Reprinted 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.

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 engulfed successfully and experienced no GvHD during 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-
Case Report

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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. 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. 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 | Dooxorubicin: 25 mg/m² for 2 days (1&15) | 6 | Induction failure |
| | Bleomycin: 10 mg/m² for 2 days (1&15) | | |
| | Vinblastine: 6 mg/m² for 2 days (1&15) | | |
| | Dacarbazine: 400 mg/m² for 2 days (1&15) | | |
| | Cyclophosphamide: 200 mg/m² for 2 days (1&8) | | |
| | Vinristine: 1.5 mg/m² for 2 days (1&8) | | |
| | Procarbazine: 100 mg/m² for 10 days | | |
| | Prednisone: 1 mg/kg for 10 days | | |
| AHOD0521 | Ifosfamide: 3000 mg/m² for 4 days (1-4) | 2 | Very good partial response |
| | Vinorelbine: 25 mg/m² for 2 days (1&8) | | |
| | Bortezomib: 1.2 mg/m² for 3 days (1, 4 &8) | | |
| BEAM | Carmustin (BCNU): 300 mg/m² for 1 day (D-6) | 1 | Disease progression: 9 months post autoSCT |
| | Etoposide: 100 mg/m² for 4 days (D-5 to -2) | | |
| | Cytarabine: 200 mg/m² for 4 days (D-5 to -2) | | |
| | Melphalan: 160 mg/m² for 1 days (D-1) | | |
| Bv | Brentuximab vedotin: 1.8 mg/m² for 1 day | 8 | Disease progression |
| BvB | Brentuximab: 1.8 mg/m² for 1 day | 3 | Very good partial response |
| | Bendamustine: 90 mg/m² for 2 days | | |
| Thiotepa, fludarabine and cyclophosphamide | Thiotepa: 7 mg/m² for 1 day (D-7) | 1 | Disease progression: 3 months post alloSCT |
| | Fludarabine: 30 mg/m² for 3 days (D-5 to -3) | | |
| | Cyclophosphamide: 50 mg/m² for 2 days (D-5 & -4) | | |

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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.13 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 alloSCT 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 alloSCT. In a prospective phase I/Iib multicenter 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 Onizuka 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...
have not been clarified yet and therefore, well-designed prospective studies with large series of patients are warranted.

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