Annals of Clinical Case Reports

Short Communication
Published: 08 Jul, 2022

PD-1 Blockade with Pembrolizumab in Relapsed/ Refractory Primary Mediastinal B-Cell Lymphoma

Halahleh K[1], Ma'koseh M[1], Rawashdeh M[1], Barakat F[2], Odai AA[3], Nofal A[3], Lina H[4], Muradi I[5] and Akram Al[6]*

[1]Department of Internal Medicine, Medical Oncology Hematology & Bone Marrow Transplantation, King Hussein Cancer Center, Jordan

[2]Department of Hematopathology, King Hussein Cancer Center, Jordan

[3]Department of Radiology, King Hussein Cancer Center, Jordan

[4]Al-Quds University College of Medicine, Palestine

[5]Department of Internal Medicine, University of Tripoli, Tripoli, Libya

[6]Department of Nuclear Medicine, King Hussein Cancer Center, Jordan

Abstract

Primary Mediastinal Large B-Cell Lymphoma (PMBCL) is rather rare aggressive B-cell lymphoma characterized by frequent amplification and chromosomal rearrangements involving 9p24.1, resulting in the expression of the Programmed cell Death-1 (PD-1) ligands PD-L1 and PD-L2, leading to the inhibition of cytotoxic T lymphocytes. Pembrolizumab, a humanized IgG4 monoclonal antibody, binds PD-1 and blocks the interaction of PD1-PDL1 and 2, resulting in enhanced activity of the immune system against tumor cells. Pembrolizumab has shown activity in PMBCL and in some cases of primary and Secondary Central Nervous System (CNS) and testicular lymphomas. We report 4 patients with advanced refractory PMBCL, who were treated with Pembrolizumab and achieved complete remission, 3 patients prior to Autologous Bone Marrow Transplantation (ABMT) and 1 after ABMT relapse with reasonable median remission duration of 13.25 months (range: 8 to 28 months).

Keywords: Primary mediastinal lymphoma; PMBCL; Pembrolizumab; Autologous transplantation

Introduction

Primary Mediastinal Large B-Cell Lymphoma (PMBCL) is rather infrequent aggressive lymphoma of thymic origin, shares some clinical, pathologic, and genetic features with classical Hodgkin's Lymphoma, and accounts for 5 percent of all non-Hodgkin lymphomas [1]. PMBCL is characterized by type 2 T-Helper Cell (TH2)-skewed cytokine profile and constitutive activation of Nuclear Factor κB (NF-κB), resulting in the inhibition of cytotoxic T lymphocytes via the PD-1-PD-L1 axis [2].

PD-L1 is expressed in 36% to 100% of PMBCL cases [3,4]. Chromosome 9p24.1 copy number gains are also frequently detected in PMBCL (29% to 55%) [3,5]. Though, PD-L2 protein rare in Diffuse Large B Cell Lymphoma (DLBCL), it is robustly expressed by most PMBCL cases and is often associated with PDCD1LG2 copy gain [3,5], chromosomal rearrangements involving 9p24.1 were detected in 20% PMBCL samples [3]. The presence of genetic alterations enhances the expression of PD-L1 and PD-L2 [3].

Although the majority of newly diagnosed patients can be cured with multiagent chemoimmunotherapy with or without consolidative radiation [6,7], the outcome for patients with relapsed or refractory PMBCL (rrPMBCL) is poor, especially for patients who are ineligible for or relapse after second-line Autologous stem-cell Transplantation (ABMT) [8,9]. Axicabtagene ciloleucel, anti CD30 immunoconjugate brentuximab vedotin have non-significant activity in PMBCL [10,11].

Frequent amplification of 9p24.1 in PMBCL result in an enhanced tumor expression of the Programmed cell Death-1 (PD-1) ligands PD-L1 and PD-L2, increase susceptibility of PMBCL to PD-1 blockade. In the phase IB KEYNOTE-013 (ClinicalTrials.gov identifier: NCT01953692) on 21

OPEN ACCESS

Correspondence:
Khalid Halahleh, Department of Internal Medicine, Medical Oncology Hematology & Bone Marrow Transplantation, King Hussein Cancer Center, Queen Rania Al Abdullah Street, P.O. Box 1269, Amman 11941, Jordan, Tel: +962-6-530-0460(Ext: 1346); Fax: +962-6-534-2567; E-mail: Kh.06314@khcc.jo

Received Date: *26 Apr 2022*
Accepted Date: *05 Jul 2022*
Published Date: *08 Jul 2022*

Citation:
Halahleh K, Ma'koseh M, Rawashdeh M, Barakat F, Odai AA, Nofal A, et al. PD-1 Blockade with Pembrolizumab in Relapsed/Refractory Primary Mediastinal B-Cell Lymphoma. Ann Clin Case Rep. 2022; 7: 2243.

ISSN: 2474-1655

Table 1: Patients characteristics.

Disease	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	37	43	20	41
Female/Male	M	M	F	F
B-Symptoms (Yes/No)	Yes	Yes	Yes	Yes
Objective response	Complete remission	Complete remission	Complete remission	Complete remission
Prior lines of therapy	3	3	5	4
Prior radiation (Yes/No)	No	Yes	Yes	No
Prior rituximab (Yes/No)	Yes	Yes	Yes	Yes
N of Pembrolizumab cycles	6	5	4	5
Progression-free survival (mo)	8.5+	8+	28+	18+

patients with rrPMBCL, and phase II KEYNOTE-170 (ClinicalTrials.gov identifier: NCT02576990) study on 53 patients, the ORR was 48% and 45% (CR 33%, 18%), median PFS was 10.4 and 5.5 months and overall survival of 31.4 months and not reached in Keynote 170, respectively [12]. The magnitude of abnormality in the 9p24 region in 42 evaluable patients in keynote 170 trial was associated with PD-L1 expression, which in turn was significantly associated with PFS [10]. Based on keynote 170 study, in June 2018, pembrolizumab was granted accelerated approval by the United States Food and Drug Administration (US FDA) for use in rrPMBCL patients, who have progressed after two or more lines of prior therapy [13]. The activity of PD-1 blockade in classical Hodgkin lymphoma [14] prompted us to evaluate this approach in rrPMBCL.

Patients, Treatment and Results

Here, we report 4 patients with rrPMBCL, who were treated with Pembrolizumab, a human immunoglobulin G4 monoclonal antibody that targets PD-1 and blocks engagement of the PD-1 ligands. Informed written consent for off-label use of Pembrolizumab was obtained from all 4 patients. This is a consecutive series of 4 patients, from King Hussein Cancer Center-Amman-Jordan between first of August 2016 and 24th of January 2017. Patients details illustrated in Table 1. Median follows up of 13.25 months (range: 8 to 18 months).

The median age at the time of recurrent/refractory disease was 39 years (range, 20-43), and the median Karnofsky Performance Status (KPS) was 70% (range, 60 to 90). Four patients had stage IVB disease associated with disease bulk, and pleuropericadial involvement in 2 patients; one patient had thyroid gland and localized bone involvement (T11 vertebrae).

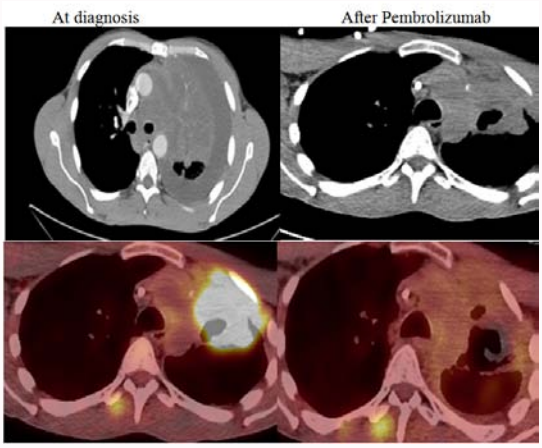

Figure 1: Case 1 at diagnosis and after pembrolizumab.

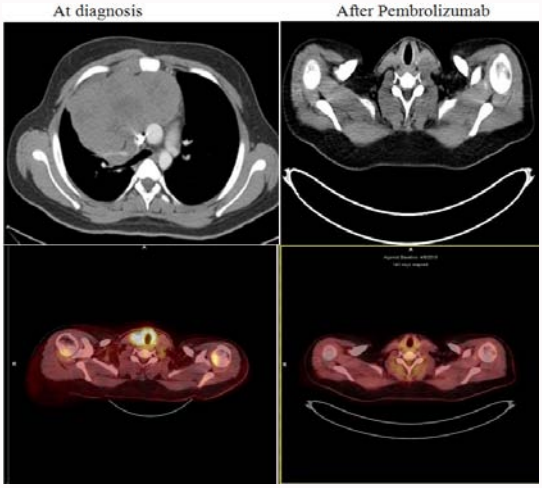

Figure 2: Case 2 at diagnosis and after pembrolizumab.

All patients were treated with standard-of-care regimens and had no other available options. All 4 patients were Refractory to First Line Treatment (RCHOP), and had multiply recurrent disease; one patient relapsed with diffuse bone and pulmonary involvement. All 4 patients received a median of 4 previous chemotherapy lines (range: 3-5), 1 patient required re-irradiation to mediastinal disease bulk due to recurrent mediastinal disease associated with compressive pulmonary symptoms. Salvage treatments including GDP, ICE, and DHAP chemotherapy regimens. All 4 patients received pembrolizumab at fixed dose of 200 mg/kg IV every 3 weeks at a median of 5 cycles (range: 4-6). All 4 patients had objective response and achieved complete remission at a median of 4 cycles (range: 3-4). Three patients received high dose chemotherapy consolidation (BEAM) conditioning after Pembrolizumab (patients 1-3) and patient 4 relapsed after ABMT received salvage Pembrolizumab and planned for allogeneic Hematopoietic Transplantation (allo-HCT) consolidation. He achieved complete remission and continued in remission at 18 months of follow up after the last dose of pembrolizumab.

All 4 patients were symptomatic prior to start of Pembrolizumab. All patients improved clinically with improved KPS. Objective metabolic and radiological responses (PET-CT) to treatment with Pembrolizumab were achieved in 4 patients (Table 1). Responses were confirmed by PET CT and no disease recurrence identified at last follow up. The median number of pembrolizumab treatments to objective radiographic response was 4 (range, 3-4), (Figures 1-4).

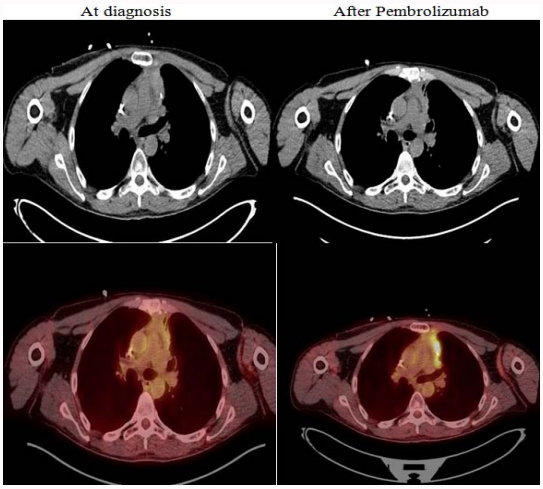

Figure 3: Case 3 at diagnosis and after pembrolizumab.

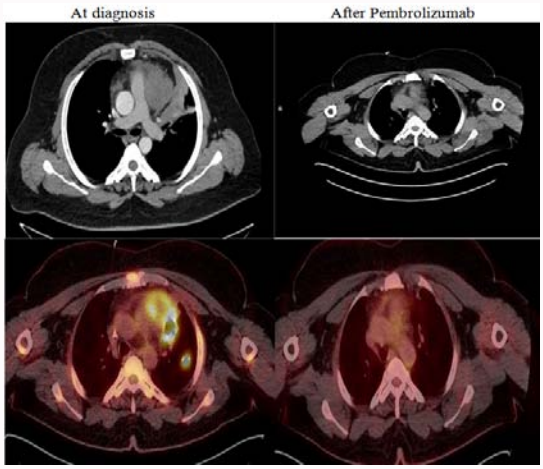

Figure 4: Case 4 at diagnosis and after pembrolizumab.

The median duration of follow-up was 13.25 months. At last follow up, 3 patients after ABMT were alive and continued in complete metabolic remission at 8+, 5+ and 28+ months; 1 patient who relapsed after ABMT, received 5 doses of pembrolizumab, achieved complete remission, but unfortunately discontinued due to pulmonary toxicity grade 3. He declined allo-HCT fairing of complications. He continued to have complete metabolic remission at 18 months follow up.

Pembrolizumab was well tolerated in 2 patients. The toxicities of pembrolizumab, including grade 2 pneumonitis, that may have exacerbated by previous radiation in 1 (patient 4) with moderate to severe restriction and decreased diffusion capacity, which prompted discontinuation of Pembrolizumab after the fifth cycle and improved with inhalers and steroid treatment; grade 2 fatigue in another patient, both thought to be drug-related. One patient developed thyroiditis-like picture with normal thyroid function, which improved spontaneously.

Discussion and Conclusion

Relapsed/refractory PMBCL remains a major unmet need in lymphoma. In this report, 4 patients with primary refractory disease following standard therapies, responded to off-label treatment with pembrolizumab and remain progression-free at a median of 13.25 months. Our data supporting reports of others that pembrolizumab is active in rrMBCL and support further investigation of PD-1 blockade in this rare entity.

Contribution

All authors have the concept of the study, Dr. KH collected the data, data analysis, wrote the initial and final typescript. Dr. AA arranged the PET CT images; Dr. OA arranged the CT images. I.M and H.L helped in data curation and draft editing. Final typescript was reviewed and approved by all authors.

Acknowledgement

Patients and their families and medical care providers.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
2. Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268-77.
3. Shi M, Roemer MGM, Chapuy B, Liao X, Sun H, Pinkus GS, et al. Expression of Programmed Cell Death 1 Ligand 2 (PD-L2) Is a distinguishing feature of primary mediastinal (Thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain. Am J Surg Pathol. 2014;38(12):1715-23.
4. Menter T, Bodmer-Haecki A, Dirnhofer S, Tzankov A. Evaluation of the diagnostic and prognostic value of PDL1 expression in Hodgkin and B-cell lymphomas. Hum Pathol. 2016;54:17-24.
5. Hebart H, Lang P, Woessmann W. Nivolumab for refractory anaplastic large cell lymphoma: A case report. Ann Intern Med. 2016;165(8):607-8.
6. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368(15):1408-16.
7. Rieger M, Österborg A, Pettengell R, White D, Gill D, Walewski J, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: Results of the Mabthera International Trial Group study. Ann Oncol. 2011;22(3):664-70.
8. Kuruvilla J, Pintilie M, Tsang R, Nagy T, Keating A, Crump M. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. Leuk Lymphoma. 2008;49(7):1329-36.
9. Vardhana S, Hamlin PA, Yang J, Zelenetz A, Sauter CS, Matasar MJ, et al. Outcomes of relapsed and refractory primary mediastinal (thymic) large B-cell lymphoma treated with second-line therapy and intent to transplant. Biol Blood Marrow Transplant. 2018;24(10):2133-8.
10. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-44.
11. Zinzani PL, Pellegrini C, Chiappella A, Di Rocco AD, Salvi F, Cabras MG, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: Results from a phase 2 clinical trial. Blood. 2017;129(16): 2328-30.
12. Armand P, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. J Clin Oncol. 2019;37(34):3291-9.

13. FDA Approves Pembrolizumab for Hodgkin Lymphoma. Accessed 17 September 2021.

14. Moskowitz CH, Zinzani PL, Fanale MA, Armand P, Johnson NA, Radford JA, et al. Pembrolizumab in relapsed/refractory classical Hodgkin lymphoma: Primary end point analysis of the phase 2 Keynote-087 Study. Blood. 2016;128(22):1107.