*Case Report*

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# Nivolumab plus gemcitabine, dexamethasone, and cisplatin chemotherapy induce durable complete remission in relapsed/refractory primary mediastinal B-cell lymphoma: a case report and literature review

**Gang Huang[1], Ju Huang[2], Zhili Zhang[2], Chongchong Xue[1] and Yuan Liu[2]**

**Abstract**

Primary mediastinal large B-cell lymphoma (PMBCL) is an uncommon, but aggressive, type of B-cell lymphoma. Patients with relapsed refractory PMBCL (rrPMBCL) have limited therapeutic options and usually have a relatively poor outcome. Immune checkpoint blockade has become a potential treatment for this disease. We report here a case of a female patient with rrPMBCL who was treated with nivolumab plus gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy. Complete remission was achieved after four cycles of combined therapy. With continued nivolumab maintenance monotherapy, she has remained in complete remission for longer than 28 months. This is the first report of nivolumab plus GDP chemotherapy inducing complete remission in patient with rrPMBCL. This case supplements the limited literature and provides implications for clinical trial designs regarding the potential use of nivolumab in the treatment of rrPMBCL.

[1]Department of Hematology, Yuebei People's Hospital, Shantou University Medical College, Shaoguan, Guangdong Province, China
[2]Guangdong Women and Children Hospital, Guangzhou, Guangdong, China

**Corresponding author:**
Yuan Liu, Medical Genetic Centre, Guangdong Women and Children Hospital, No. 521 Xingnan Rd, Panyu District, Guangzhou, Guangdong 511400, China.
Email: yuanliu005@163.com

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## Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) is an uncommon, but aggressive, tumor that accounts for 2% to 3% of non-Hodgkin lymphoma.[1] PMBCL is distinguished from diffuse large B-cell lymphoma by virtue of distinct clinical, pathological, and genetic features.[2–4] Recently, PMBCL was listed as a separate entity in the latest World Health Organization 2016 classification of hematopoietic and lymphoid tumors.[5] PMBCL has a similar clinical presentation as classical Hodgkin lymphoma (cHL), and PMBCL also shares certain features at the molecular level, particularly 9p24.1 alterations and programmed cell death protein ligand 1/ligand 2 (PD-L1/PD-L2) expression.[6–8] At present, management and outcome of PMBCL are still critical, and a more serious situation is faced by people who are diagnosed with relapsed and refractory PMBCL (rrPMBCL).[1,9] The optimal salvage chemotherapy and autologous stem cell transplant for rrPMBCL are of limited efficacy.[1,9]

Recently, agents targeting programmed cell death 1 (PD-1) and PD-L1 have been developed in tumor immunotherapy.[10] Anti-PD-1 therapy with monoclonal antibodies has been approved for the treatment of several types of solid tumor and cHL. The therapeutic potential of anti-PD-1 therapy in other malignancies is likely to be approved soon. In 2018, a humanized immunoglobulin G1 recombinant monoclonal antibody for the PD-1 receptor pidilizumab was approved by the US Food and Drug Administration (FDA) for treating adult and pediatric patients with rrPMBCL.[11] Another agent that targets the PD-1 receptor called nivolumab is a fully humanized immunoglobulin G4 monoclonal antibody that has been granted approval by the US FDA for treating several solid malignancies and cHL. The therapeutic efficacy of nivolumab in patients with rrPMBCL remains unclear.

We report here a patient with rrPMBCL who received combined treatment with off-label nivolumab and GDP chemotherapy. Complete remission (CR) was achieved after four cycles of such combined treatment. At the time of this submission, the patient has remained in CR for longer than 28 months with continued nivolumab maintenance monotherapy.

## Case report

A 32-year-old woman presented to Yuebei People's Hospital with intermittent dyspnea and chest pain. A positron emission tomography (PET) scan showed a 10-cm mass in the anterior superior mediastinum with a standardized uptake value of 13.5. The mass showed unclear margins and compressed the ascending aorta and pulmonary trunk. Small pericardial and left pleural effusions were also observed.

The mass was diagnosed as PMBCL by a subsequent biopsy. Immunohistochemical staining showed that large lymphocytes were positive for CD20, CD79a, Pax-5, BCL-6, CD23, CD30, and multiple myeloma-1, and negative for CD10, CD3, CD5, synaptophysin, chromogranin A,

endomysial, terminal deoxynucleotidyl transferase, cytokeratin (CK), CK19, and S-100. Ki-67 was 80% positive and Epstein–Barr encoding region *in situ* hybridization was negative. She was initially treated with six cycles of front-line chemotherapy, including two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), and four cycles of dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) were administered. The timeline of treatment is shown in Figure 1a. She received tumor resection by thoracoscopic surgery after she continued two cycles of gemcitabine, dexamethasone, cis-platinum, etoposide, and rituximab therapy. Her first CR was achieved in December 2016.

However, 4 months later, a PET-computed tomography (CT) scan showed hypermetabolic lesions located at the left lung and right adrenal gland, but not in the primary mediastinal site (Figure 1b). The patient reported no physical symptoms and received a repeat tissue biopsy, which confirmed a relapse with PMBCL. She was treated with each cycle of a dexamethasone, ifosfamide, cisplatin, and etoposide regimen and ibrutinib, bendamustine, and cytarabine therapy. A chest CT scan showed

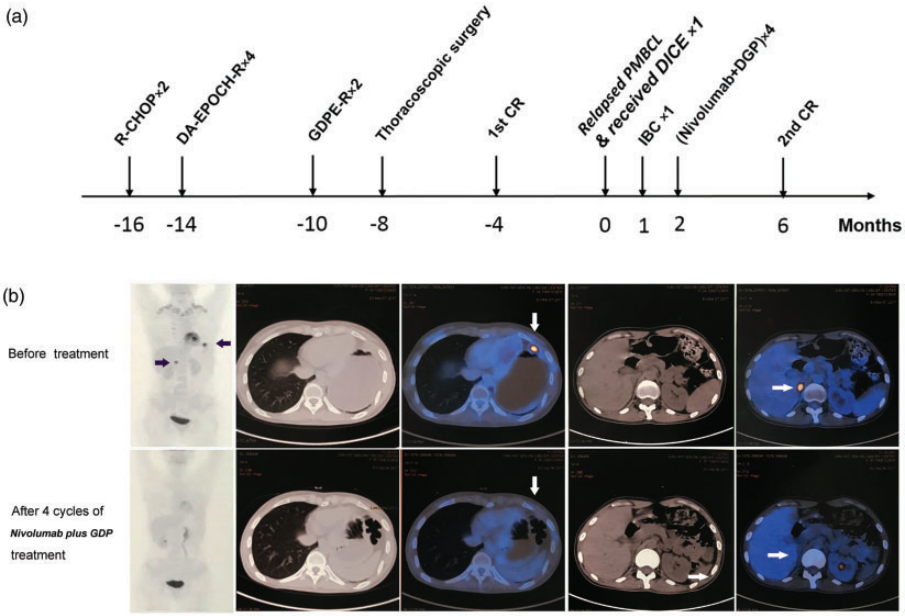


**Figure 1.** Summary of treatment and monitoring the tumor response. (a) Patient's timeline chart with the dates of treatment and monitoring the tumor response. (b) Positron emission tomography images. Upper panel: a scan of the relapsed hypermetabolic lesions located at the left lung and right adrenal gland before combined treatment. Lower panel: complete remission was achieved after four cycles of nivolumab plus GDP chemotherapy.
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; GDPE-R, gemcitabine, dexamethasone, cis-platinum, etoposide, and rituximab; CR, complete remission; PMBCL, primary mediastinal large B-cell lymphoma; DICE, dexamethasone, ifosfamide, cisplatin, and etoposide; IBC, ibrutinib, bendamustine, and cytarabine; GDP, gemcitabine, dexamethasone, and cisplatin.

that the right adrenal gland lesion had partially responded, while the lesions in the left lung had progressed. After those cycles of chemotherapy, the patient showed Grade IV myelosuppression and had to receive blood transfusion treatment. Moreover, a cerebrospinal fluid examination showed the presence of atypical lymphocytes and no symptoms of infection of the central nervous system were observed. Intrathecal chemotherapy (cytarabine 50 mg, methotrexate 10 mg, and dexamethasone 5 mg) was then administered and no atypical lymphocytes were detected by repeated cerebrospinal fluid analysis. These findings highly suggested a potential risk of metastasis of the central nervous system.

Because the disease had progressed with severe myelosuppression and there were no standard chemotherapy guidelines or alternative treatment options for the patient, other salvage treatments of her refractory disease needed to be considered. After much discussion with the patient and her family, she declined autologous hematopoietic stem cell transplantation and received combined treatment of gemcitabine 1400 mg, dexamethasone 50 mg, and cisplatinum 150 mg (GDP) chemotherapy and the off-label anti-PD1 antibody nivolumab (140 mg). After four cycles of combined treatment, a repeated PET/CT scan showed that she had secondary CR (Figure 1b). She received two more cycles of combined treatment with nivolumab and GDP chemotherapy, and then continued single nivolumab maintenance treatment (100 mg). Since her first dose in May 2017, she received 16 doses of nivolumab. She reported moderate fatigue and pyrexia in 2 to 3 days after each administration of nivolumab. Blood tests indicated normal function of the liver, kidney, and thyroid (Figure 2). She also had normal blood levels of creatinine, albumin, globulin, lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, total bilirubin, and urea nitrogen during the whole process of nivolumab therapy (Figure 2b). Neutrophil and platelet counts were decreased in the first four combined therapies because of toxicity of GDP chemotherapy, but they recovered to normal levels during continued nivolumab maintenance monotherapy (Figure 2c). Furthermore, no adverse signs and symptoms were observed in the lungs, brain, and skin. At the time of this submission, she has remained in CR for longer than 28 months with continued nivolumab maintenance therapy.

Ethics approval was obtained from the ethical committee of Yuebei People's Hospital. Written informed consent was obtained from the patient for analysis of the samples and publication.

## Discussion

Treatment and outcome are critical in managing PMBCL. Because there is no established standard approach, the first-line treatment of PMBCL is generally the same as that for diffuse large B-cell lymphoma, including R-CHOP and DA-EPOCH-R. Relapse of PMBCL usually occurs in the first 6 to 12 months after completion of front-line therapy, with a lower incidence (approximately 10%–30%) than diffuse large B-cell lymphoma.[1,9] There are various second-line immunochemotherapy regimens for patients with rrPMBCL, including the rituximab, ifosfamide, carboplatin, and etoposide regimen, the rituximab, dexamethasone, cytarabine, and cisplatin regimen, and rituximab-GDP.[12] Because of a lack of standard guidelines or treatment options for PMBCL, the outcome greatly depends on the patients' response to the regimen. This response remains poor, despite these second-line salvage chemotherapies and subsequent autologous hematopoietic stem cell transplantation.[9,12]

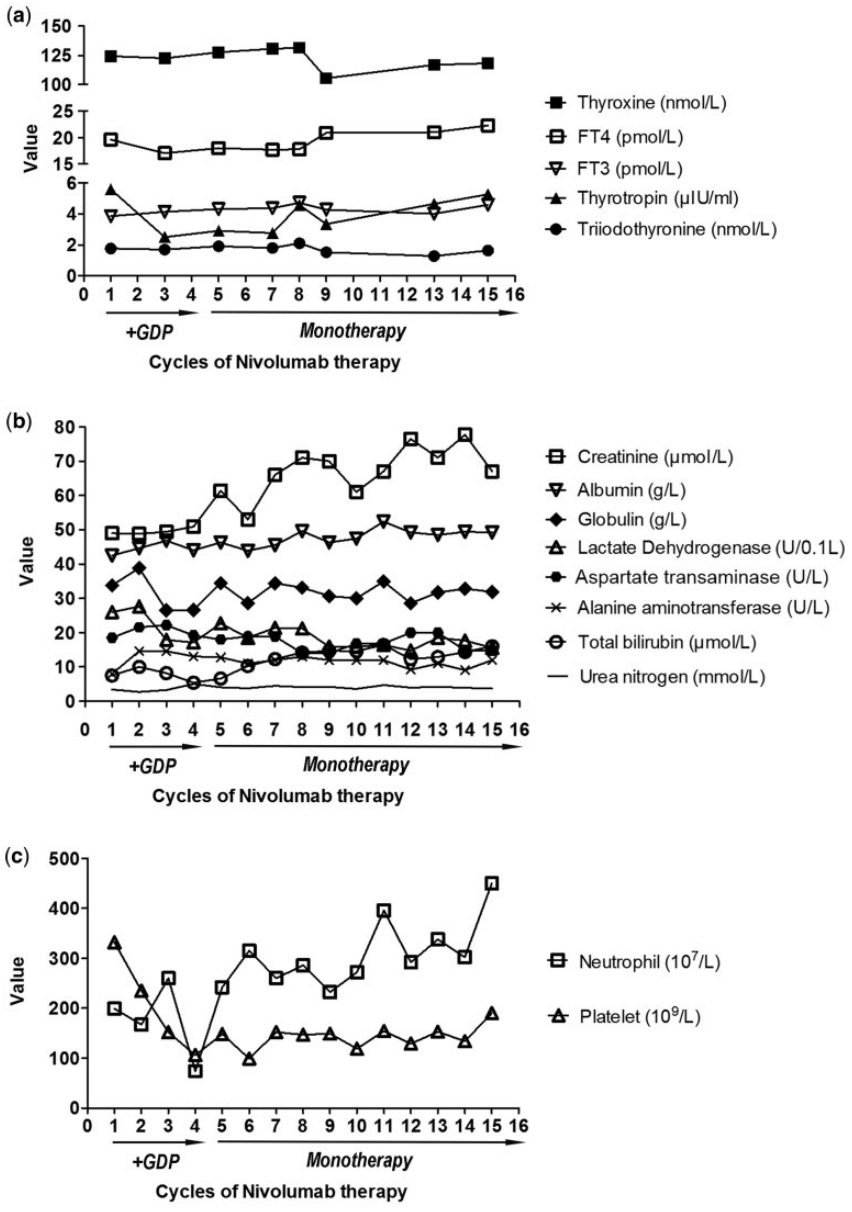


**Figure 2.** Blood test values during the whole treatment process since the first dose of nivolumab. The first four cycles were nivolumab plus GDP chemotherapy, and nivolumab maintenance monotherapy was administered since the fifth cycle. (a) Thyroxine, thyrotropin, FT3, and FT4 levels. (b) Levels of creatinine, albumin, globulin, lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, total bilirubin, and urea nitrogen. (c) Neutrophil and platelet counts.
FT4, free thyroxine; FT3, free triiodothyronine; GDP, gemcitabine, dexamethasone, and cisplatin.

In recent years, strategies focusing on the checkpoint blockade have been developed in tumor immunotherapy.[10] Therapeutic antibodies targeting the PD-1–PD-L1 axis possess clinical activity and an acceptable safety profile in treating a growing list of solid tumors and B-cell lymphomas.[13] Based on a clinical study of 53 patients with rrPMBCL, pidilizumab was approved by the US FDA for treatment of adult and pediatric patients with rrPMBCL in 2018.[11] Another antibody, nivolumab, has been granted approval for treating several solid malignancies and cHL. However, studies regarding application of nivolumab for PMBCL are limited. Only five reports have described using nivolumab for treatment of PMBCL/rrPMBCL (Table 1) as follows. In a phase I study published in 2016, two patients with PMBCL were recruited and treated with nivolumab at doses of 1 or 3 mg/kg every 2 weeks after previous systemic treatments.[14] No objective responses were observed in this previous study. In another phase I study, one patient with PMBCL received combined therapy of nivolumab and ipilimumab, and died during the therapeutic process.[15] Recently, two reports showed the potential therapeutic efficiency of nivolumab for patients with refractory PMBCL/rrPMBCL who showed failure with conventional immunochemotherapy.[16,17] Both of these two cases had immune-related adverse effects during the antibody treatment process. One patient with high-grade neutropenia had nivolumab stopped temporarily and was treated with intravenous immunoglobulin.[16] The other patient with zoster reactivation was controlled by administration of valacyclovir.[17] Recently, Zinzani and colleagues showed that combined treatment of nivolumab and brentuximab vedotin had promising antitumor activity and a manageable safety profile in patients with rrPMBCL.[18] In this phase II study, 30 patients were recruited and treated with nivolumab 3 mg/kg and brentuximab vedotin 1.8 mg/kg every 3 weeks. The objective response rate was 73%, and 37% achieved

**Table 1.** Reports regarding application of nivolumab in primary mediastinal large B-cell lymphoma/relapsed and refractory primary mediastinal large B-cell lymphoma.

| Reports | Number of cases | Dose | Combined treatment | Adverse events | Response (yes/no) |
|---|---|---|---|---|---|
| Lesokhin AM et al., 2016[14] | 2 | 1 or 3 mg/kg | – | – | No |
| Ansell S et al., 2016[15] | 1 | 3 mg/kg | Ipilimumab | – | No |
| Wright Z et al., 2017[16] | 1 | – | No | High-grade neutropenia | Yes |
| Yassin R et al., 2019[17] | 1 | 3 mg/kg | No | Zoster reactivation | Yes |
| Zinzani, PL et al., 2019[18] | 30 | 240 mg | Brentuximab vedotin | Neutropenia, thrombocytopenia, and peripheral neuropathy (83% of patients) | 73% of patients |
| Present case | 1 | 2–3 mg/kg | GDP chemotherapy | Mild fatigue and pyrexia | Yes |

Note: – means not indicated in the report.

CR and 37% achieved partial remission. Of 30 patients, 25 of them had drug-related adverse events and the most common were neutropenia, thrombocytopenia, and peripheral neuropathy.[18] In the present case, we attempted several available approaches in treating the patient's relapsed disease, but failed to control the progress of the mass. After much discussion with the patient and her family, we considered an off-label nivolumab and GDP chemotherapy as salvage treatment for the patient. In September 2017, her second CR was achieved after four cycles of combined treatment. Currently, with continued nivolumab maintenance monotherapy, the patient has remained in CR for longer than 28 months.

Immune-related adverse events that are associated with checkpoint blockade often start within the first few weeks to months after treatment, but can occur any time and in any organ. The most common immune-related adverse events are hypothyroidism, nausea, diarrhea, pyrexia, and fatigue.[19,20] In the present case, we were concerned about immune-related organ damage since the first dose of nivolumab. The patient reported moderate fatigue and pyrexia after each administration of nivolumab, and soon recovered within 2 to 3 days. Blood testing was performed during the whole therapeutic process and the data were reviewed and analyzed. Blood levels of thyroxine, thyrotropin, free triiodothyronine, and free thyroxine indicated no thyroiditis (Figure 2a). Our patient also showed normal metabolic data during the whole process of nivolumab therapy (Figure 2b). Neutrophil and platelet counts were decreased in the first four combined therapies because of toxicity of GDP chemotherapy but they then recovered to normal levels during continued nivolumab maintenance monotherapy (Figure 2c).

Unlike other lymphomas, prognostic biomarkers are largely lacking in PMBCL.[12] Some serum molecules, such as CCL17 and CD163, are considered as potential biomarkers for predicting and monitoring responses and detection of relapses in patients with Hodgkin lymphoma.[12,21] The role of serum biomarkers in PMBCL remains to be investigated. Radiological imaging should only be used in patients who have new clinical symptoms or signs suggestive of relapse, but not in asymptomatic patients.[9,22]

To the best of our knowledge, this is the first reported case of nivolumab plus GDP chemotherapy that induced CR with no severe immune-related organ damage in a patient with rrPMBCL. We also report the longest follow-up observation of successful application of nivolumab in a patient with rrPMBCL.

This report supplements the limited literature of nivolumab for treatment of PMBCL/rrPMBCL and provides implications for clinical trial design regarding the potential use of nivolumab in treatment of rrPMBCL. Further investigation needs to be performed for potential application of single or combined use of nivolumab for patients with rrPMBCL who experience failure with conventional therapeutic approaches.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## ORCID iD

Yuan Liu https://orcid.org/0000-0003-4880-5185

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