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Polatuzumab Vedotin for Relapsed/Refractory Aggressive B-cell Lymphoma: A Multicenter Post-marketing Analysis

Stephen D. Smith,[1,2] Paolo Lopedote,[3] Yazeed Samara,[4] Matthew Mei,[4] Alex F. Herrera,[4] Allison M. Winter,[5] Brian T. Hill,[5] Mazyar Shadman,[2] Chaitra Ujjani,[1,2] Ryan C. Lynch,[1,2] Caron A. Jacobson,[6] Austin I. Kim,[6] Paolo Caimi,[7] Filippo Milano,[2] Ajay K. Gopal[1,2]

Abstract

Relapsed or refractory diffuse large B-cell lymphoma poses a significant therapeutic challenge. The approval of polatuzumab, in combination with bendamustine and rituximab, represents a new treatment option. To clarify post-marketing use of polatuzumab-based therapy, we pooled data from 5 medical centers in the United States. We report that the application, toxicity, and outcomes vary from results reported in the pivotal trial.

Introduction: Polatuzumab vedotin is approved therapy in the United States for relapsed/refractory diffuse large B-cell lymphoma in combination with bendamustine and rituximab (Pola+BR). However, the safety and efficacy of Pola+BR outside of a clinical trial setting is unknown. **Patients and Methods:** We analyzed use of pola-based therapy at 5 centers in the United States, including dose, response rates, progression-free survival (PFS), survival, and toxicity. **Results:** Sixty-nine patients with aggressive B-cell lymphoma, including 66 with diffuse large B-cell lymphoma/high-grade B-cell lymphoma and 84% refractory to prior therapy, were treated. Responses occurred in of 50%, including 24% complete response. Median duration of response was 5.1 months, PFS was 2.0 months, and survival was 5.3 months, at 4 months median follow-up. Inferior PFS was associated with prior refractory disease (median, 57 days vs. not reached; $P = .003$) and lack of response to Pola+BR (PFS, 27 days vs. 152 days; $P < .001$). Discontinuation owing to planned cellular therapy was seen in 36% and owing to toxicity occurred in 12%; unplanned hospitalizations occurred in 36%. **Conclusions:** We conclude that commercial Pola is applied to highly refractory lymphomas at our centers, often with intent to bridge to subsequent therapy. Although some clinical benefit was observed, efficacy was inferior to clinical trial data, especially among those with refractory disease.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) remains difficult to treat in the relapsed or refractory (R/R) setting.[1] Hematopoetic stem cell transplantation (HSCT) and chimeric antigen receptor-T cell therapy (CAR-T) cure a minority of R/R patients, and are primarily offered to younger, fit patients with adequate organ function.[2-5] For

[1]Division of Medical Oncology, Department of Internal Medicine, University of Washington, Seattle, WA
[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
[3]Institute of Hematology, University of Bologna, Bologna, Italy
[4]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA
[5]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH
[6]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA
[7]Department of Medicine-Hematology and Oncology, University Hospital/Case Western Reserve Medical Center, Cleveland, OH

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Address for correspondence: Stephen D. Smith, MD, Fred Hutchinson Cancer Research Center, Department of Internal Medicine, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109
E-mail contact: Ssmith50@seattlecca.org

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those ineligible for intensive therapies, gemcitabine- or lenalidomide-based regimens are recommended, but few patients achieve long-term remissions.[6-9]

Recently, the antibody-drug conjugate polatuzumab vedotin-piiq (Pola) was granted accelerated approval, in combination with bendamustine and rituximab (BR), for treatment of R/R DLBCL after 2 or more prior therapies.[10] The pivotal trial found an improved progression-free survival (PFS) (9.5 months) and overall survival (OS) (12 months) with Pola+BR compared with BR alone in 40 transplant-ineligible patients with R/R DLBCL.[11] In context, BR lacks high-level consensus support for use in R/R DLBCL; treatment delivery is often limited by toxicity or progression when dosed at 120 mg/m^2, and the median PFS is 4 to 7 months.[6,12,13] Since the approval of Pola+BR and incorporation into National Comprehensive Cancer Network (NCCN) treatment guidelines,[6] our centers have increasingly employed Pola-based therapy for treatment of R/R aggressive B-cell lymphoma. Herein, we report our multicenter retrospective analysis of Pola in treatment of R/R aggressive B-cell non-Hodgkin lymphoma, analyzing patient and disease characteristics, toxicity, and outcomes.

Materials and Methods

Patients receiving commercial Pola since its approval in June 2019 for relapsed aggressive B-cell lymphoma were identified from pharmacy records, tumor boards, and clinical conferences. Records were reviewed under Institutional Review Board approval at the respective institutions.

Baseline patient and tumor features, prior treatment history and regimen details, clinician-defined responses, toxicity, and outcomes were collected. Reason for treatment discontinuation, emergency department visits within 30 days of Pola administration, and unplanned hospitalizations were assessed.

PFS was measured from the start of Pola to progression or death. Patients undergoing subsequent HSCT or CAR-T were censored at the time of conditioning or lymphodepletion, to avoid confounding Pola and cellular therapy outcomes. Univariate analysis for baseline and treatment features impacting PFS and OS was performed. As reported by Cassaday and colleagues,[14] we calculated and explored the predictive impact of remission quotient (RQ), calculated by dividing months from diagnosis of aggressive lymphoma by the number of preceding regimens (among patients undergoing prior cellular therapy, salvage, lymphodepletion or conditioning, and cellular therapy are counted as 1 regimen).

Results

Patient Characteristics

Sixty-nine patients from 5 academic medical centers in the United States with aggressive B-cell lymphoma received Pola in the commercial setting. Patient characteristics are shown in Table 1. Sixty-one (88%) patients had DLBCL or high-grade B-cell lymphoma with MYC and BCL2 translocations, and 10 had a history of antecedent indolent B-cell lymphoma. Fifty-nine (84%) patients had refractory disease, defined as no response or relapse within 6 months of the immediate prior regimen, 52 (75%) patients had received prior chemotherapy with a platinum agent, and 8 (12%) patients had received prior bendamustine. In addition, 18 (26%) and 11 (16%) patients had received prior CAR-T and HSCT, respectively.

Table 1 Patient Characteristics (N = 69)

Characteristic	N (%)
Median no. prior treatments (range)	3 (1-9)
Female sex	26 (38)
Median age, y (range)	62 (17-88)
LDH > ULN	43 (62)
EN sites >1	39 (57)
ECOG >1	23 (33)
DLBCL NOS/high-grade BCL (double hit)	61 (88)/5 (7)
History of indolent NHL/transformed	12 (17)
DLBCL NOS and non-transformed	51 (74)
PMBCL, Burkitt	1,2
Refractory to prior regimen (no response or progressed < 6 mos)	58 (84)
Prior platinum-based chemotherapy	52 (75)
Prior bendamustine	8 (12)
Prior CAR T-cell/transplant	18 (26), 11 (16)

Abbreviations: BCL = B-cell lymphoma; CAR T-cell = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group performance status; EN = extranodal; LDH = lactate dehydrogenase; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal large B-cell lymphoma; ULN = upper limit of normal.

The median time from diagnosis to Pola administration was 18 months (range, 2-209 months; mean, 32 months). The median RQ (months from diagnosis of aggressive lymphoma/number of distinct regimens) was 6.

Treatment Received

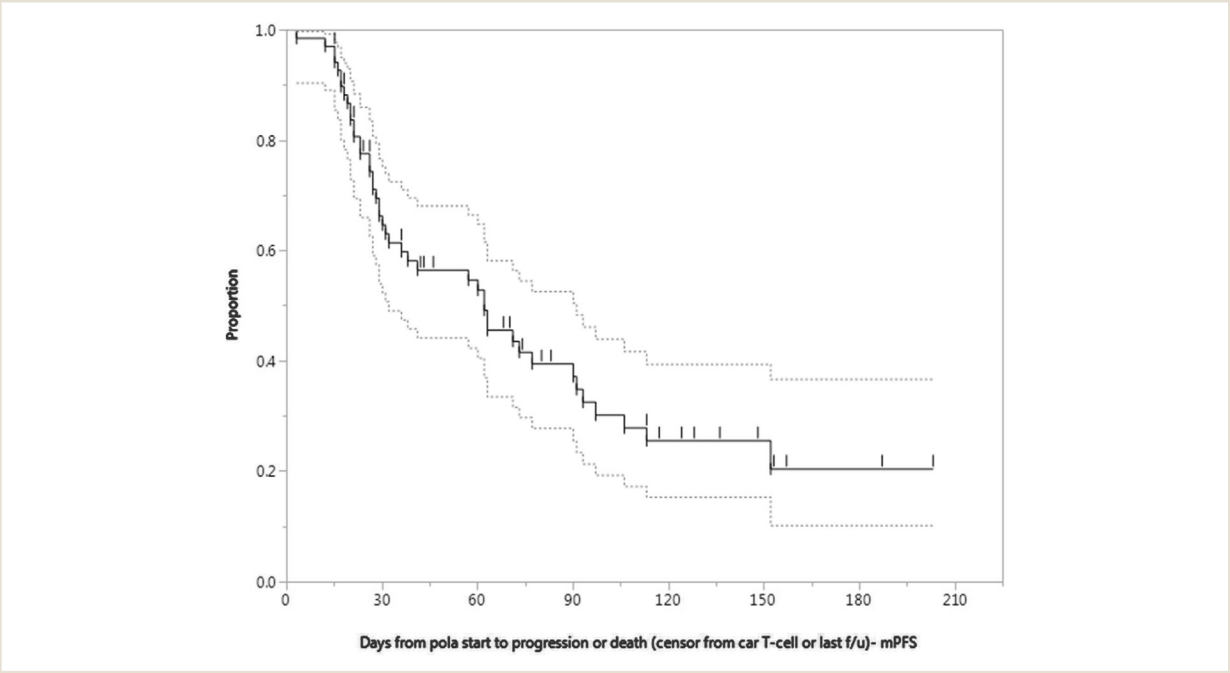
Pola+BR at the standard dose[11] (bendamustine 90 mg/m^2, day 1 and 2) was the most common starting regimen (70%); bendamustine was reduced in 9 (13%) or omitted in 12 (16%) of patients at the time of treatment initiation. Among the 12 patients receiving no bendamustine, 2 received monotherapy, 6 received Pola with rituximab, and 4 received other Pola combinations. Only 3 of these 12 had received prior bendamustine.

A median of 2 cycles of Pola were given (range, 1-6); only 4 patients received 6 cycles of therapy. Pola dose reductions or delays were required in 3 and 8 patients after starting therapy. Reasons for discontinuation included intent to proceed to CAR-T or HSCT in 25 (36%), progressive disease in 21 (20%), and toxicity in 8 (12%). Twenty-two patients eventually underwent CAR-T, and 2 underwent autologous HSCT.

Efficacy

Responses in the entire cohort were observed in 29 (50%) of 58 efficacy evaluable patients, including 14 (24%) complete response (CR). All CR were confirmed by fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography. Responses among 43 evaluable patients with non-transformed, DLBCL not otherwise specified were similar: 53% overall response rate (ORR) with 13 CR (30%) and 10 partial response (PR) (23%). Among the 12 patients treated without bendamustine, 3 responses were observed (2 PR, 1 CR).

Figure 1 Progression-free Survival



Abbreviations: CAR T-cell = chimeric antigen receptor T-cell; f/u = follow-up; Pola = polatuzumab.

The median PFS (Figure 1; includes 95% confidence interval) was 62 days (2.0 months) and median OS (Figure 2) was 161 days (5.3 months). Duration of response was 152 days and was not reached for patients achieving CR. The median follow-up was 121 days. The median PFS and OS in non-transformed DLBCL not otherwise specified were similar to the overall cohort at 63 days; duration of response was 152 days, and the median OS was not reached. Among the 18 patients treated with prior CAR-T, responses were observed among 7 (41%) of 17 evaluable patients with 2 (11%) CR.

PFS was superior among patients achieving CR compared with all others (PFS not reached vs. 36 days; $P < .001$), or any response to Pola (PFS, 152 days vs. 27 days; $P < .001$). Patients refractory to the immediate prior regimen had inferior PFS (57 days vs. not reached; $P = .003$). RQ < 6 months/regimen also predicted inferior PFS (36 days vs. 97 days for RQ ≥ 6 months/regimen; $P = .02$). There was no impact of gender, history of transformation, median age, elevated lactate dehydrogenase, Eastern Cooperative Oncology Group performance status > 1, extranodal sites >1, prior bendamustine (in 8 patients), or prior CAR-T. The only factors associated with superior OS were attainment of CR (OS $P = .005$) or any response to therapy ($P < .001$).

Safety

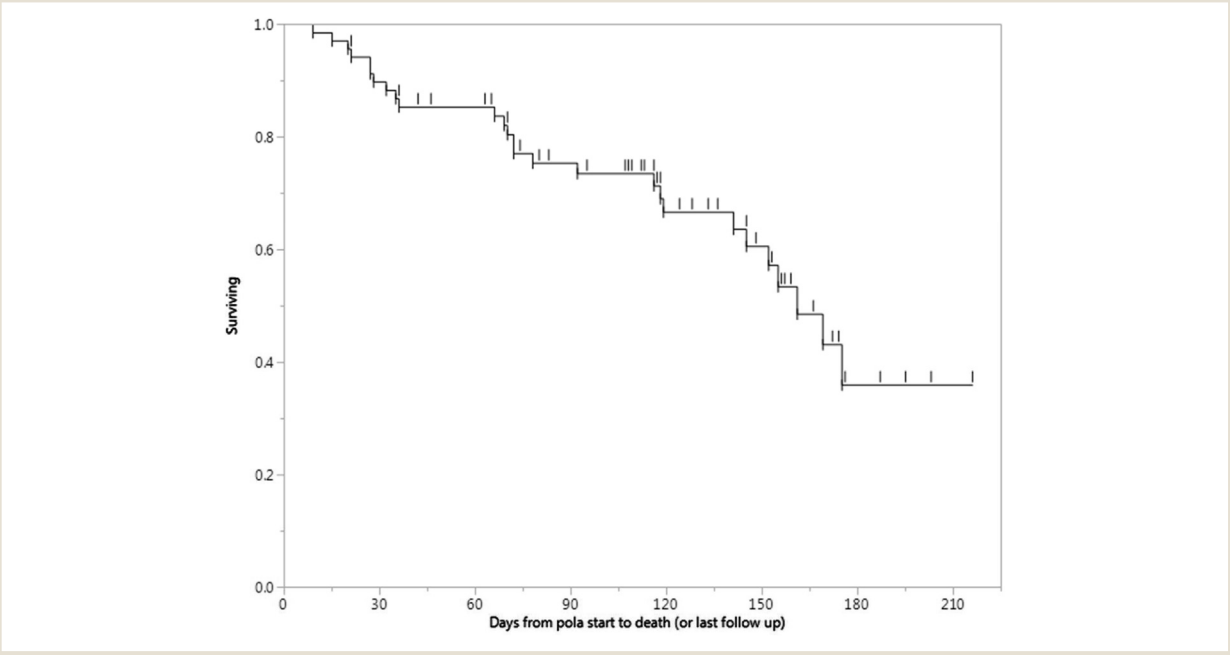
During or within 30 days of Pola, 23 (33%) patients had unplanned emergency department visits, and 25 (36%) patients had unplanned hospitalizations (16 with infection). Fifty-two (75%) received granulocyte colony-stimulating factor, 18 (26%) required packed red blood cell transfusion, and 12 (17%) required platelet transfusion. Of the 8 patients who discontinued owing to toxicity, only 2 were owing to peripheral neuropathy, after 3 and 4 cycles, respectively. There were no deaths attributed to Pola-containing therapy.

Discussion

Development of effective treatments for patients with chemotherapy-refractory aggressive B-cell lymphoma remains a critical priority, particularly for those ineligible for intensive therapies. Treatment selection relies on data from nonrandomized trials, and an individualized evaluation of disease risk, comorbidities, and preferences for each patient. The recent accelerated approval of Pola+BR adds an important therapeutic option. However, the treatment landscape continues to evolve as more patients receive CAR-T cell therapy or emerging immunotherapies including lenalidomide and tafasitamab, and novel bispecific antibodies such as mosunetuzumab, which have shown promising efficacy in recent clinical trials.[15,16] Thus, not only the efficacy of Pola+BR in the trial setting, but its relevance amid emerging therapeutic sequences and available clinical trials must be considered.

As a single agent and in combination with rituximab for R/R DLBCL, polatuzumab affords responses in about one-half of patients and CR in approximately 20%, but is associated with significant neutropenia and moderate neurotoxicity.[17,18] The randomized study of Pola+BR was designed to achieve a CR rate of 65% versus 40% with BR alone and did not meet this endpoint.[11] Although achieving a superior PFS and OS compared with BR, a minority of patients received all planned Pola+BR cycles, and 33% discontinued treatment for adverse events.

Figure 2 Overall Survival



Abbreviation: Pola = Polatuzumab.

Our post-marketing analysis was conceived to provide context outside of the clinical trial setting. Compared with the pivotal trial, our cohort unsurprisingly bears some differences: patients were younger (median age, 62 vs. 67 years in the pivotal trial), received 3 prior therapies (vs. 2), and included subsets with transformed lymphoma and those intended to receive subsequent HSCT or CAR-T. Although a similar proportion had refractory disease to the preceding regimen, more of our patients had previously received bendamustine (12%) or HSCT/CAR-T (16%/26%).

In context of these differences, we observed a similar ORR (50%), but the median PFS was only 62 days, and the median OS was less than 6 months (161 days). Outcomes were similar for the subset of patients with non-transformed DLBCL in this cohort. We identified no baseline features able to predict PFS and OS other than refractory disease and the RQ: patients failing their last regimen, or multiple regimens for aggressive B-cell non-Hodgkin lymphoma in a short period of time (RQ < 6), showed minimal benefit from treatment with Pola+BR. This suggests Pola-containing therapy is unable to break the pervasive cycle of chemorefractoriness seen in a subset of patients with DLBCL. Notably, PFS was superimposable for the 18 patients who received prior CAR-T (data not shown).

Toxicity was notable in our cohort. Although 36% of patients discontinued therapy for planned CAR-T, a similar proportion of patients required emergency department visits or unplanned hospitalizations despite frequent use of growth support (in 75%). Only 2 stopped therapy for neurotoxicity, but given that most patients discontinued for progression or planned cellular therapy, treatment exposure was relatively short. In conjunction with toxicity data from the pivotal trial, we suggest cautious patient selection for Pola+BR and use of maximal supportive care. This could include planning for transfusional support, growth factor administration, and appropriate antimicrobial prophylaxis and monitoring for infection.

Limitations inherent to retrospective trials apply to our dataset, including a heterogenous population of patients, nonstandard (clinical) response assessments, and lack of a comparator group. Thirty-six percent of patients stopped Pola to proceed to CAR-T/transplant, and because we censored data at time of lymphodepletion or conditioning, our median follow-up was relatively short at 121 days. For these reasons, and lacking the predefined patient selection employed by the pivotal trial, we do not suggest direct comparison of our efficacy findings to the pivotal trial. We did not analyze the specific impact of Pola on T-cell collection, toxicity of CAR-T, and other parameters relevant to a role in "bridging" for CAR-T. Further studies are needed to clarify a potential role for Pola+BR in bridging therapy, especially given the T-cell lymphodepletion associated with bendamustine.[19]

Another recent post-approval analysis of 47 patients treated with polatuzumab-based therapy found an ORR of 61% with 40% CR.[20] Patients in that dataset were slightly older (median age, 66 years), and fewer had received prior CAR T-cell therapy, but comprised similar proportions of refractory disease and prior platinum chemotherapy. The median PFS was 5.6 months and OS 8.3 months and 7 proceeded to allogenic SCT and 2 to CAR T-cell therapy, and PFS was inferior in patients with primary refractory disease. There was a 25% febrile neutropenia rate with Pola+BR, and 3 patients suffered treatment-related mortality in that series.

This data confirms that although responses are observed, as a whole, disease control with Pola-containing therapy is transient, and that toxicity can be significant.

Conclusions

Our post-approval analysis suggests Pola-containing therapy is associated with frequent modifications, a relatively short PFS, and considerable toxicity when applied to patients with largely refractory DLBCL. Hospitalization and transfusional support are relatively common. The PFS reported in our series of 2.0 months, in conjunction with a PFS of 5.6 months reported by Segman and colleagues,[20] suggest inferior efficacy of Pola-containing therapy in refractory DLBCL when used outside of a formal clinical trial context. Ultimately, further data around use of Pola-containing therapy prior to CAR T-cell therapy and HSCT are needed to assist in guiding therapy for the highest-risk, refractory patients.

Clinical Practice Points

- Pola+BR, approved for R/R DLBCL after at least 2 prior therapies, relies on a chemotherapy backbone associated with modest efficacy in DLBCL and is associated with infectious risk. Post-marketing data is needed to elucidate the practical application, toxicity, and efficacy of Pola-containing therapies and is limited to date.
- Our analysis of 69 R/R patients with DLBCL, including a predominantly refractory and platinum-exposed cohort, shows this regimen is frequently applied as a bridge to CAR T-cell or other cellular therapy, but is associated with significant toxicities including unplanned hospitalizations and a 2.0 month median PFS.
- We suggest that Pola-containing therapy has limited efficacy in refractory subsets of DLBCL, and that attention to supportive care and toxicity management are key considerations when selecting patients for its use.

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