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Polatuzumab Vedotin for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Transplant-Ineligible Patients

MELANIE DOUGLAS, MS, PA-C

From Memorial Sloan Kettering Cancer Center, New York, New York

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Correspondence to: Melanie Douglas, MS, PA-C, 1275 York Avenue, New York, NY 10065. E-mail: douglasm@mskcc.org

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Abstract

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma. Although 5-year survival rates in the first-line setting can range from 60% to 70%, up to 50% of patients become refractory or relapse after treatment (Crump et al., 2017). The standard treatment for relapsed/refractory diffuse large B-cell lymphoma is salvage chemotherapy followed by autologous stem cell transplant. Nonetheless, over 60% of patients are transplant ineligible, and there is currently no standard treatment option for these patients (Sarkozy & Sehn, 2018). Age, comorbidities, performance status, and disease deemed not responsive to chemotherapy conditioning are various factors potentially disqualifying patients for transplant. There is a strong demand for novel therapies. Polatuzumab vedotin, a targeted immunotherapy, was approved in 2019 by the U.S. Food & Drug Administration for the treatment of relapsed/refractory diffuse large B-cell lymphoma and is recommended by the National Comprehensive Cancer Network for patients who are transplant ineligible. This article reviews the pharmacology of polatuzumab vedotin, along with its performance in clinical trials, financial considerations, and management of adverse effects.

Lymphoma is the most common hematologic malignancy, accounting for 5% of newly diagnosed malignancies (Ku, Chong, & Hawkes, 2017; National Cancer Institute, 2019). In the United States, approximately 2.2% of individuals will be diagnosed with non-Hodgkin lymphoma (NHL) in their lifetime (National Cancer Institute, 2019). Non-Hodgkin lymphoma has a higher incidence rate in males than in females, and is most common in individuals of Caucasian descent (National Cancer Institute, 2019).

More than 90% of adult lymphomas are B-cell NHL (Ku et al.,

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2017). The most common subtype of B-cell NHL is diffuse large B-cell lymphoma (DLBCL), with a median age of 70 years at diagnosis (Smith et al., 2015). B-cell NHL arises as clones of precursor B cells in various differentiation stages. Activation of surface B-cell antigens leads to downstream intracellular signaling and subsequent stimulation of tumor proliferation (Ku et al., 2017).

Chemotherapy has been the mainstay of treatment for lymphoma for decades (Ku et al., 2017). However, patients with relapsed/refractory (R/R) disease are challenging to treat, often requiring a personalized approach (Sarkozy & Sehn, 2018). Development of novel targeted therapies has been evolving as a result of the advancement in knowledge of lymphoma pathophysiology and molecular characteristics (Ku et al., 2017). These new targeted therapies may be considered in patients who have an inadequate response to first-line immunochemotherapy (Sarkozy & Sehn, 2018).

High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is the standard of care for patients with R/R DLBCL (Sarkozy & Sehn, 2018) and chemotherapy-sensitive disease (Hashmi, Hamadami, & Awan, 2018). Patients should be under 65 to 70 years of age without major comorbidities in order to qualify (Sarkozy & Sehn, 2018). Patients who are ineligible for ASCT or do not respond to second-line therapy have a poor prognosis (Gisselbrecht & Van Den Neste, 2018), and there is a need for effective salvage therapies. Novel targeted therapies are being developed; one such agent, polatuzumab vedotin (Polivy), has recently been approved by the U.S. Food & Drug Administration (FDA) for transplant-ineligible patients with R/R DLBCL. A phase II trial has demonstrated promising results with the use of this new agent in conjunction with previously established therapies. The objective response rate (ORR) was 70%, with median overall survival (OS) of 12.4 months (Herrera, 2019).

An important consideration is that "the tumor's mutational status may inevitably guide choice of therapy" (Sarkozy & Sehn, 2018). Patients with double-hit or triple-hit lymphoma (dual or triple mutations of *MYC* and *BCL2* and/or *BCL6* genes) are observed to have a dismal prognosis (Kesavan, Eyre, & Collins, 2019; Sarkozy & Sehn, 2018). Polatuzumab vedotin is indicated for patients with translocations of these oncogenes (National Comprehensive Cancer Network [NCCN], 2019).

MECHANISM OF ACTION

Rituximab (Rituxan), a monoclonal antibody, was developed over 20 years ago as a novel treatment for CD20-positive B-cell NHL. Monoclonal antibodies bind to tumor-specific surface antigens and block downstream intracellular pathways (Ku et al., 2017). In contrast to traditional chemotherapy, rituximab targets tumor cells with the goal to spare normal tissue.

Polatuzumab vedotin belongs to a new class of cancer therapies called antibody-drug conjugates (ADCs), which are gaining popularity in development. The quantity of these therapies featured in clinical trials has more than tripled over the past 5 years (Birrer, Moore, Betella, & Bates, 2019). Antibody-drug conjugates target tumor-associated antigens; they consist of a monoclonal antibody that selectively binds to tumor-associated antigens then releases cytotoxins in order to specifically kill tumor cells (Peters & Brown, 2015). Brentuximab vedotin (Adcetris), targeted against CD30, was the first ADC established for the treatment of hematologic malignancies, specifically Hodgkin lymphoma (Herrera, 2019).

Polatuzumab vedotin is the first ADC approved by the FDA for the treatment of DLBCL ("Polatuzumab vedotin approved for DLBCL," 2019). Polatuzumab vedotin consists of the antimitotic cytotoxic agent monomethyl auristatin E (MMAE), which is linked to the monoclonal antibody that selectively binds to CD79b on the cell surface (Deeks, 2019; Genentech, Inc., 2019a). After binding, "The linker is cleaved, releasing MMAE into the cell, where it inhibits division and induces apoptosis" (Deeks, 2019).

Polatuzumab vedotin is indicated in adults for the treatment of R/R DLBCL and for high-grade B-cell lymphoma with translocations of *MYC* and *BCL2* and/or *BCL6* genes after having already received at least two prior therapies (NCCN, 2019). Polatuzumab vedotin is not utilized as a bridge to transplant; rather, it is indicated for patients who are transplant ineligible (NCCN, 2019).

CLINICAL TRIALS AND ADVERSE EVENTS

In June 2019, polatuzumab vedotin was approved by the FDA in combination with bendamustine and rituximab for adult patients with R/R DLBCL who have completed at least two prior therapies (Kayata, 2019). This approval was based on a phase Ib/II open-label multicenter trial (Kayata, 2019).

In the phase II portion of this clinical trial, 80 transplant-ineligible patients with R/R DLBCL were randomized to 6 cycles of polatuzumab vedotin plus bendamustine and rituximab (pola-BR) or to 6 cycles of bendamustine and rituximab (BR; Sehn et al., 2017; Sehn et al., 2018). Forty patients were randomized to each arm. The primary aim was to evaluate the efficacy of each arm at 6 to 8 weeks after the last study treatment by an independent review committee. Assessment criteria used modified Lugano classification; complete response (CR) "required PET negativity and bone marrow biopsy confirmation of clearance if positive at screening" (Sehn et al., 2017).

Based on these criteria, it was concluded that the addition of polatuzumab vedotin to rituximab and bendamustine increased response rates in the studied patient population and prolonged progression-free survival (Sehn et al., 2017). The ORR was 70% and the CR rate was 57.5% for patients who received pola-BR, compared with an ORR of 32.5% and CR of 20% in patients who received BR (Herrera, 2019). In the pola-BR arm, 64% had a duration of response (DoR) of at least 6 months, while in the BR arm, 30% of patients had a DoR of at least 6 months (Genentech, Inc., 2019a).

Adverse events in this trial occurred more in patients randomized to the pola-BR arm than in those randomized to the BR arm. These included cytopenia, diarrhea, infection, fatigue, pyrexia, decreased appetite, constipation, peripheral neuropathy, and infusion-related reaction (Sehn et al., 2017). The most common grade 3 or 4 adverse events for the pola-BR arm compared with the BR arm included neutropenia (42% vs. 36%), thrombocytopenia (40% vs. 26%), anemia (24% vs. 18%), and pneumonia (16% vs. 2.6%; Stenger, 2019). Neutropenia and thrombocytopenia were the most common adverse effects leading to treatment discontinuation (Genentech, Inc., 2019a). Serious adverse events occurring in ≥ 5% of subjects in the pola-BR arm included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%; Genentech, Inc., 2019a). Table 1 includes data on adverse events from the trial.

Although there were more documented adverse events in the pola-BR arm, the treatment completion rate was higher in the pola-BR arm in comparison with the BR arm (Sehn et al., 2020). Sehn and colleagues (2020) commented, "[Progression of disease] resulted in treatment discontinuation in 53.8% and 15.4% of patients treated with BR and pola-BR, respectively." Fatal adverse events were similar in number; they occurred in 9 patients randomized to the pola-BR arm and in 11 patients randomized to the BR arm (Sehn et al., 2020).

DOSING AND ADMINISTRATION

Polatuzumab vedotin, as well as other antibody-drug conjugates (ADCs), are administered intravenously so that they will not be destroyed by gastric acids or digestive enzymes. Rather, these agents work by circulating in the bloodstream so that they can target tumor-specific cell-surface antigens (Peters & Brown, 2015).

The recommended dose for polatuzumab vedotin is 1.8 mg/kg as an intravenous infusion every 21 days for 6 cycles in combination with bendamustine and rituximab (Genentech, Inc., 2019a). The initial dose should be administered as a 90-minute infusion, and if this is well tolerated, subsequent doses may be administered as 30-minute infusions (Genetech, Inc. 2019a). An antihistamine and antipyretic should be given as premedication in order to try to offset infusion-related reactions (Genentech, Inc., 2019a).

There are no absolute contraindications, yet polatuzumab vedotin should be avoided in patients with moderate to severe hepatic impairment (Genentech, Inc., 2019a). This agent's metabolism has not been studied in humans, although it is known that its cytotoxic molecule MMAE is a substrate for the liver enzyme CYP3A4 (Genentech, Inc., 2019a).

Based on animal studies, it is recommended to advise pregnant women of possible risk to the fetus (Genentech, Inc., 2019a). Females of reproductive age should use contraception during treat-

Table 1. Adverse Events Occurring in > 10% of Patients With Relapsed or Refractory DLBCL and ≥ 5% in the Polatuzumab Vedotin Plus Bendamustine and Rituximab Group

	Polatuzumab vedotin + BR (n = 45)		BR (n = 39)	
Adverse events by body system	**All grades, %**	**Grade 3 or higher, %**	**All grades, %**	**Grade 3 or higher, %**
Blood and lymphatic system disorders				
Neutropenia	49	42	44	36
Thrombocytopenia	49	40	33	26
Anemia	47	24	28	18
Lymphopenia	13	13	8	8
Nervous system disorders				
Peripheral neuropathy	40	0	8	0
Dizziness	13	0	8	0
Gastrointestinal disorders				
Diarrhea	38	4.4	28	5
Vomiting	18	2.2	13	0
General disorders				
Infusion-related reaction	18	2.2	8	0
Pyrexia	33	2.2	23	0
Decreased appetite	27	2.2	21	0
Infections				
Pneumonia	22	16[a]	15	2.6[b]
Upper respiratory tract infection	13	0	8	0
Investigations				
Weight decreased	16	2.2	8	2.6
Metabolism and nutrition disorders				
Hypokalemia	16	9	10	2.6
Hypoalbuminemia	13	2.2	8	0
Hypocalcemia	11	2.2	5	0

Note. The table includes a combination of grouped and ungrouped terms. Events were graded using NCI CTCAE version 4. Reprinted with permission from Genentech, Inc. (2019).
[a]Includes 2 events with fatal outcome.
[b]Includes 1 event with fatal outcome.

ment and for at least 3 months following the final dose. Breastfeeding is not recommended during treatment and for at least 2 months following the last dose (Lexicomp Online, 2019a).

DRUG INTERACTIONS

Polatuzumab vedotin is metabolized by CYP3A4; coadministration with inhibitors or inducers of CYP3A4 may alter serum concentrations of this drug (Lexicomp Online, 2019a). Concomitant use of a strong CYP3A4 inhibitor such as ketoconazole is predicted to increase the plasma concentration-time curve of polatuzumab vedotin. Coadministration of a strong CYP3A4 inducer such as rifampin is predicted to decrease the plasma concentration-time curve of polatuzumab vedotin (Genentech, Inc., 2019a). Table 2 lists CYP3A4 inhibitors and inducers.

Polatuzumab vedotin may enhance myelosuppressive, adverse, and toxic effects of other myelosuppressive agents, such as chloramphenicol, cladribine, clozapine, leflunomide, mesalamine, and promazine (Lexicomp Online, 2019a). Polatuzumab vedotin may enhance the immunosup-

pressive effects of immunosuppressants such as cladribine, denosumab, fingolimod, roflumilast, and siponimod. This drug may enhance adverse and toxic effects of topical tacrolimus (Lexicomp Online, 2019a).

MONITORING AND MANAGING ADVERSE EFFECTS

Due to metabolism by the liver as well as potential myelosuppressive effects, liver function tests and complete blood counts should be monitored throughout treatment with polatuzumab vedotin (Lexicomp Online, 2019a). In cases of neutropenia and/or thrombocytopenia of grade 3 or above, it is recommended to interrupt treatment until counts recover. Growth factor support should be considered in subsequent cycles if the treatment course is complicated by grade 3 or higher neutropenia (Genentech, Inc., 2019a). Tumor lysis labs should be monitored in patients with high tumor burden (Genentech, Inc., 2019a).

Health-care professionals should monitor for infusion-related reactions such as fever, chills, flushing, dyspnea, hypotension, and urticaria. If an infusion-related reaction occurs, treatment should be interrupted and then the reaction managed medically; then, the infusion can be resumed at a lower rate once symptoms resolve (Genentech, Inc., 2019a). If the infusion-related reaction is grade 4 or higher, the drug should be discontinued (Genentech, Inc., 2019a). Polatuzumab vedotin may also cause peripheral neuropathy. Depending on the severity, this side effect may require a delay, dose reduction, or discontinuation of the drug (Genentech, Inc., 2019a). Progressive multifocal leukoencephalopathy has been reported as an adverse reaction in 0.6% of patients treated with polatuzumab vedotin. If this diagnosis is suspected, the drug should be permanently discontinued (Genentech, Inc., 2019a). Management guidelines of adverse events are listed in Table 3.

It is recommended to administer prophylaxis for *Pneumocystis jiroveci* pneumonia and for herpesvirus throughout treatment, as opportunistic infections have been reported (Genentech, Inc., 2019a). Patients should be monitored carefully during treatment for signs of infection and managed appropriately.

Table 2. List of CYP3A4 Inhibitors and Inducers

CYP3A4 inhibitors

- Fluconazole
- Ketoconazole
- Posaconazole
- Voriconazole
- Isoniazid
- Nelfinavir
- Ritonavir
- Indinavir
- Atazanavir
- Verapamil
- Diltiazem
- Amiodarone
- Azithromycin
- Erythromycin
- Clarithromycin
- Grapefruit juice

CYP3A4 inducers

- Phenytoin
- Carbamazepine
- Rifampin
- Efavirenz

FINANCIAL CONSIDERATIONS

Polatuzumab vedotin is $18,000 per 140-mg intravenous solution vial (Lexi-Drugs, 2019). This drug is dosed as 1.8 mg per kg; the average patient's weight of 70 kg would require one vial for each of the 6 cycles when dosed with rituximab and bendamustine (Lexicomp Online, 2019b). Therefore, the cost of 6 rounds of polatuzumab vedotin for a patient with average (or below average) weight comes out to $108,000. If a patient requires an additional vial of this drug for each round of administration, a replacement for the second vial would be offered by the manufacturer's supplement program so that the patient would only be charged for one vial (Genentech, Inc., 2019b).

Polatuzumab vedotin is not the only therapy that can confer a cost burden; rituximab and bendamustine are also both expensive. Six cycles of rituximab, assuming a patient has an average body surface area of 1.8 m^2, comes out to $47,350.80 (Lexicomp Online, 2019c); rituximab is dosed intravenously on day 1 of each cycle (Lexicomp Online, 2019c). Moreover, 6 cycles of bendamustine comes out to $71,245.44 (Lexicomp Online, 2019d); bendamustine is dosed intravenously on days 1 and 2 of each cycle (Lexicomp Online, 2019d).

R-GemOx, consisting of rituximab, gemcitabine, and oxaliplatin, is an alternate salvage regimen for patients with DLBCL who are transplant ineligible (Hubel, 2018). Gemcitabine and oxaliplatin are both much cheaper agents; a vial of gemcitabine costs about $5 (Lexicomp Online, 2019e), and a vial of oxaliplatin costs about $20 or less (Lexicomp Online, 2019f). Nonetheless, for this regimen, the 5-year

Table 3. Management of Adverse Events of Polatuzumab Vedotin: Peripheral Neuropathy, Infusion-Related Reactions, and Myelosuppression

Event	Dose modification
Grade 1–3 infusion-related reaction	• Interrupt polatuzumab vedotin infusion and give supportive treatment. • For the first instance of grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab vedotin. • For recurrent grade 2 wheezing or urticaria, or for recurrence of any grade 3 symptoms, permanently discontinue polatuzumab vedotin. • Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. • For the next cycle, infuse polatuzumab vedotin over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 infusion-related reaction	• Stop polatuzumab vedotin infusion immediately. Give supportive treatment. • Permanently discontinue polatuzumab vedotin.
Grade 3–4 neutropenia[a,b]	• Hold all treatment until ANC recovers to greater than 1,000/µL. • If ANC recovers to greater than 1,000/µL on or before day 7, resume all treatment without any additional dose reductions. Consider granulocyte colony-stimulating factor prophylaxis for subsequent cycles, if not previously given. • If ANC recovers to greater than 1,000/µL after day 7: » Restart all treatment. Consider granulocyte colony-stimulating factor prophylaxis for subsequent cycles, if not previously given. If prophylaxis was given, consider dose reduction of bendamustine. » If dose reduction of bendamustine has already occurred, consider dose reduction of polatuzumab vedotin to 1.4 mg/kg.
Grade 3–4 thrombocytopenia[a,b]	• Hold all treatment until platelets recover to greater than 75,000/µL. • If platelets recover to greater than 75,000/µL on or before day 7, resume all treatment without any additional dose reductions. • If platelets recover to greater than 75,000/µL after day 7: » Restart all treatment, with dose reduction of bendamustine. » If dose reduction of bendamustine has already occurred, consider dose reduction of polatuzumab vedotin to 1.4 mg/kg.

Note. Reprinted with permission from Genentech, Inc. (2019).
[a]Severity on day 1 of any cycle.
[b]If primary cause is due to lymphoma, dose delay or reduction may not be needed.

progression-free survival was only 12.8% in a phase II study (Hubel, 2018).

There is a need for superior salvage therapies, and so far, the data on polatuzumab vedotin in combination with bendamustine and rituximab is promising. Although polatuzumab vedotin is extremely costly, its encouraging results in treating transplant-ineligible patients with R/R DLBCL deserves to be highlighted. At this point in time, cheaper traditional therapies for these patients are limited and associated with weak survival outcomes.

ONGOING CLINICAL TRIAL

Currently, polatuzumab vedotin is being investigated in a phase III international, randomized, double-blind clinical trial as therapy in patients with untreated DLBCL. Patients with CD20-positive DLBCL are included (Tilly et al., 2019). Subjects are randomized to 6 cycles of polatuzumab vedotin plus R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) or to 6 cycles of current standard first-line therapy R-CHOP, which consists of rituximab, cyclophosphamide, vincristine (Oncovin), doxorubicin, and prednisone. All subjects receive rituximab monotherapy for two subsequent cycles: cycles 7 and 8 (Tilly et al., 2019). PET-CT and CT scans are performed at screening, after 4 cycles, and 6 to 8 weeks after the completion of study treatment. The follow-up will continue for 5 years after treatment (Tilly et al., 2019).

SUMMARY

At this time, there is no standard approach to treating transplant-ineligible patients with R/R DLBCL. Traditional treatment has been generally

palliative (Sarkozy & Sehn, 2018). There is a need for novel therapies, and polatuzumab vedotin has demonstrated promising results in treating this patient population. Furthermore, these exemplary results have led to the phase III trial that is currently underway and investigating the use of this drug as a first-line therapy for patients with DLBCL (Sarkozy & Sehn, 2018). Polatuzumab vedotin is one of various new targeted immunotherapies developed that reflects promise and advancement in treating malignancies.

Disclosure

The author has no conflict of interest to disclose.

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