AFMN BIOMEDICINE

CASE REPORT

# POLATUZUMAB-VEDOTIN+BENDAMUSTIN+RITUXIMAB AS SALVAGE AND BRIDGING THERAPY IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

**Ivan Petković**[1,2] **Marija Elez**[3,4] **Aleksandar Popović**[2] **Slavica Stojnev**[5,6] **Irena Conić**[1,2] **Miljana Džunić**[2] **Dane Krtinić**[2,7]

[1]Department of Oncology, University of Niš Faculty of Medicine, Niš, Serbia [2]Clinic of Oncology, University Clinical Center Niš, Serbia [3]University of Defence, Medical Faculty of the Military Medical Academy, Belgrade, Serbia [4]Hematology Clinic, Military Medical Academy Belgrade, Belgrade, Serbia [5]Department for Pathology, University of Niš Faculty of Medicine, Niš, Serbia [6]Center for Pathology and Pathological Anatomy, University Clinical Center Niš, Serbia [7]Department for Pharmacology, University of Niš Faculty of Medicine, Niš, Serbia

Although diffuse large B-cell lymphoma (DLBCL) represents a paradigm of highly curative disease with a complete remission (CR) rate of ≈ 60%–70% in an upfront setting, the remaining 30%–40% of patients present a relapse/refractory setting. These population are highly critical and amended for salvage treatment approach. Novel approaches and agents can overcome a problem in 20%–25%. Regarding this problem, polatuzumab vedotine represents one of the options. The use of this agent as bridging to further consolidation has been introduced from the real world experience with encouraging results.

We present a 54-year-old male patient diagnosed with primary gastric relapse/refractory (R/R) DLBCL who had been successfully treated by the introduction of antibody-drug conjugate polatuzumab-vedotine. After achieving complete response patient has been further consolidated with a high-dose chemotherapy followed by autologous graft.

Given the lack of availability of cellular therapies in developing countries, antibody-drug conjugate may be a plausible approach.

Keywords: polatuzumab-vedotine, bridging, relapse/refractory diffuse large B-cell lymphoma

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**Correspondence to:**
Ivan Petković
Department of Oncology
University of Niš Faculty of Medicine
Bulevar dr Zorana Đinđića 48, Niš, Serbia
E-mail: ivan.petkovic@medfak.ni.ac.rs

## INTRODUCTION

Although diffuse large B-cell lymphoma (DLBCL) represents a paradigm of highly curative disease with a complete remission (CR) rate of ≈ 60%–70% in an upfront setting (1-3), the remaining 30%–40% of patients present a challenge. Recently, the treatment algorithm for relapse/refractory (R/R) DLBCL profoundly changed with the introduction of cellular therapies (CD19 CAR-T), particularly in patients suitable for this approach, relapsing early (≤ 12 months). Patients relapsing late (> 1 year) remained amenable for high-dose consolidation with an autologous stem cell transplantation (ASCT). Nevertheless, cumulatively, both approaches raised the cure rate by almost 20%–25% in relapse/refractory setting (4, 5). It should be added that a significant number of new compounds entered a regular use in R/R DLBCL: bispecific antibodies (glo-fitamab, epcoritamab) and others, such as polatuzumab-vedotin, tafasitamab, loncastuximab-tesirine as monoclonal agents and selinexor as the first in class nuclear export protein inhibitors. Notably, all of the novel agents have been primarily designated for transplant ineligible patients (6). Nevertheless, real world evidence data showed that all of the compounds emerged may be used as a bridging option to further high-dose consolidation in responding and fit patients by inclusion of chimeric antigen receptor (CAR-T-cell) therapy, allogeneic SCT or eventually by ASCT (7).

## CASE REPORT

We present a 54-year-old male patient diagnosed with primary gastric R/R DLBCL. The disease started with typical gastrointestinal symptoms (nausea, dyspepsia, vomiting, weight loss). An endoscopic biopsy performed in May 2020 revealed a “bulky” unresectable tumor, initially marked as an anaplastic gastric carcinoma. As a result of misdiagnosis, the patient received three cisplatinum-based chemotherapy cycles. Magnetic resonance imaging showed progressive disease and radiological signs of highly suspected gastric lymphoma. A new biopsy was performed in August 2020, with a definitive diagnosis of DLBCL, not otherwise specified (NOS), non-germinal center B-like (non-GCB) with consequent immune profile: LCA+, CD20+, CD3+, bcl2+, bcl6-, CD10-, CyclinD1-, MUM1+, Ki 67 > 80%. The patient underwent R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 4, and R-COEP x 4 inductions (doxorubicin➔etoposide due to left ventricular ejection fraction decrease). A minimum of partial response (PR) was achieved, and the final 18-fluoro-deoxygenase positron emission tomography/computed tomography (FDG-PET/CT) scan assessment was planned. However, a massive relapse followed by gastric perforation occurred in less than a month upon the induction completion. After the palliative surgical treatment, and patient stabilization, ICE (ifosfamide, carboplatin, etoposide) salvage regimen was introduced with PR after three cycles. The molecular assessment showed no genetic alterations (double/triple hit rearrangements). Although PR was achieved, the patient was still transplant-ineligible and further treatment was continued with polatuzumab-vedotin + bendamustin + rituximab. After six cycles of treatment, a clinical complete response (CR) was achieved. The patient underwent high-dose consolidation and autologous stem cell transplantation (ASCT). Post-ASCT FDG-PET/CT showed metabolic CR in September 2022. Currently, the patient is on regular follow-up, with persistent two-year CR.

## DISCUSSION

Polatuzumab-vedotin is an anti-CD79b targeted agent as antibody-drug conjugate with a monomethyl auristatin E (MMAE) payload recently approved for transplant ineligible R/R DLBCL patients after at least two prior therapies. The MMAE, as an immunotoxine, leads to a microtubule disruption which further drives to the G2/M-phase cell cycle arrest causing cell death. Polatuzumab-vedotin has been investigated as a single agent and in com-bination in relapse/refractory setting with other agents reaching an overall response rate (ORR) of > 50% (CR 16%–28.5%) (8). Toxicity profile was acceptable, mostly hematological (neutropenia grade 3/4 in ≈ 20% in phase 1 and 2 and low-grade peripheral neuropathy in 36% of patients (9-11). Real world data shows comparable activity with an ORR of 33%–60% (CR 14%–40%) without new safely concerns (12-16).

Polatuzumab-vedotin in combination with bendamustin and rituximab has been approved as salvage regimen in transplant-ineligible patients after two prior lines (6-8). The stronger benefit has been obtained in non-primary refractory patients and when this salvage was used in the earlier line (i.e. 2$^{nd}$ line). The retrospective real-world data showed that polatuzumab-vedotin regimens may be implemented as a successful bridging therapy to CAR-T cell therapy or allogeneic SCT in responding and fit patients (6). However, data on ASCT as a consolidation was obtained in

a very small cohort of patients based on real-world single-center experiences. Our patient received polatuzumab-vedotin with rituximab and bendamustin as a salvage in the 3rd line, achieving CR after six cycles. No serious adverse event was detected during treatment. Due to the aggressiveness of the disease, primary refractoriness, and a high risk of another consecutive relapse, we decided to use ASCT as a consolidation tool.

Although cellular therapies (i.e. CAR-T-cell) significantly changed the therapeutic landscape in the group of patients with R/R DLBCL relapsing early, they are still inaccessible in many countries given the high cost and lack of infrastructure. Therefore, antibody-drug conjugates, bispecific antibodies and agencies similar to the drugs we used historically, polatuzumab-vedotin remains a plausible treatment of choice in countries without cellular therapies, considering the fact the benefits do not differ significantly.

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**Competing Interest**

The authors declare no relevant conflicts of interest.

**Statement of Ethics**

Complete written informed consent was obtained from the involved patient for the publication of the study.



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