Refractory Primary Mediastinal B-Cell Lymphoma: A Case Report of Conventional Chemotherapies, Immune Checkpoint Inhibitors, Polatuzumab Vedotin, Transplantation, and Post-Transplant Large Granular Lymphocytosis

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Ind J Med Paediatr Oncol 2022;43:523–527.

Abstract

We report a case of stage IV primary mediastinal B-cell lymphoma in a 27-year-old young woman, who was refractory and chemoresistant to frontline conventional rituximab-based intensive chemotherapy and subsequent lines of conventional and immune checkpoint inhibitor-based therapies. She was successfully treated using a polatuzumab-based regimen and consolidated with an allogeneic haploidentical hematopoietic stem cell transplantation. She developed post-transplant large granular lymphocytosis that was managed conservatively. She is now relapse-free, 600 days post-transplant. The management of this patient provided several teaching points in the use of different modalities of immunotherapies in a hard-to-treat cancer and its related conditions.

Keywords

- primary mediastinal B-cell Lymphoma
- relapsed refractory disease
- chemoresistance
- polatuzumab vedotin
- haploidentical transplantation

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a relatively rare subtype of non-Hodgkin lymphoma (NHL) mainly occurring in adolescents and young adults.[1] The malignant cells express B-cell markers CD19, CD20, CD22, CD79a.[2] Optimal first-line treatment options vary based on center experience and include da-EPOCH-R, CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone-rituximab) and R-V/MACOP-B (rituximab, etoposide or methotrexate, doxorubicin,

DOI https://doi.org/10.1055/s-0042-1749412.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

cyclophosphamide, vincristine, prednisone, bleomycin) followed by radiotherapy (RT) in selected cases.[1,3]

Although it has a more favorable outcome to initial therapy than diffuse large B-cell lymphoma (DLBCL), 10 to 30% of PMBCL patients have primary refractory or relapsed (R/R) disease. The outcomes of the latter condition are poor.[4] Relapse generally occurs in the initial 12 months, is more likely to be widespread, and can involve the central nervous system (CNS). Once relapsed or progressive disease, the median overall survival is ~16 months.[5] RT alone can be curative in patients with limited disease and RT-naïve patients.[6] Second-line treatment regimens are similar to those used in DLBCL and include rituximab, ifosfamide, carboplatin, and etoposide, rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP), and others, including autologous hematopoietic cell transplantation (HCT).[7] For patients undergoing autologous HCT for chemotherapy-sensitive disease, outcomes are more favorable and comparable to relapsed DLBCL. Incomplete response to initial therapy, an advanced Ann Arbor stage at disease progression, and failure to achieve a partial remission or better to second-line therapy are scenarios associated with inferior event-free and overall survival following transplant.[8] As there is no single standard of care, institutions choose treatment regimens that are appropriate for their setting based on available and emerging peer-reviewed evidence. We share our experience with the management of a young woman diagnosed with PMBCL and the lessons we learnt as we managed the relapsed and refractory course of her disease.

Case Presentation

A 27-year-old woman presented with gradually progressive breathing difficulty and chest pain in January 2017. On evaluation elsewhere with CT chest, she was diagnosed with a bulky mediastinal mass ($11.5 \times 12 \times 9$ cm) and a whole-body positron emission tomography-computed tomography (PET-CT) scan revealed mediastinal mass with additional multiple extra nodal sites of disease (hypermetabolic lesions in adrenals, kidneys, both ovaries). A guided core biopsy was suspicious of NHL and immunohistochemistry revealed tumor cells to be positive for CD20, PAX 5, CD23, and CD30 and diagnosis was consistent with PMBCL. She received her initial therapy with six cycles of dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab (da-EPOCH-R) as well as CNS prophylaxis with intrathecal methotrexate. Post-chemotherapy, PET-CT revealed a persistent mediastinal low-grade metabolic lesion (standardized uptake value [SUV]: 2.6) and a biopsy revealed necrotic tissue. She was consolidated with involved field radiotherapy and followed up. After an initial asymptomatic period of 6 months, she complained of pain in abdomen. PET-CT scan showed a new lesion in the left retrosternal space, duodenojejunal flexure, and proximal jejunum with minimal increase in the metabolic activity of the anterior mediastinal soft tissue mass. Biopsies were repeated from both sites and confirmed B-cell NHL. She was then referred to our center.

After a review of biopsies (►**Fig. 1**) to confirm PMBCL and imaging, she received first-line salvage chemoimmunotherapy with R-DHAP for three cycles. PET-CT scan thereafter was suggestive of residual disease (metabolically active retrosternal mass, Deauville score 4). She then received a second-line salvage chemoimmunotherapy with three (28 day) cycles of pembrolizumab (200 mg intravenously, day 1), rituximab (375 mg/m^2, day 1), bortezomib (1.3mg/m^2, days 1, 8, 15), and vinorelbine (25mg/m^2, days 1 and 8) combination in a 21-day cycle. This was started after special permission from the institutional lymphoma multidisciplinary team discussion based on emerging evidence in R/R PMBCL and the refractory nature of disease.

The usage and approval of checkpoint inhibitors (pembrolizumab) in PMBCL are biomarker agnostic. The determination of programmed death receptor-1 or programmed death receptor ligand-1 status is not mandatory and was not done in this patient. Following this regimen, however, PET-CT scan suggested progressive disease with new lesions in the transverse colon. She was lost to follow-up for 3 to 4 months when she apparently received some form of alternative therapy (dendritic-cell immunotherapy × 6

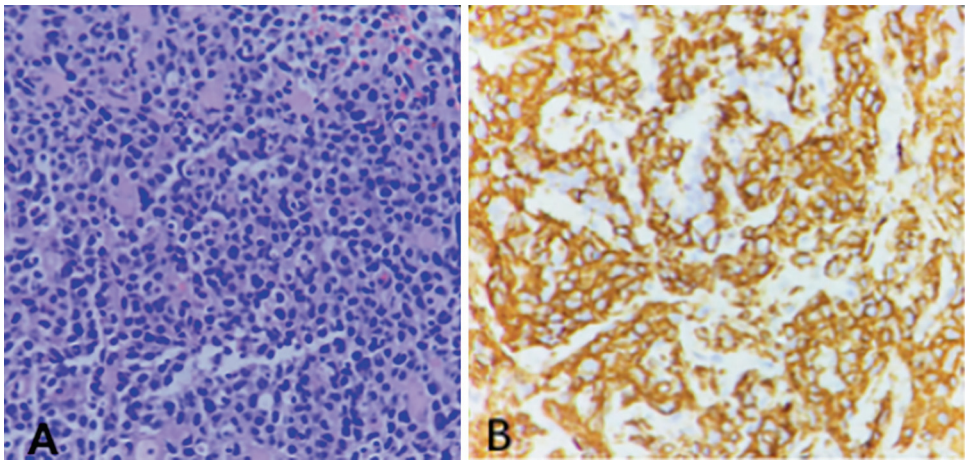

Fig. 1 (A) Hematoxylin and eosin (200X) showing large atypical lymphoid cells with mitosis and apoptosis in diffuse sheets; (B) immunohistochemistry: CD79a; 400x of the lymph node showing strong positivity.

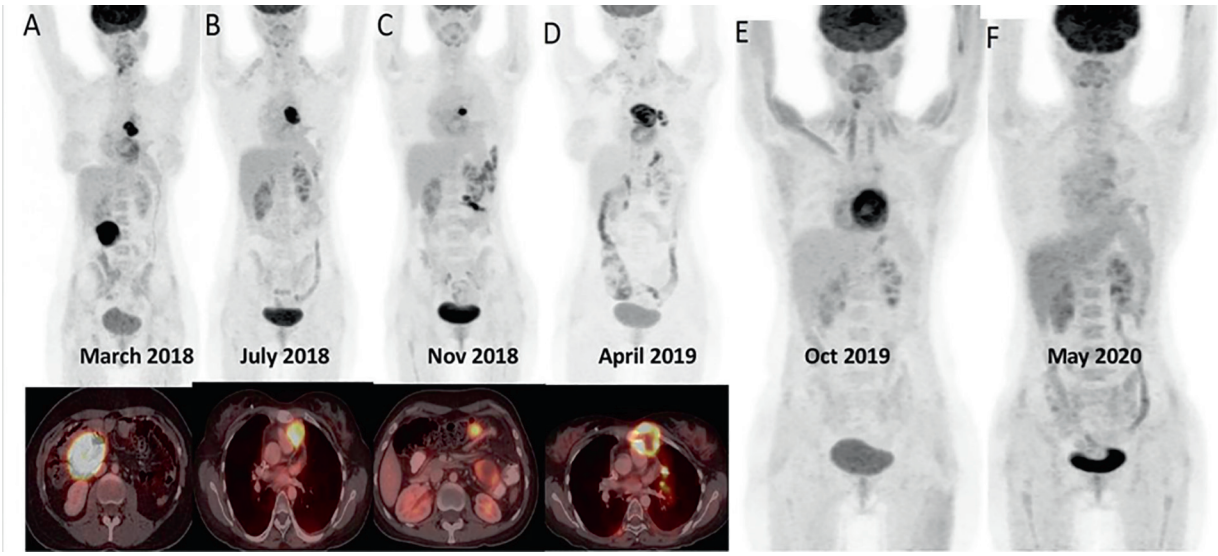

Fig. 2 Comparative positron emission tomography images from relapse diagnosis till post-transplant complete response status. (**A**) At relapse; (**B**) post- dexamethasone, high-dose cytarabine, and cisplatin (1st salvage); (**C**) post-pembrolizumab-based therapy; (**D**) pre-polatuzumab; (**E**) post-six cycles polatuzumab-based therapy; (**F**) post-transplant.

cycles), details of which were not furnished to our team. She had progressive disease with the alternative therapy as well. With limited options, she was then administered four cycles of metronomic chemotherapy using oral cyclophosphamide (300mg/m^2/week), lenalidomide (10mg/day, days 1–14), and dexamethasone (20 mg twice weekly) in a 28-day cycle with palliative intent. Thereafter, the PET-CT scan was suggestive of progressive disease (size and avidity) in the sternal lesion, development of new nodules in upper lobe of left lung and pleura, with resolution of jejunal and transverse colon lesions (►**Fig. 2**).

As she was refractory to three lines of therapy, she was now eligible for a polatuzumab vedotin compassionate access program from Roche pharmaceuticals in India. Accordingly, she received six cycles of polatuzumab-rituximab and bendamustine (Pola-BR) after which she was in a complete metabolic response (CR). As she was in a CR, she was keen on pursuing a curative therapy and was offered the option of an allogeneic HCT as consolidation, to which she agreed. Two more cycles of bendamustine and rituximab were used to bridge until she was ready for transplant. Her pre-HCT workup was unremarkable, and a pre-HCT PET-CT scan was again in a metabolic CR (with a metabolically inert lytic lesion in the manubrium of sternum with anterior mediastinal mass). She underwent a haploidentical matched (6/10 HLA match) related donor (mother) allogeneic peripheral blood HCT after reduced intensity conditioning (RIC) regimen with fludarabine-treosulfan. She received fludarabine (30 mg/m^2/day for 5 days: 240 mg) from day 6 to day 2 and inj. treosulfan (10 g/m^2/day: total 48 g) from day 6 to day 4, FT10 regimen. Graft-versus-host disease (GVHD) prophylaxis used was post-transplant cyclophosphamide-mycophenolate mofetil and tacrolimus. Her post-HCT period was uneventful except Grade 4 nausea and vomiting along with mucositis and a left Internal Jugular vein thrombus. On day 42, she had transient cytomegalovirus (CMV) viremia that was managed with oral valganciclovir. On day 60, PET-CT was in complete metabolic response (inert anterior mediastinal mass). Her post-engraftment day 28 and day 215 chimerism confirmed 100% donor cells.

►**Supplementary Fig. S1** shows the sequential lines of treatment received by the patient. On regular follow-up, she was diagnosed with a T-cell-large granular lymphocytosis (T-LGL, ►**Supplementary Fig. S2**) by day 165, on workup for persistent pancytopenia with lymphocytosis. On flow cytometry (►**Supplementary Fig. S3**), the gated abnormal T-cells were positive for sCD3, CD2, CD5, CD7, CD8, CD16, CD57 TCR α/ β. There was an oligoclonal band on TCR-G gene rearrangement polymerase chain reaction (►**Supplementary Fig. S4**). Her immunosuppression was tapered. However, pancytopenia persisted, and she was started on low-dose methylprednisolone with cyclophosphamide for T-LGL from day 210. On her last follow-up, she had completed 600 days (>1 year) of HCT without any evidence of GVHD or relapse. Her blood counts have now improved, and she is on tapering doses of steroids and cyclophosphamide.

Discussion

PMBCL is a rare and unique subtype of B-cell NHL. PMBCLs harbor numerous molecular alterations and surface antigen immunophenotypic features. These may be amenable to targeting with novel therapies including checkpoint inhibitor immunotherapy, as shown in ►**Table 1**. Underrepresentation of PMBCL in large-B-cell lymphoma clinical trials precludes a clear interpretation of the effects of novel immunotherapies and targeted therapies tested in these studies to PMBCL as a disease entity. Studies exclusively looking at R/R PMBCL are scanty and unlikely in the future. With the advent of chimeric-antigen receptor-T (CAR-T) cell therapy, response rates in R/R large B-cell lymphoma are

Table 1 Novel therapies for relapsed/refractory PMBCL[4]

Agent	Mechanism	Comments
Pembrolizumab	Check point inhibitor	High response rate, manageable safety (KEYNOTE 013 AND KEYNOTE 170)
Ruxolitinib	JAK 2 inhibitor	Phase 1 study, efficacy to be determined
SB518	JAK2/FLT3 inhibitor	Phase 1 study, efficacy to be determined
Brentuximab vedotin	ADC targeting CD30 antigen	Phase 2 study, low response rate

Abbreviation: PMBCL, primary mediastinal B cell lymphoma.

encouraging with an overall response rate of 83% and CR rate of 58%; R/R PMBCL patients are underrepresented.[9] In an NCI (National Cancer Institute, USA) study evaluating the role of CAR-T therapy in R/R B-cell lymphoma, of the four patients with R/R PMBCL, two (50%) had CR and one (25%) had stable disease.[4]

Our patient received an accepted upfront therapy for PMBCL that was followed by an early relapse. She thereafter received sequential lines of therapy that included conventional chemotherapy, immune checkpoint inhibitor-based treatment, and immunomodulatory therapy. However, she continued to have persistent/refractory disease. Polatuzumab vedotin (Pola) is an antibody drug conjugate comprising of an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin, a microtubule-disrupting cytotoxin. Polatuzumab vedotin, in its first phase 1 study in NHL patients, showed an objective response in 14 of 25 patients as monotherapy and 7 of 9 patients in combination with rituximab. Fifty-eight percent of the patients experienced grade 3 to 4 adverse effects when the drug was administered at a higher dose (2.4 mg/kg).[10] Subsequently, in the phase 2 study, Pola at dose of 2.4 mg/kg in combination with rituximab showed an objective response and CR of 54 and 21% patients, respectively. Grade 3 to 4 adverse events occurred in 77% of patients, most common being neutropenia.[11] Although Pola-BR was found to achieve a CR of 40% in R/R-DLBCL in a large phase 2 study, it had only one patient with PMBCL.[12] In recent preclinical studies, Pola alone and in combination with obinutuzumab was found to be cytotoxic to PMBCL cells.[13] Our patient achieved PR following three cycles of Pola-BR and a CR on completion of six cycles of Pola-BR.

Allogeneic HCT is an accepted consolidation strategy in salvage therapy of refractory or relapsed aggressive B-cell lymphomas and haploidentical HCT has demonstrated efficacy in such situations.[14,15] As she had no matched donors in her family or accessed donor registries, consolidation was achieved using a RIC haploidentical allogeneic HCT, which was largely uneventful. She developed T-LGL around day 165 post-HCT, which manifested as persistent cytopenia and lymphocytosis. T-LGL leukemia is a heterogeneous disorder characterized by persistent peripheral blood lymphocytosis and falls under the mature T and NK cell neoplasm in the World Health Organization (WHO) classification of hematolymphoid neoplasm (ICD-O code: 9831/3).[2] This complication is observed following allogeneic HCT in 0.5 to 18.4% of patients. The development of LGL has been associated with and attributed to various conditions such as immune system reconstitution, CMV viremia, and GVHD.[16] Our patient had transient CMV viremia post-HCT. First-line treatment is usually with steroids that leads to normalization of counts in 65% of patients. Thirty-four percent of those treated required $\geq$2 lines of treatment.[17] Our patient did not qualify the diagnostic criteria for T-LGL leukemia as diagnosis and treatment was initiated before "6 months of persistent lymphocytosis" due to persistent cytopenias. Hence, she was labeled as T-LGL. Epstein–Barr virus status was not checked in our patient at T-LGL diagnosis. Our patient had improvement in cytopenia following second-line treatment with immunosuppressive therapy for T-LGL using cyclophosphamide and continued steroids. On last-follow-up, nearly 600 days post-HCT, she maintains CR and is on tapering doses of immunosuppressive therapy of T-LGL.

The strengths of our approach to the case scenario were the appropriate and timely use of a novel agent after careful review of its role from initial studies. The patient, in CR, thereafter, received consolidation therapy in the form of allogeneic HCT considering the refractory nature of the disease and her young age. Limitation in our report was the use of combination of checkpoint inhibitor-based immunotherapy with chemotherapy, based on limited evidence from monotherapy studies using pembrolizumab.[18] An additional limitation in our report is that the cause of T-LGL was not exhaustively evaluated. Detailed evaluation of differential diagnoses would ideally include a workup to rule out viral infections and auto-immune conditions as well.

Conclusions

The treatment of this patient provided many learning opportunities to our team, in the complex management of R/R PMBCL. One, it illustrates that not all PMBCL respond well to upfront intensive therapy and early relapse remains a major challenge in improving outcomes. Two, the advent of novel therapies has provided treating physicians with opportunities to persist with treatment to achieve a response and a potential cure, in selected patients. Three, polatuzumab vedotin is an active agent in aggressive R/R B-cell lymphomas. Four, in young and fit patients, allogeneic HCT, including haploidentical donor HCT, is a feasible consolidation strategy in R/R disease who respond to salvage therapy. Five, T-LGL is a recognized side effect of HCT, and its management needs a nuanced approach. Six, the human side of this experience is the patient herself who persevered with the team, endured multiple lines of therapy, continues regular follow-up for her care and taught us the same.

Authors' Contribution

VSR conceived and led the idea for the case report. VSR, RP, and RN wrote the manuscript, contributed to the design, and edited the manuscript. LZ, SSV, DKM, and JD contributed to pathology, laboratory hematology, and imaging inputs, respectively, pictures and edited the manuscript. VSR, RN, RP, JK, SB, AN, and MC examined and treated the patient, and edited the manuscript.

Availability of Data and Material (data transparency)

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of Patient Consent

Informed consent was taken from the patient.

Funding

None.

Conflict of Interest

VSR reports advisory fees (institutional) and nonfinancial Institutional support from PFIZER, institutional grants and nonfinancial support from INTAS Pharmaceuticals, institutional grants from NATCO Pharmaceuticals, institutional grants from ROCHE, institutional grants from BMS, institutional grants and nonfinancial support from CIPLA Pharmaceuticals, institutional grants from EMCURE, personal fees (institutional) from ASTRA ZENECA, nonfinancial institutional support from Dr. REDDY's Laboratories, outside the submitted work. RN has received research grants, advisory board fees as well as Speaker fee from Cipla, Freisenius Kabi, Johnson and Johnson, Mylan, Novartis, and Dr. Reddy's Laboratory, outside the submitted work. MC reports advisory fees (institutional) and nonfinancial Institutional support from PFIZER, institutional grants and nonfinancial support from INTAS Pharmaceuticals, and institutional grants from NATCO Pharmaceuticals, outside the submitted work. Other authors declare no relevant conflicts of interest with respect to the submitted work.

Acknowledgments

This article was published with the written consent of the patient. The authors would like to acknowledge the role of all the nursing and healthcare supportive staff who helped care for this patient over a long duration of her illness. The authors would like to thank the compassionate access program team from Roche pharma which provided Polatuzumab-vedotin free to the patient, and Mr. Manik Ghosh (coordinator).

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