

Repeated courses of escalating doses of Nivolumab in refractory Hodgkin lymphoma with recurrent relapses post allografting: A safe and effective treatment approach

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Abstract

For patients with Hodgkin Lymphoma (HL) who experience relapse post allogeneic stem cell transplantation, limited treatment options exist, and the ultimate outcome is poor. Recently, the programmed cell death protein-1 (PD-1) inhibitors have shown remarkable efficacy in patients with refractory/relapsed HL, also demonstrating an acceptable safety profile. However, due to effects on T-cell activity, the use of PD-1 inhibitors post allografting may potentially increase the risk of treatment-emergent graft versus host disease. We herein report the clinical course of a patient who experienced multiple relapses of HL post allogeneic stem cell transplantation. He failed several treatment modalities but he responded to escalating doses of the PD-1 inhibitor nivolumab, given at two different treatment time points, also demonstrating minimal and easily manageable toxicity.

Introduction

In patients allografted for refractory Hodgkin Lymphoma (HL) who experience disease recurrence post allogeneic hematopoietic stem cell transplantation (alloSCT), the traditional immunomodulatory approaches [reduction or discontinuation of immunosuppressive treatment (IST) with or without donor's lymphocytes infusions (DLIs)] are only partially effective and are usually accompanied with high incidence of induced graft-versus-host disease (GvHD), while chemotherapeutic approaches are mostly unsuccessful.^{1,2} It has been shown that HL cells have a unique biologic dependence on the programmed cell death protein-1 (PD-1), which is expressed on activated T-cells, and other

lymphoid and myeloid cells.^{3,4} Nivolumab (Opdivo®, Bristol-Meyers Squibb), a fully humanized IgG4 anti-PD-1 monoclonal antibody, has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of adults with relapsed/refractory classical Hodgkin Lymphoma (cHL) after autoHSCT and Brentuximab Vendotin (BV) treatment.^{5,6}

For patients who have relapsed HL post allograft, the inhibition of the PD-1 pathway, might theoretically enhance the graft *versus* HL (GvHL) effect by upregulating the activation of donor-derived T-cells however, the increased alloreactivity of donor T-cells may also promote severe treatment-emergent GvHD (te-GvHD), thus contributing to increased risk for morbidity and mortality.⁷

Herein, we describe the clinical course of a patient with HL, who experienced early relapse post alloSCT and failed to achieve disease control after immunomodulatory approaches (including anti-CD30 infusion), but responded twice to Nivolumab treatment. To reduce the risk of GvHD without negatively affecting the GvHL effect, we treated the patient with escalating doses of Nivolumab.

Case Report

A young male patient, diagnosed at the age of 11 years with nodular sclerosis cHL and stage IIIBS, was initially treated in a pediatric center with the ABVD/COPP regimen. After 6 cycles of treatment he failed to achieve remission and therefore a Bortezomib-based salvage regimen was given, followed by autoSCT after BEAM conditioning regimen (Table 1). Nine months post autoSCT, he experienced disease progression with liver, marrow and multiple sites of lymph node involvement and he subsequently received BV (Table 1). Although there was an initial partial response, eventually, 8 months later, the disease progressed again, and the combination of BV with Bendamustine (BvB) was given as previously described by La Casce *et al.*⁸ After 3 cycles of the BvB combination, the disease was assessed to be in very good partial remission (VGPR) and since he had a suitable fully matched sibling donor, he proceeded to alloSCT after a reduced-intensity conditioning regimen, consisting of thiotepa, fludarabine and cyclophosphamide (Table 1). Cyclosporine plus mycophenolate mofetil were administered as GvHD prophylaxis. He engrafted successfully and experienced no GvHD during

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the early post-transplant period. Three months later, the disease progressed (first relapse post alloSCT), and in addition to IST discontinuation, BV at standard doses was given. With this treatment modality, partial disease control was achieved. However, the patient developed induced GvHD. Steroids plus cyclosporine were initiated, but the GvHD proved to be steroid-dependent, therefore the patient continued on steroid-based treatment. Four months later (16 months post allografting), while he was on double IST, he complained of cough and fever. High resolution computed tomography (HRCT) along with lung biop-

sy confirmed second disease progression post alloSCT (Figure 1A). IST was tapered and Nivolumab was chosen as the next treatment option, since the patient fulfilled the criteria for Nivolumab initiation as per FDA approved indications.^{5,6} PD-1 expression was not evaluated on the tissue biopsy because this test was not available in our center at that time. Although the standard dose for Nivolumab in adult patients is 240 mg every two weeks, because our patient was a young adolescent and underweight (42 kg), we chose to treat him with at the dose of 3 mg/kg every two weeks in order to minimize treatment-related toxicity and risk of te-GvHD.⁹ After 2 cycles, significant clinical improvement was noticed. However, the patient complained of severe abdominal pain and diarrhea. Colonic biopsies confirmed te-GvHD; no other organ involvement. The IST doses were increased while Nivolumab dose was reduced to 2 mg/kg every 3 weeks. After two additional cycles at the aforementioned dose, significant disease improvement according to CT criteria was documented (Figure 1B), and the patient became completely asymptomatic from the respiratory and gastrointestinal systems. At this time point, patient's family asked for a second opinion from another center. Following the new medical advice, nivolumab treatment was held and the patient continued only IST to control the residual GvHD. Six months after Nivolumab discontinuation, he presented to our center with the third relapse post alloSCT (Figure 2A). He was re-treated with Nivolumab, and in order to avoid severe toxicities and to minimize the risk of severe te-GvHD, we used escalating doses

of Nivolumab, starting from 1.5 mg/kg every 2 weeks, with a planned dose increase of 0.5 mg/kg every 2 cycles, if the previous dose was well tolerated. After 8 cycles he achieved a complete metabolic response (mCR) according to PET/CT criteria (Figure 2B). He continued on escalating doses of Nivolumab and since no treatment-related toxicity was noticed, he finally was able to receive the maximum dose of 3 mg/kg. He was also on low dose IST (tacrolimus 1 mg daily and prednisone 10 mg every other day) to minimize the risk of the te-GvHD. After the 15th infusion of the treatment, he developed diarrhea. New colon biopsies revealed non-specific colitis changes, and the symptoms attributed to the well-described adverse reaction of the check-point inhibitors.¹⁰ Since the patient was in a prolonged remission (7 months

after the second course of treatment with PD-1 inhibitor), the decision was to discontinue the Nivolumab infusions and to continue only with low doses of IST treatment of GvHD. After eight months post Nivolumab discontinuation, the patient was evaluated to be in continued mCR with full (100%) donor-derived hematopoietic chimerism.

Discussion

Despite the well-described GvHL effect, relapse post alloSCT is a major cause for treatment failure, resulting in low likelihood of cure.^{1,2} The mechanism of evasion from donor-derived T-cell surveillance by malignant cells has not been elucidated yet. It has been reported that T-cells from some

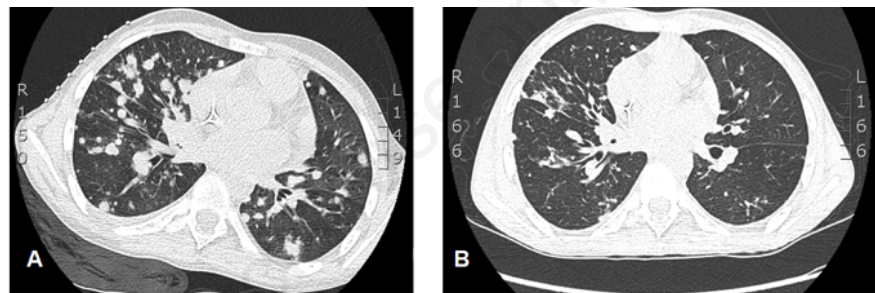


Figure 1. HRCT during the first course of Nivolumab treatment. A) Before Nivolumab administration HRCT showed multiple nodules in the lungs bilaterally. The CT guided biopsy confirmed relapse of cHL. B) After the first 4 cycles of Nivolumab administration the HRCT showed excellent response since the majority of the malignant nodules have been disappeared. HRCT: High resolution computed tomography, cHL: classical Hodgkin Lymphoma.

Table 1. Summary of treatment.

Regimen	Drugs and dosage	Courses	Response
ABVD/COPP	Doxorubicin: 25 mg/m ² for 2 days (1&15) Bleomycin: 10 mg/m ² for 2 days (1&15) Vinblastine: 6 mg/m ² for 2 days (1&15) Dacarbazine: 400 mg/m ² for 2 days (1&15) Cyclophosphamide: 200 mg/m ² for 2 days (1&8) Vincristine: 1.5 mg/m ² for 2 days (1&8) Procarbazine: 100 mg/m ² for 10 days Prednisone: 1 mg/kg for 10 days	6	Induction failure
AHOD0521	Ifosfamide: 3000 mg/m ² for 4 days (1-4) Vinorelbine: 25 mg/m ² for 2 days (1&5) Bortezomib: 1.2 mg/m ² for 3 days (1, 4 &8)	2	Very good partial response
BEAM	Carmustin (BCNU): 300 mg/m ² for 1 day (D-6) Etoposide: 100 mg/m ² for 4 days (D-5 to -2) Cytarabine: 200 mg/m ² for 4 days (D-5 to -2) Melphalan: 160 mg/m ² for 1 days (D-1)	1	Disease progression: 9 months post autoSCT
Bv	Brentuximab vedotin: 1.8 mg/m ² for 1 day	8	Disease progression
BvB	Brentuximab: 1.8 mg/m ² for 1 day Bendamustin: 90 mg/m ² for 2 days	3	Very good partial response
Thiotepa, fludarabine and cyclophosphamide	Thiotepa: 7 mg/m ² for 1 day (D-7), Fludarabine: 30 mg/m ² for 3 days (D-5 to -3) Cyclophosphamide: 50 mg/m ² for 2 days (D-5 & -4)	1	Disease progression: 3 months post alloSCT

patients who experience relapse after alloSCT demonstrate an exhausted T cell phenotype, having also a low capacity to produce cytokines necessary for T-cell cytotoxic activity.¹¹⁻¹³ The well-documented overexpression of PD-1 molecules on circulating lymphocytes and HL cells at the time of relapse, suggests that alterations in signaling across the PD1-synapse could be at least an additional pathway for the post alloSCT immune evasion.¹¹ Based on this knowledge, the PD-1/PDL-1 pathway inhibitors could be an effective alternative treatment for HL patients who experience relapse after alloSCT.

Our patient had disease refractory to multiple treatment approaches including autoSCT, alloSCT and antiCD30 monoclonal antibody administration; he eventually achieved mCR after Nivolumab treatment. Timmerman *et al.* reported the results of Nivolumab treatment in patients with HL who had previously treated with Brentuximab after autoSCT failure. After a median follow-up of 15.4 months (minimum 12 months), the overall response rate (ORR) was 68%, the CR incidence was 8%, while the 1-year progression-free and overall survival were 54% and 94%, respectively.¹⁴ The experience of Nivolumab for relapsed disease post alloSCT is limited and based on small series of patients or case reports. Two retrospective studies reported promising results with ORR of 80% and 95% and high rates of durable complete remissions 42% and 50%.¹⁵⁻¹⁷ It is noteworthy

that the published ORR for patients who received PD-1 inhibitors for relapsed HL post alloSCT are higher as compared to the response rates that have been observed in patients who were treated with PD-1 inhibitors for disease recurrence post autoSCT or conventional chemotherapy. A plausible explanation for this efficacy inferiority in the autoSCT/conventional chemotherapy setting, could be that the PD-1 inhibitor acts on patient T-cells and therefore, either intrinsic patient's lymphocytes deficiency or the previous exposure to chemotherapy, adversely affect the immune response despite priming by PD-1 inhibitor. Oppositely, in the allograft setting, the PD-1 inhibitor acts on healthy donor-derived T-cells which are also naïve to chemotherapy.

A major complication of Nivolumab administration after alloSCT, apart from the other common side effects, is the increased donor-derived T-cell alloreactivity, thus resulting in te-GvHD.^{10,15-18} Our patient, after the first 2 cycles of Nivolumab at the dose of 3 mg/kg, developed severe gut te-GvHD which was effectively controlled with IST treatment plus Nivolumab dose reduction. It is worth mentioning that prior to Nivolumab treatment, the patient had already experienced induced-GvHD which is a well-known predisposing factor for GvHD flare after PD-1 inhibitor treatment.¹⁸ So far, there are no definite guidelines regarding the dosing and the duration of treatment with PD-1 inhibitors post allograft. In a prospective phase I/Ib multicen-

ter study, 8 patients were treated with Nivolumab after allograft for relapsed HL (6 patients at 1 mg/kg and 2 patients at 0.5 mg/kg). In the 1 mg/kg cohort there were 2 non-relapse related deaths while 2 patients experienced severe chronic GVHD. On the contrary, no significant toxicities have been observed in the 0.5 mg/kg cohort of patients.¹⁹ Onizuca *et al.* published the clinical course of a patient who received Nivolumab at escalating doses for relapsed HL post alloSCT, starting from 0.5 mg/kg. The dose-escalating ratio was 100% every 4 cycles, with the maximum reached dose of 2 mg/kg; finally, due to te-GvHD occurrence, the dose was reduced to 1 mg/kg. In terms of the primary disease response, the authors reported that only VGPR was achieved.²⁰ In a recent report, Herbaux *et al.* recommend initiating Nivolumab at a low dose (0.5 mg/kg) followed by escalating doses if no te-GvHD occurs.²¹ In our case, during the second course of nivolumab treatment, we chose to start with a higher dose (1.5 mg/kg), followed by a lower escalating ratio (0.5 mg/kg every 2-3 cycles) if the medication was well tolerated. By using this treatment schedule, the patient was able to receive in total 15 cycles and after the 7th cycle/infusion he reached the maximum Nivolumab dose of 3 mg/kg without any major complication. Interestingly, the efficacy of Nivolumab was robust even at the lower doses, as our patient, during the second escalating Nivolumab course, achieved mCR after the 7th infusion (ranges of the given doses 1.5-2 mg/kg).

It has not been reported in the literature whether previous exposure to Nivolumab adversely affects its efficacy or exacerbates toxicity in the case of subsequent administration. Our patient received two nivolumab courses with an interval period of 6 months, and both times he responded successfully, suggesting that at least in certain cases, Nivolumab re-administration retains its efficacy even if malignant cells have been previously exposed to it.

Conclusions

In this heavily pretreated patient with refractory disease, Nivolumab, given at intermediate dose followed by low rate of dose escalation, was a well-tolerated treatment, offering also the desired efficacy leading to mCR attainment. Documentation of mCR even after previous exposure to Nivolumab, merits further investigation. Because of the limited existing data, the treatment duration and the exact dose of PD-1 inhibitors in the post alloSCT setting

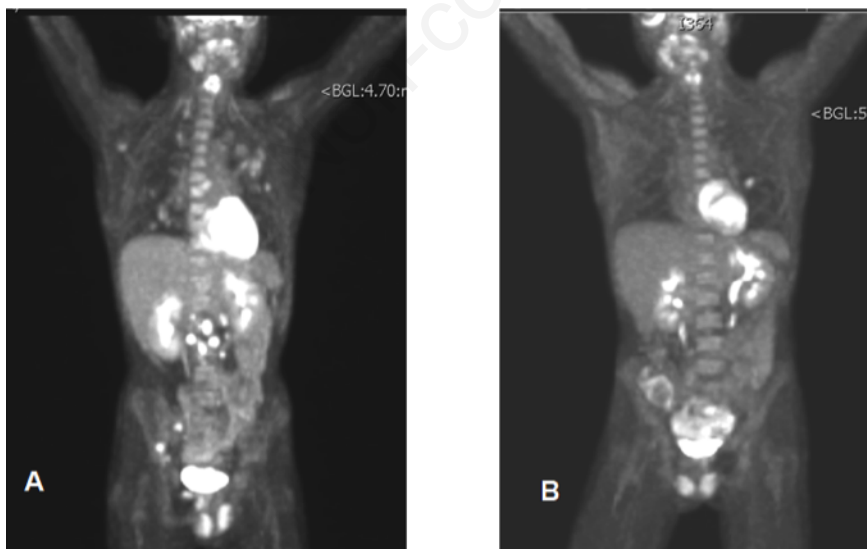


Figure 2. PET/CT scan during the second course of Nivolumab administration. A) Six months after Nivolumab discontinuation the PET/CT showed disease recurrence in the lungs, axillary and retroperitoneal lymph nodes. B) After 8 cycles of Nivolumab re-administration, mCR was documented according to PET/CT criteria. PET/CT: Positron emission tomography/computed tomography, mCR: metabolic complete remission.

have not been clarified yet and therefore, well-designed prospective studies with large series of patients are warranted.

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