


# Successful treatment with low-dose nivolumab in refractory Hodgkin lymphoma after allogeneic stem cell transplantation

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Received: 8 October 2016 / Revised: 10 January 2017 / Accepted: 10 January 2017 / Published online: 17 January 2017  
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**Abstract** Previous studies have reported that an antibody that blocks programmed cell death 1 (PD-1) has therapeutic activity in patients with refractory/relapsed Hodgkin lymphoma (HL). However, the safety and efficacy of these agents in the post-allogeneic stem cell transplantation (allo-SCT) setting are not well known. Here, we describe a patient who was diagnosed as classical HL and treated with five regimens of chemotherapies with autologous SCT. Complete remission (CR) was not achieved following this initial treatment, so we performed allo-SCT from an HLA-matched sibling donor. Since his disease progressed at day 403 after allo-SCT, we decided to use nivolumab in the treatment of his refractory disease. To prevent the worsening of his chronic graft-versus-host disease (GVHD), we reduced the initial dose and frequency of nivolumab compared with the previous report. After four courses of 0.5 mg/kg of nivolumab every three weeks, FDG-PET imaging showed partial response (PR) to the treatment, a remarkable result. However, since the escalated dose of 2 mg/kg resulted in worsening of dyspnea and skin sclerosis, we initiated systemic administration of prednisolone

and reduced nivolumab to 1 mg/kg. At the time of this report, his HL is in stable PR with three weekly administration of nivolumab and steroid controlled mild chronic GVHD.

**Keywords** Hodgkin lymphoma · Nivolumab · GVHD · PDL-1

## Introduction

Immune checkpoint inhibitors have shown clinical efficacy in cancer treatment. One such agent is nivolumab, a humanized antibody against programmed cell death 1 (PD-1) with substantial therapeutic activity in patients with refractory/relapsed Hodgkin lymphoma (HL) [1]. PD-1 is a receptor of the Ig superfamily that negatively regulates T cell antigen receptor signaling by interacting with specific ligands including PD-L1. Interaction between PD-L1 on tumor cells and PD-1 on T-cells results in impaired anti-tumor responses [2–4]. However, the PD-1/PD-L1 signaling axis also contributes to establishing immune tolerance; thus, nivolumab treatment for post-allogeneic stem cell transplantation (allo-SCT) could increase the risk of a patient's allo-reaction causing graft-versus-host disease (GVHD). Indeed, the PD-1 inhibitor pembrolizumab induced fatal GVHD in patients undergoing allo-SCT for refractory HL [5], while other post-allo-SCT patients receiving nivolumab developed pneumonitis and hepatitis that responded to prednisolone [6]. Based on these few reports, the safety dose and interval of PD-1 inhibitor treatment for allo-SCT patients remain unknown. Here, we report a case treated by nivolumab for refractory HL after allo-SCT.

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## Case report

### Onset and treatment before allo-SCT

A 25-year-old man who developed non-productive cough and general fatigue showed mediastinal lymphadenopathy on chest X-P at another hospital. Admission was recommended for diagnosis and treatment, but denied. Eight months later, this man was admitted to our hospital for lymphadenopathy spread throughout his body and face as well as edema of his right hand. Pathological examination of a needle inguinal lymph node biopsy specimen revealed nodular sclerotic classical HL. He reported sweats and weight loss as systemic symptoms. Based on HL lesions also detected in bone marrow and pleural effusion, the clinical stage was diagnosed as IVB. His initial performance status score was 2 and his international prognostic score was 6 (male, serum Alb, Hb, clinical stage, white blood cell count of 20,200/ $\mu$ l, and lymphocytes in peripheral blood at <8%) [7]. The patient received six courses of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine); however, fluoro-deoxyglucose positron emission tomography (FDG-PET) examination after the final course revealed progression disease (PD). Then, several regimens of salvage chemotherapy were attempted for his refractory HL; however, no CR or PR was achieved (Table 1). We, therefore, initiated stem cell transplantation. The first treatment was by autologous peripheral blood stem cell transplantation (auto-PBSCT) with a conditioning regimen of melphalan (70 mg/m<sup>2</sup> for 2 days) and 10 Gy of total body irradiation. At the 17th day of stem cell transplantation, FDG-PET revealed residual lesions in the lungs, clavicle, sternum, thoracic vertebra, sacrum, pelvis, and abdominal and inguinal lymph nodes; thus, we considered allo-SCT with 20 Gy of local irradiation. When he reached 28 years, the allo-SCT was performed from an HLA-matched sibling donor, with fludarabine (25 mg/m<sup>2</sup> for 5 days) and busulfan (3.2 mg/kg 4 times for 2 days) as conditioning regimen and cyclosporine and short-term methotrexate as prophylactics of GVHD. The clinical course is shown in Fig. 1.

### After allo-SCT

An FDG-PET examination at day 30 after allo-SCT revealed residual lesions only in thoracic and lumbar vertebra (Fig. 2a). Because of not in complete remission even though allo-SCT, we rapidly decreased cyclosporine to improve the allo-reaction. The onset of acute GVHD was evident on the skin at day 14 (stage 1). Thereafter, the acute GVHD reached Grade III with skin stage 3 and gut stage 1 at day 63. We immediately started systemic administration of 1 mg/kg prednisolone to gradually decrease the symptoms of GVHD. To control the residual HL lesion without reducing graft-versus-lymphoma reaction, we subsequently administered six courses of brentuximab vedotin, two courses of gemcitabine, and six courses of donor lymphocyte infusion (DLI); however, these treatments were not effective.

After 6 courses of DLI (day 340 after allo-SCT), the patient developed dry cough and shortness of breath. Computed tomography of the chest showed bilateral ground glass opacity, infiltration, and pleural effusion, and his worsened condition precluded a broncho-fiber examination. Although his blood and sputum culture,  $\beta$ -D glucan, anti-aspergillus antigen, and serum CMV pp65 testing were all negative, we started the patient on antibiotics, an anti-fungal agent, and ganciclovir. After no effect with three days of this treatment, we resumed 1 mg/kg of prednisone and his condition immediately improved. From the clinical manifestation, we diagnosed his lung dysfunction as late-onset non-infectious pulmonary complication (NIPC).

The FDG-PET examination at day 403 after allo-SCT showed massive progression of the HL (Fig. 2b), and thereafter we applied to the ethics committee at Tokai University School of Medicine in June 2015 for off-label use of nivolumab in this patient.

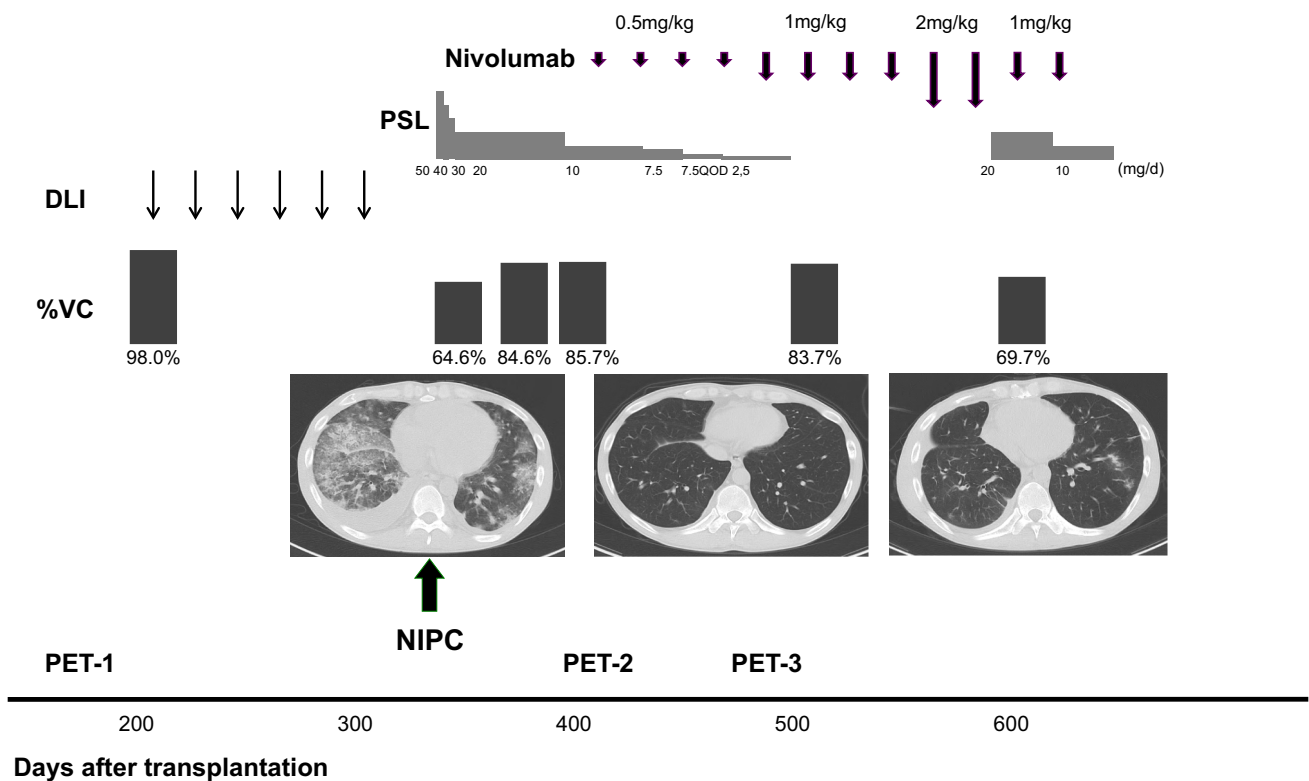
### Nivolumab treatment

In the submitted study protocol, the initial nivolumab dose was 0.5 mg/kg every 3 weeks, with the dose changed appropriately according to disease progression or adverse events. Given that this patient had DLI-induced pulmonary

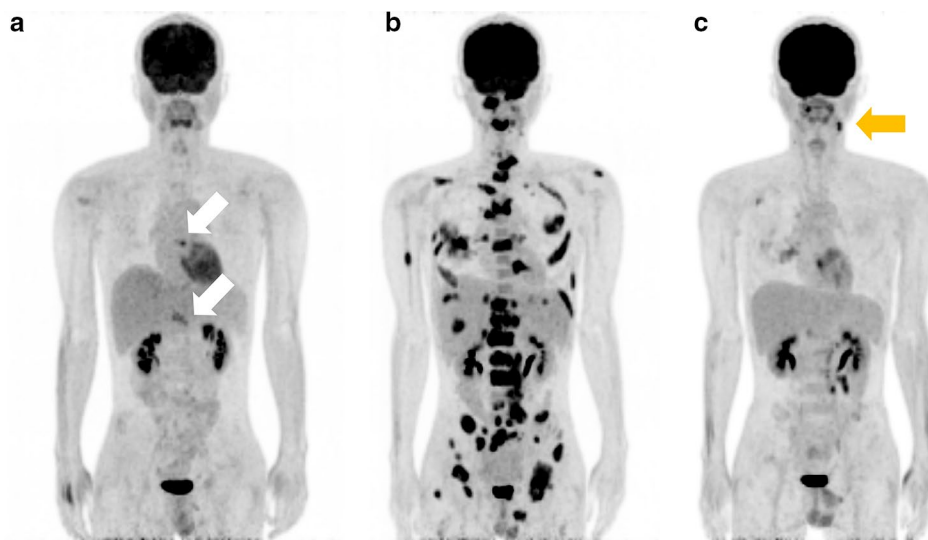
**Table 1** Salvage chemotherapies after ABVD

Regimen	Drugs	Course	Result
CHASE	Cyclophosphamide, cytarabine, etoposide, dexamethasone	2	PD
EPOCH	Cyclophosphamide, etoposide, doxorubicin, vincristine, prednisone	2	PD
BV	Brentuximab vedotin	2	PD
IVAM	Ifosfamide, cytarabine, etoposide, methotrexate	1	PD

PD progression disease



**Fig. 1** Clinical course and treatment of the case. PET-1, PET-2, and PET-3 are represented in Fig. 2a–c, respectively. PSL, Prednisolone (mg/day); DLI, donor lymphocyte infusion; NIPC, non-infectious pulmonary complication; %VC, % vital capacity; PET, positron emission tomography

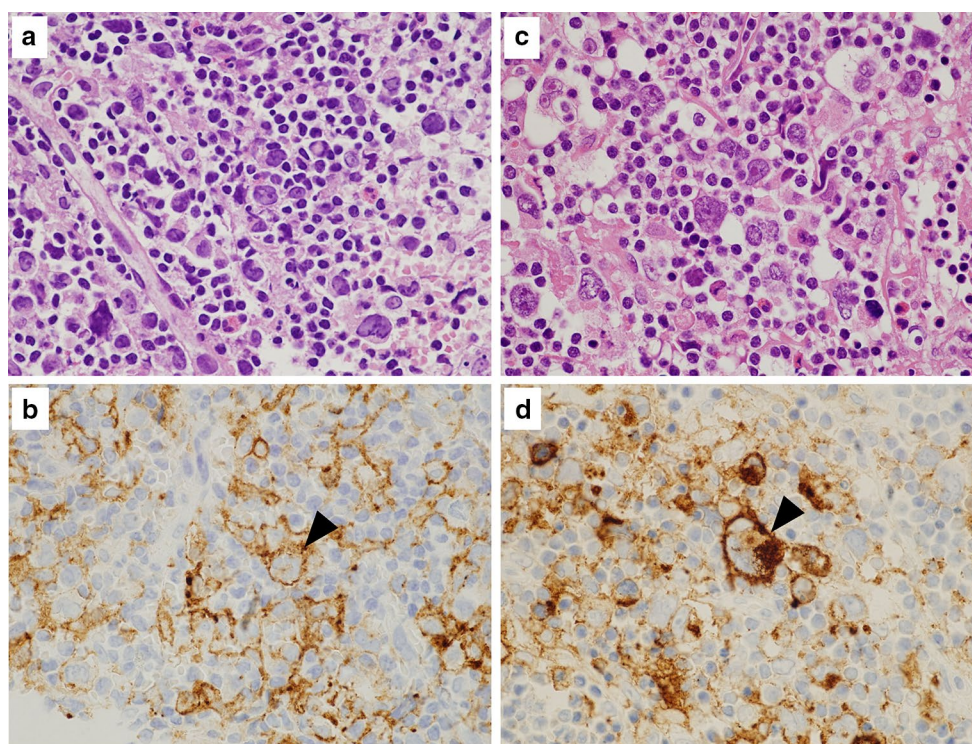


**Fig. 2** **a** FDG-PET at day 30 after allo-SCT. *White arrows* indicate residual lesions in the thoracic and lumbar vertebra. **b** FDG-PET at day 403 after allo-SCT shows massive recurrence of HL lesions. **c**

FDG-PET after 4 courses of 0.5 mg/kg nivolumab treatment. *Yellow arrow* indicates a residual lymph node, which was excised and examined for PD-L1 expression

complications, we chose to reduce the initial dose by 1/6 administered every four weeks to avoid exacerbating his allo-reaction. This change to the initial dose and

treatment schedule was approved (Tokai University School of Medicine IRB-ID; 15M003), considering the influence of nivolumab on GVHD and possible adverse lung



**Fig. 3** Histopathological findings from the initial biopsy (**a, b**) and following nivolumab treatment (**c, d**). Hematoxylin–eosin staining shows Hodgkin cells and Reed–Sternberg cells before and after

nivolumab treatment specimens (**a, c**). Large atypical cells expressing PD-L1 initially and after the nivolumab treatment (**b, d, arrowhead**). Mag.  $\times 400$

effects, and the treatment started once patient consent was obtained. After 4 courses of nivolumab, the FDG-PET showed remarkable effects of the treatment, with only three lesions detected at the cervical lymph node, right lung, and right hilar lymph node (Fig. 2c). We then performed a cervical lymph node biopsy to assess resistance of the HL to nivolumab. Pathological examination of the node revealed strong expression of PD-L1 in Hodgkin/Reed–Sternberg cells (Fig. 3d); thus, we increased the next dose of nivolumab to 1 mg/kg, and subsequently to 2 mg/kg, following no adverse event after three courses of 1 mg/kg nivolumab. The patient then developed reduced %VC by spirometer examination and worsening sclerotic skin chronic GVHD. Since his chronic GVHD required treatment with prednisolone, his ongoing treatment was changed to a three weekly maintenance dose of 1 mg/kg nivolumab. At the submission of this manuscript, the patient had undergone 4 months of nivolumab infusion.

## Discussion

Cumulative knowledge from case reports such as the present study is a crucial part of establishing the safety and efficacy profile of immune checkpoint inhibitors such as

nivolumab in post-auto-SCT patients [8]. In particular, establishing safe dosage regimens, treatment intervals, and endpoints will help to plan prospective trials. In murine models, PD-1 blockade increased the incidence of GVHD [9], whereas selective blockade of CTLA-4 to treat late relapse after transplantation augmented graft-versus-tumor effects without accelerating GVHD [10, 11]. However, our experimental case report shows that low-dose, 3-weekly nivolumab is tolerable for post-allo-SCT patients, even in those with active chronic GVHD.

After 6 courses of DLI, the patient was diagnosed with NIPC, based on sterile blood and sputum cultures, the ineffectiveness of antibiotic, anti-fungal, and anti-viral treatments, and his immediate response to prednisone. His NIPC resolved after a brief period, but worsened again immediately with the increase in nivolumab dose to 2 mg/kg. This clinical course of NIPC suggested that nivolumab induced GVHD in the lungs of this patient. Thus, although he did not have severe GVHD in other organs, the clinical effects suggested that the dose and interval of nivolumab for patients with post-allo-SCT should be determined carefully.

Yared et al. [6] previously reported a patient who developed pneumonitis and hepatitis one week after nivolumab administration, and other authors reported

anti-PD-1-related pneumonitis [12, 13]. The present patient did not develop hepatitis, but did show decreasing %VC by spirometry after maintenance therapy with 2 mg/kg nivolumab. In all cases, oral prednisone was effective for the complication; however, based on the poor prognosis of patients with NIPC after allo-SCT, strict monitoring of pulmonary function and/or chest X-ray is recommended in post-allo-SCT patients during the nivolumab therapy.

Auto-PBSCT is a standard therapy for classical HL that is refractory to chemotherapy. When the patient relapses after auto-PBSCT, allo-SCT is the most effective candidate therapy [14]; however, little is known about the effectiveness of therapy for patients who relapse after allo-SCT. Previous studies and our case suggest that checkpoint inhibitors have excellent efficacy in refractory HL after allo-SCT [5, 6], and that further such studies should establish safe use of these agents in post-allo-SCT patients.

#### Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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