



Pembrolizumab 투여로 Pseudoprogression 이후 완전 관해에 도달한 호지킨 림프종 1예

성균관대학교 의과대학 삼성서울병원 ¹내과, ²병리과

홍주현¹ · 배주환¹ · 이상글¹ · 임민기¹ · 고영혜² · 김석진¹ · 김원석¹

Complete Remission after Pseudoprogression in Refractory Classical Hodgkin Lymphoma Treated with Pembrolizumab

Joohyun Hong¹, Joohwan Bae¹, Sang geul Lee¹, Mingi Lim¹, Young Hye Ko², Seok Jin Kim¹, and Won Seog Kim¹

Departments of ¹Internal Medicine, ²Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Classical Hodgkin lymphoma (cHL) is a highly curable disease, but the prognosis for relapsed/refractory cHL is grave. Pembrolizumab has recently shown impressive effects in patients with relapsed/refractory cHL in a phase Ib study (KEYNOTE-013). This report presents a case of a 17-year-old male with refractory cHL who received multiple chemotherapy regimens and radiotherapies, including brentuximab vedotin. Following both the second and fourth cycles of intravenous pembrolizumab 100 mg (2 mg/kg), positron emission tomography/computed tomography (PET/CT) scan showed progression. However, because performance status and fever improved, treatment was continued, and complete remission was confirmed by PET/CT after eight cycles of pembrolizumab. This case suggests that clinicians need to be aware of the potential for pseudoprogression in patients treated with pembrolizumab. (Korean J Med 2017;92:415-418)

Keywords: Hodgkin disease; Pembrolizumab

INTRODUCTION

Classical Hodgkin lymphoma (cHL) is highly curable with a combination of chemotherapy and radiotherapy [1]. In contrast, patients with relapsed/refractory disease have much poorer prognosis. Pembrolizumab has shown outstanding results in a phase Ib study of relapsed/refractory cHL (KEYNOTE-013) [2].

Here, we report the case of a 17-year-old male with refractory cHL after treatment with multiple chemotherapies, radiotherapies, and brentuximab vedotin (BV), who showed complete remission (CR) after pseudoprogression when treated with pembrolizumab.

Received: 2017. 4. 7

Revised: 2017. 5. 7

Accepted: 2017. 6. 2

Correspondence to Won Seog Kim, M.D., Ph.D.

Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea

Tel: +82-2-3410-6548, Fax: +82-2-3410-1754, E-mail: wonseog.kim@samsung.com

Copyright © 2017 The Korean Association of Internal Medicine

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

CASE REPORT

A 17-year-old male presented with face and neck swelling and was diagnosed with nodular sclerosis-type cHL in September 2012. A chest computed tomography (CT) scan revealed a 10-cm-sized mediastinal mass corresponding to stage IA (unfavorable, bulky). He was treated aggressively with multiple chemotherapy regimens and radiotherapies. He received three cycles of ABVD (doxorubicin, bleomycin, vincristine, and dacarbazine), one cycle of AVD without bleomycin due to bleomycin-induced pneumonitis, and involved field radiotherapy (IFRT) targeting the anterior mediastinum, which led to stable disease. Less than 2 months after completing IFRT, he was treated with two cycles of ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), which produced a minor response, and one cycle of C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone), which resulted in a partial response (PR). He refused further chemotherapy. After 1 year he

received two cycles of ruxolitinib, two cycles of brentuximab, palliative local RT targeting the lung lesion, four cycles of rituximab + bendamustine, two cycles of lenalidomide, two cycles of vincristine, and three cycles of gemcitabine + dexamethasone over 15 months, but his disease was resistant and progressed.

As the disease showed progression despite extensive therapy, treatment with intravenous (IV) pembrolizumab 100 mg (2 mg/kg) every 3 weeks was started. However, after one cycle of pembrolizumab, dyspnea and pain in the left shoulder, flank, and anterior chest wall was aggravated, due to seeding nodules in the lung. Consequently, pembrolizumab was stopped and palliative RT at 15 Gy was used to target the seeding nodules. Pembrolizumab was resumed after completing RT, but a positron emission tomography/computed tomography (PET/CT) scan showed disease progression with a mixed response after completion of the second and fourth cycles. This was consistent with immune-related progressive disease (irPD), based on the immune-related response evaluation criteria in solid tumors

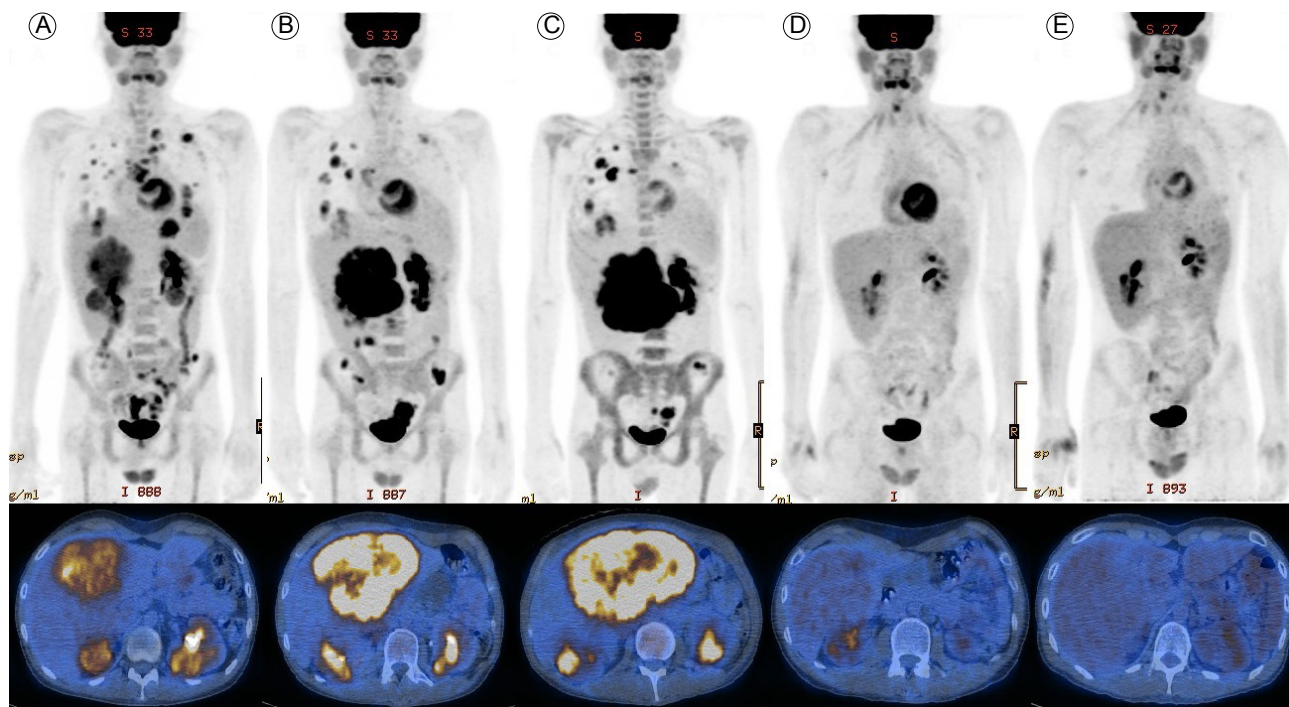


Figure 1. (A) Baseline positron emission tomography/computed tomography (PET/CT) before pembrolizumab. (B) PET/CT after the second cycle showing aggravated high uptake in the liver, newly developed lesions, and some resolving lesions. (C) PET/CT after the fourth cycle demonstrating immune-related progressive disease (irPD) based on immune-related response criteria (irRC), immune-related response evaluation criteria in solid tumors (irRECIST) and immune-confirmed progressive disease (iCPD) based on iRECIST. (D) PET/CT after the eighth cycle showing complete remission (CR). (E) PET/CT after the 14th cycle showing CR maintenance.

(irRECIST) 1.1, and immune-confirmed progressive disease (iCPD) based on iRECIST (Fig. 1). In spite of irPD and iCPD, the patient's fever resolved, and his Eastern Cooperative Oncology Group performance status improved from 2 to 0, such that he was able to walk; before starting pembrolizumab, he had required a wheelchair. We thus decided to continue the therapy under the assumption that PET/CT showed pseudoprogression. After the fifth cycle of pembrolizumab, grade III dyspnea and mild fever developed suddenly. Pembrolizumab treatment was resumed after a month of recovery. After the eighth cycle, PET/CT revealed CR (Fig. 1). PET/CT done after the 14th cycle, the last imaging evaluation to date, indicated maintenance of CR (Fig. 1). As of January 2017, the patient had received 18 cycles of pembrolizumab and was living a normal life without any side effects, with on-going pembrolizumab treatment every 3 weeks.

DISCUSSION

The phase Ib trial KEYNOTE-013 was a pivotal study of the use of pembrolizumab in relapsed or refractory cHL after BV failure. Among 31 patients, 5 achieved CR and 15 achieved PR, for an overall response rate of 65% [2]. Based on these promising data, pembrolizumab was chosen as the treatment for our refractory cHL patient. However, the present case varies from the KEYNOTE-013 study, in that our patient received a much lower dose of pembrolizumab: 100 mg (2 mg/kg) IV every 3 weeks rather than 10 mg/kg every 2 weeks. Another report showed an overall response rate of 100% (CR: 80%, PR: 20%) among five cHL patients treated with low-dose pembrolizumab (median dose 100 mg, 100-200 mg every 3 weeks) [3].

A unique characteristic of immunotherapy is that tumors often seem to grow on imaging during initial cycles, even if they are responding to treatment [4]. Abundant T-cell infiltration during immunotherapy accounts for this phenomenon [5]. This effect has given rise to new response-assessment criteria, such as immune-related response criteria (irRC) and irRECIST, which are based on existing World Health Organization criteria and on response evaluation criteria in solid tumors (RECIST) [6]. Although they are slightly different, both evaluate response ac-

cording to the concept of total measured tumor burden, which includes baseline target lesions and new measurable lesions. These criteria also include non-target measurable lesions and non-measurable lesions. Even if irPD is diagnosed based on irRC or irRECIST, confirmation is needed or recommended by repeated assessment at least 4 weeks from the date of initial irPD diagnosis [6]. Recently, the RECIST working group also developed iRECIST, which was modified from RECIST 1.1 to standardize and validate response criteria for immunotherapy. In iRECIST, initial PD based on RECIST 1.1 is called immune-unconfirmed progressive disease (iUPD), which requires reassessment between 4 and 8 weeks after initial iUPD diagnosis to be classified as iCPD [7].

Although the present case revealed irPD by irRC, and irRECIST and iCPD by iRECIST, which were confirmed by follow-up PET/CT more than 4 weeks apart, pseudoprogression was eventually confirmed. Consequently, clinical manifestations of this disease during immunotherapy are as important as imaging evaluation and, even if progression is suspected, decisions regarding cessation of treatment should be carefully weighed. In a study that evaluated pseudoprogression during pembrolizumab treatment in advanced melanoma patients, early pseudoprogression was observed before week 12 at a frequency of 4.6%, and delayed pseudoprogression was observed after week 12 at a frequency of 2.8% [4]. The appropriate reassessment time point after iUPD is thus more than 8 weeks in some tumor types, such as melanoma treated with a CTLA4 inhibitor, because pseudoprogression is well-described in these tumors and because there are no effective salvage therapies available after progression [7]. Because the appropriate reassessment time point for pseudoprogression in cHL has not been established, in cases where there is definite clinical improvement despite imaging data indicating progression, treatment should be continued until further follow-up, regardless of the number of cycles.

Further studies are needed to identify the median response cycle and frequency of pseudoprogression in cHL.

Pembrolizumab could be a useful treatment option, without significant toxicity, for patients with relapsed or refractory cHL. Clinicians should be aware of the potential for pseudoprogression, and treatment cessation should be weighed carefully, es-

pecially in patients showing clinical improvement.

Further studies are needed not only to establish a dose and schedule that will minimize side effects and cost while maximizing anti-tumor effects, but also to determine patterns of pseudoprogression in cHL.

중심 단어: 호지킨림프종; 펌브롤리주맙

REFERENCES

1. Horwitz SM, Zelenetz AD, Gordon LI, et al. NCCN guidelines insights: non-hodgkin's lymphomas, version 3.2016. *J Natl Compr Canc Netw* 2016;14:1067-1079.
2. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol* 2016 Jun 27 [Epub]. <http://dx.doi.org/10.1200/JCO.2016.67.3467>.
3. Chan TS, Luk TH, Lau JS, Khong PL, Kwong YL. Low-dose pembrolizumab for relapsed/refractory hodgkin lymphoma: high efficacy with minimal toxicity. *Ann Hematol* 2017;96:647-651.
4. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol* 2016;34:1510-1517.
5. Di Giacomo AM, Danielli R, Guidoboni M, et al. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 2009;58:1297-1306.
6. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412-7420.
7. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143-e152.