After resolution, the infusion may be resumed at 50% of the prior rate. If patients experience a grade 4 IRR, polatuzumab vedotin should be stopped and permanently discontinued.

Advanced practitioners should also be able to manage cytopenias that occur with treatment. Patients may need blood or platelet transfusions to manage anemia and thrombocytopenia. Febrile neutropenia occurred more frequently in the pola-R-CHP arm (14.3%) compared with the R-CHOP arm (8%), so primary prophylaxis with pegfilgrastim should be utilized in patients receiving pola-R-CHP. Herpes simplex virus prophylaxis with acyclovir or valacyclovir should also be considered while patients are receiving treatment and after if immunosuppressed (NCCN, 2021).

Financial toxicity is also a concern for patients and health systems. The added cost of polatuzumab vedotin for an 80-kg patient is approximately $18,000 per cycle, which is an additional $108,000 for six cycles (Lexicomp, 2021).

CASE STUDY CONTINUED

Mr. D receives four cycles of pola-R-CHP with grade 1 peripheral neuropathy developing in his

feet after cycle three. An interim PET scan after four cycles reveals complete remission. Mr. D completes the final two cycles with stable neuropathy. A post-treatment PET scan reveals continued complete remission, and Mr. D is scheduled for surveillance follow-up in 3 months (Figure 1).

CONCLUSION

Polatuzumab vedotin in combination with R-CHP provides a new treatment option for patients with newly diagnosed DLBCL. Patients over 60 years of age with IPI scores of 3 to 5, non-bulky disease, and non-GCB subtype may benefit more with pola-R-CHP over R-CHOP. Significant differences seen in PFS may be substantial enough for some clinicians to begin incorporating pola-R-CHP into their treatment approach of newly diagnosed DLBCL. Continued follow-up and further data maturation may elucidate a difference in OS. A cost-benefit comparison between the two arms

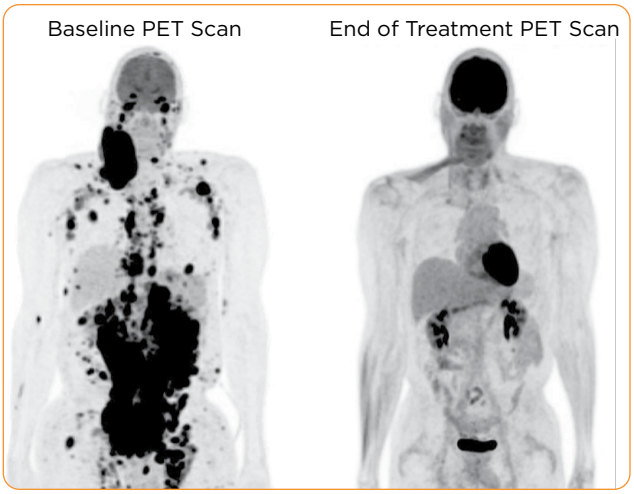

Figure 1. Post-treatment PET scan.

Table 2. Select Ongoing Studies with Polatuzumab Vedotin

Clinicaltrials.gov identifier (NCT #)	Phase	Patient population	Age (yr)	Intervention	Endpoints
04231877	I	Newly diagnosed aggressive B-cell lymphoma	≥ 18	Polatuzumab vedotin + dose adjusted rituximab, etoposide, cyclophosphamide, and doxorubicin (DA-EPCH-PR)	Incidence of adverse events
04594798	II	Newly diagnosed aggressive B-cell lymphoma in older patients	≥ 75	Polatuzumab vedotin, rituximab and dose-attenuated CHP	Progression-free survival
03671018	Ib/II	Relapsed/refractory non-Hodgkin lymphoma after at least one line of therapy containing an anti-CD20 agent	≥ 18	Mosunetuzumab in combination with polatuzumab vedotin	Maximum tolerated dose of mosunetuzumab, recommended phase II dose of mosunetuzumab, percentage of participants with adverse events, best objective response rate
04665765	II	Relapsed/refractory diffuse large B-cell lymphoma after one line of therapy	≥ 18	Polatuzumab vedotin, rituximab, ifosfamide, carboplatin, and etoposide (pola-R-ICE)	Complete response, incidence of toxicities
04479267	II	Newly diagnosed high-grade large B-cell lymphoma	≥ 18	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP)	Rate of complete remission
04182204 (POLARGO)	III	Relapsed/refractory DLBCL after one line of therapy	≥ 18	Polatuzumab vedotin in combination with rituximab, gemcitabine and oxaliplatin (pola-R-GemOx)	Percentage of participants with adverse events, overall survival

Note. Information from ClinicalTrials.gov (2022).

should also be considered to ascertain whether the higher upfront costs of pola-R-CHP translate into cost avoidance of subsequent therapy. Due to the positive results with polatuzumab vedotin in the front-line and relapsed/refractory, there are ongoing studies investigating its use in combination with other therapies (see Table 2).

Disclosure

The authors have no conflicts of interest to disclose.

References

ClinicalTrials.gov. (2022). ClinicalTrials.gov. https://clinicaltrials.gov/

Cunningham, D., Hawkes, E. A., Jack, A., Qian, W., Smith, P., Mouncey, P.,...Linch, D. (2013). Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: A phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*, *381*(9880), 1817–1826. https://doi.org/10.1016/S0140-6736(13)60313-X

Davies, A., Cummin, T. E., Barrans, S., Maishman, T., Mamot, C., Novak, U.,...Johnson, P. W. M. (2019). Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (Remodl-b): An open-label, randomised, phase 3 trial. *Lancet Oncology*, *20*(5), 649–662. https://doi.org/10.1016/S1470-2045(18)30935-5

Dornan, D., Bennett, F., Chen, Y., Dennis, M., Eaton, D., Elkins, K.,...Polson, A. G. (2009). Therapeutic potential of an anti-CD79b antibody–drug conjugate, anti–CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. *Blood*, *114*(13), 2721–2729. https://doi.org/10.1182/blood-2009-02-205500

Genentech Inc. (2020). Polivy (polatuzumab vedotin) package insert. https://www.gene.com/download/pdf/polivy_prescribing.pdf

LexiComp. (2021). Polatuzumab vedotin. https://online.lexi.com/lco/action/login

Luger, D., Yang, Y., Raviv, A., Weinberg, D., Banerjee, S., Lee, M.-J.,...Wakefield, L. M. (2013). Expression of the B-cell receptor component CD79a on immature myeloid cells contributes to their tumor promoting effects. *PLoS ONE*, *8*(10), e76115. https://doi.org/10.1371/journal.pone.0076115

Lymphoma Research Foundation. (2021) Diffuse large B-cell lymphoma. https://lymphoma.org/aboutlymphoma/nhl/dlbcl

National Comprehensive Cancer Network. (2021). NCCN Clinical Practice Guidelines in Oncology: B-cell lymphomas. V5.2021. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

Nowakowski, G. S., & Czuczman, M. S. (2015). ABC, GCB, and double-hit diffuse large B-cell lymphoma: Does subtype make a difference in therapy selection? *American Society of Clinical Oncology Educational Book*, *35*, e449–457. https://doi.org/10.14694/EdBook_AM.2015.35.e449

Schmitz, N., Nickelsen, M., Ziepert, M., Haenel, M., Borchmann, P., Schmidt, C.,...Glass, B.. (2012). Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: An open-label, randomised, phase 3 trial (DSHNHL 2002-1). *Lancet Oncology*, *13*(12), 1250–1259. https://doi.org/10.1016/S1470-2045(12)70481-3

Sehn, L. H., & Salles, G. (2021). Diffuse large B-cell lymphoma. *New England Journal of Medicine*, *384*(9), 842–858. https://doi.org/10.1056/NEJMra2027612

Sehn, L. H., Herrera, A. F., Flowers, C. R., Kamdar, M. K., McMillan, A., Hertzberg, M.,...Matasar, M. J. (2020). Polatuzumab vedotin in relapsed or refractory diffuse large b-cell lymphoma. *Journal of Clinical Oncology*, *38*(2), 155–165. https://doi.org/10.1200/JCO.19.00172

Sehn, L. H., Martelli, M., Trněný, M., Liu, W., Bolen, C. R., Knapp, A.,...Vitolo, U. (2019). Final analysis of GOYA: A randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large b-cell lymphoma. *Blood*, *134*(Supplement_1), 4088. https://doi.org/10.1182/blood-2019-123433

Tilly, H., Morschhauser, F., Sehn, L. H., Friedberg, J. W., Trněný, M., Sharman, J. P.,...Cheung, M. C. (2022). Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *New England Journal of Medicine*, *386*(4), 351–363. https://doi.org/10.1056/nejmoa2115304

Younes, A., Sehn, L. H., Johnson, P., Zinzani, P. L., Hong, X., Zhu, J.,...Wilson, W. (2019). Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non–germinal center B-cell diffuse large B-cell lymphoma. *Journal of Clinical Oncology*, *37*(15), 1285–1295. https://doi.org/10.1200/JCO.18.02403

Young, R. M., Shaffer, A. L., Phelan, J. D., & Staudt, L. M. (2015). B-cell receptor signaling in diffuse large B-cell lymphoma. *Seminars in Hematology*, *52*(2), 77–85. https://doi.org/10.1053/j.seminhematol.2015.01.008