

## BRIEF REPORT

# Tolerance and effectiveness of nivolumab after pediatric T-cell replete, haploidentical, bone marrow transplantation: A case report

Aziza T. Shad<sup>1,3\*</sup> | Jeffrey S. Huo<sup>2\*</sup> | Courtney Darcy<sup>3</sup> | Amal Abu-Ghosh<sup>3</sup> |  
Giuseppe Esposito<sup>4</sup> | Mary-Jo Holuba<sup>2</sup> | Nancy Robey<sup>2</sup> | Kenneth R. Cooke<sup>2</sup> |  
Heather J. Symons<sup>2</sup> | Allen R. Chen<sup>2</sup> | Nicolas J. Llosa<sup>2</sup>

<sup>1</sup>Department of Pediatric Hematology/Oncology, The Herman & Walter Samuelson Children's Hospital at Sinai, Baltimore, Maryland

<sup>2</sup>Department of Pediatric Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

<sup>3</sup>Department of Pediatric Oncology, Medstar Georgetown University Hospital, Washington, District of Columbia

<sup>4</sup>Department of Nuclear Medicine, Medstar Georgetown University Hospital, Washington, District of Columbia

## Correspondence

Aziza T. Shad, Department of Pediatric Hematology/Oncology, The Herman & Walter Samuelson Children's Hospital at Sinai, 2401 W. Belvedere Ave., Baltimore, MD 21215.

Email: ashad@lifebridgehealth.org

\*Aziza T. Shad and Jeffrey S. Huo contributed equally to the writing of the manuscript.

## Abstract

To date, there has been a lack of pediatric experience regarding the efficacy and tolerability of immune checkpoint inhibitors after haploidentical hematopoietic stem cell transplant (HSCT). We present the case of a 22-year-old female with multiple-relapsed Hodgkin lymphoma (HL) who presented with a new relapse after haploidentical (post-haplo) HSCT. Anti-PD-1 therapy with nivolumab resulted in significant objective disease response and clinical improvement without notable side effects, including the absence of a graft-versus-host disease (GVHD). This case report suggests that immune checkpoint inhibition may be safely tolerated even in the setting of haploidentical HSCT, without triggering overt GVHD.

## KEYWORDS

anti-PD1, haploidentical bone marrow transplant, Hodgkin lymphoma, immunotherapy, nivolumab, relapse

## 1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplant (HSCT) is a potentially curative therapy for a wide spectrum of pediatric hematopoietic malignancies. The utility of HSCT has been hindered in part by the low availability of suitable HLA-matched donors, especially among minority populations. Nearly all patients have HLA-haploidentical (haplo)-related donors, and novel approaches have enabled the use of T-cell replete, haplo-HSCT with favorable rates of engraftment, graft-versus-host disease (GVHD), and transplant-related mortality similar to those seen after the HSCT using HLA-matched sibling donors.<sup>1-3</sup> However, the relapse of malignant disease after allogeneic HSCT remains a significant problem.

Immune checkpoint inhibition is another strategy for enhancing antitumor activity. Tumors can evade immune destruction by express-

ing ligands for immune checkpoint pathways, allowing tumors to inhibit antitumor T-cell function. Antibodies against immune checkpoint pathway ligands (or receptors) can inhibit tumor-induced downregulation of T-cell function and restore antitumor T-cell activity. This approach has shown very promising results in pretransplant patients.<sup>4</sup> In theory, immune checkpoint inhibition could be used to amplify graft-versus-tumor activity in patients who relapse after HSCT and reestablish remission. However, animal models suggest that this strategy could also potentiate severe to lethal GVHD.<sup>5,6</sup> This could be especially true in haplo-HSCT with its greater degree of HLA mismatch.

We here report nivolumab treatment of a patient 14 months after a nonmyeloablative T-cell replete, haplo-HSCT with post-transplant cyclophosphamide, mycophenolate mofetil (MMF), and tacrolimus/sirolimus for refractory Hodgkin disease. In the early post-HSCT period, the patient had 100% donor chimerism and no clinical GVHD. After a period of initial disease control, she subsequently progressed approximately 180 days after HSCT. After extensive discussion, the patient was administered off-label therapy with nivolumab. She tolerated nivolumab therapy without any evidence of

Abbreviations: CR, complete remission; FDG, [18F]-fluorodeoxyglucose; GVHD, graft-versus-host disease; GvT, graft-versus-tumor effect; HSCT, hematopoietic stem cell transplant; HL, Hodgkin lymphoma; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; PET-CT, positron emission tomography-computed tomography

auto-immune complications or GVHD, and achieved and remains in complete remission (CR).

## 2 | RESULTS

Our patient was diagnosed at 15 years of age with Stage IV-A classical Hodgkin lymphoma (HL). She was enrolled and treated on COG protocol AHOD0031.<sup>7</sup> She was classified as a slow early responder after the first two cycles and per protocol randomized to receive two cycles of DECA (dexamethasone, etoposide, cisplatin, and cytarabine), involved-field radiotherapy, and two further cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone). She was in CR at the end of therapy, but relapsed 3 months later. She subsequently received six cycles of vinorelbine, gemcitabine, prednisolone, and ifosfamide and achieved CR2. She underwent high-dose chemotherapy with carmustine, etoposide, and cyclophosphamide, followed by autologous HSCT, but relapsed for the third time 5 months later.

Over the 4 years following auto-HSCT, she received seven cycles of bendamustine, six cycles of brentuximab, eight cycles of ChLVPP (chlorambucil, vinblastine, procarbazine, and prednisone), three cycles of lenalidomide, four cycles of metronomic chemotherapy (with IV vinblastine, PO cyclophosphamide, PO methotrexate, PO celecoxib), and six cycles of gemcitabine, vinorelbine, and liposomal doxorubicin. During this time, her disease status alternated between partial response to progressive disease. After her sixth line of post-auto-HSCT therapy, her disease activity on positron emission tomography-computed tomography (PET-CT) was limited to residual

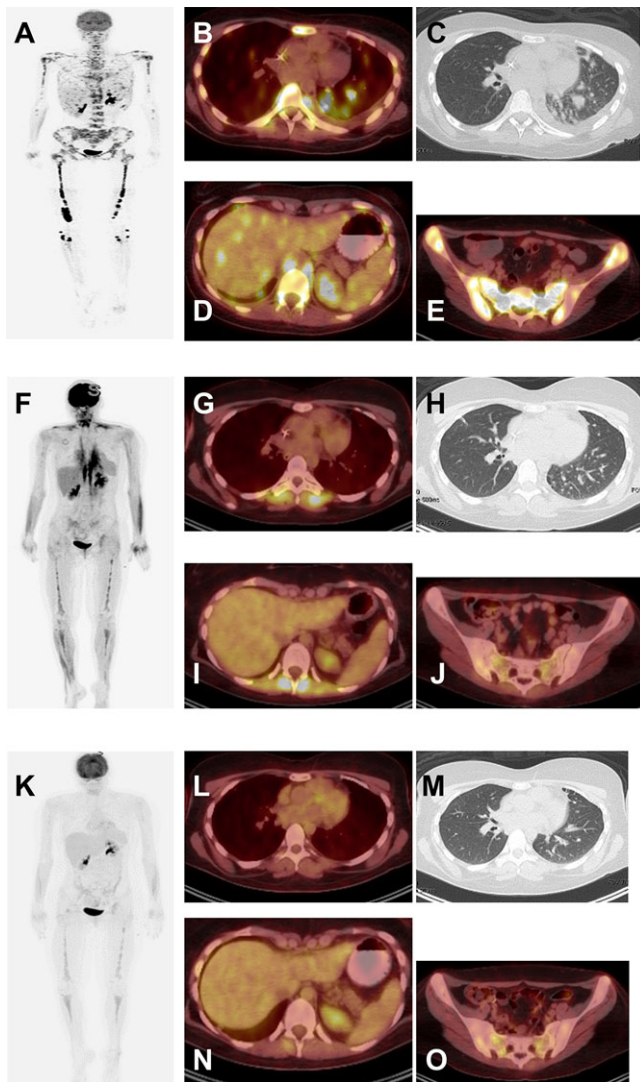
[18]F-fluorodeoxyglucose (FDG) avidity in the trochanteric region of her left femur and the vertebral body of T8, and she had a performance status (Karnofsky) of 90%. With the intent of consolidating persistent residual disease, she proceeded with haplo-HSCT.

At the age of 20 years, she underwent nonmyeloablative conditioning with fludarabine, cyclophosphamide, and low-dose total body irradiation preparative regimen as previously published<sup>2</sup> (Table 1). She received unmanipulated, T-cell replete bone marrow from her HLA haplo-identical sister. GVHD prophylaxis consisted of cyclophosphamide 50 mg/kg on days +3 and +4 with mesna, MMF (days 5–35), and tacrolimus starting on day +5 as per the institutional standard. Tacrolimus was subsequently replaced with sirolimus beginning day +16 secondary to peripheral neuropathy. Neutrophil and platelet engraftment occurred on days +19 and +31, respectively, and the peripheral blood CD3 and whole blood donor chimerism was 100% on day +28 and at all subsequently measured time points. Her most notable complications included a catheter-related superior vena cava thrombus diagnosed on day +58, which resolved following thrombolysis and 6 months of anticoagulation therapy. Our patient also developed colitis, first presenting on day +104, which waxed and waned over the next subsequent months. Pathological findings on gut biopsy were not consistent with acute GVHD, and ultimately symptoms resolved after diagnosis of pancreatic insufficiency and pancreatic enzyme replacement. She never had any manifestations of liver, skin, or other GVHD.

Day +72 PET-CT showed resolution of all abnormal FDG activity, consistent with CR. Sirolimus was ultimately discontinued on day +115. However, by day +181, she began to again have progressive fatigue and night sweats. PET-CT showed FDG avidity consistent with the relapse in mediastinum, left lung, T8–T12 thoracic spine, left

**TABLE 1** Timeline of haploidentical HSCT and posttransplant nivolumab interventions and disease assessments

Day pre/post-haplo-HSCT	
–6, –5	Cyclophosphamide 14.5 mg/m <sup>2</sup> IV
–6 to –2	Fludarabine 30 mg/m <sup>2</sup> IV
–1	Total body irradiation 200 cGy
Zero	Unmanipulated T-cell replete bone marrow from HLA-haploidentical sibling
+3, +4	Posttransplant cyclophosphamide 50 mg/kg IV with mesna
+5 to +35	MMF 15 mg/kg PO tid
+5 to +15	Tacrolimus, discontinued for peripheral neuropathy
+16 to +115	Sirolimus (goal 3–12 ng/ml)
+72	PET-CT: resolution of all abnormal FDG activity
+181	PET-CT: FDG avid masses in mediastinum, left lung, T8–T12 thoracic spine, left femur, nodes above and below diaphragm
	Palliative chemotherapy with
	- Rituximab, sirolimus, and vorinostat (single cycle)
	- Brentuximab and bendamustine (four cycles)
+423	PET-CT: further progression of FDG avid disease of mediastinum, lungs, pelvis and bone marrow and new lesions in liver and spleen (Figs. 1A–1E)
+430/cycle 1, day 1	Nivolumab 3 mg/kg IV q14 days
+484 (after cycle 4)	PET-CT: near resolution of all FDG-avid activity (Figs. 1F–1J)
+541 (after cycle 9)	PET-CT: complete resolution of all FDG-avid activity (Figs. 1K–1O)



**FIGURE 1** Response to nivolumab therapy in a patient with refractory HL after haplo-HSCT with posttransplant cyclophosphamide.  $^{18}\text{F}$ -FDG-PET-CT scans obtained before nivolumab therapy (A–E), after four cycles of nivolumab (F–J), and after nine cycles of nivolumab (K–O). Maximum-intensity projections (A, F, K), axial views of the lung by CT-PET fusion (B, G, L), and axial CT (C, H, M), and CT-PET fusion axial views of the liver and spleen (D, I, N) and pelvis (E, J, O)

femur, and nodal disease above and below the diaphragm. A variety of treatment options were discussed, and, ultimately, the patient began rituximab,<sup>8</sup> sirolimus, and vorinostat<sup>9</sup> but opted to stop after a single course in the favor of quality of life improvement. She subsequently received four cycles of palliative brentuximab and bendamustine, but PET-CT on day +423 showed further progression of the FDG avid disease, with new lesions in the liver and spleen and progression of the mediastinal, pulmonary, pelvic, and bone marrow disease (Figs. 1A–1E).

After an extensive discussion, on day +430, she began nivolumab 3 mg/kg every 2 weeks as recently described<sup>10</sup> (Table 1). She tolerated nivolumab therapy without any clinical evidence of autoimmunity or GVHD. PET-CT performed on day 2 of the fourth cycle of nivolumab showed near resolution of the previously noted hyperme-

tabolic activity (Figs. 1F–1J), and complete resolution was observed after the ninth cycle of nivolumab (Figs. 1K–1O). Her clinical symptoms of malignancy have completely resolved. She is currently in her 13th cycle of nivolumab and doing well.

### 3 | DISCUSSION

Although there are emerging reports of tolerability of immune checkpoint inhibition after an HLA-matched HSCT,<sup>11–13</sup> haplo-HSCT, with its greater mismatch, theoretically poses an even higher risk for auto- or allo-immune complications. In the only other reported patient in whom immune checkpoint blockade after haplo-HSCT was observed, nivolumab therapy had to be stopped after the development of steroid refractory Grade IV skin GVHD.<sup>12</sup> However, that patient had a prior history of Grade II acute GVHD, in contrast to our patient, who had no definitive GVHD prior to the nivolumab therapy. We thus present evidence that in a patient receiving haplo-HSCT with posttransplant cyclophosphamide without subsequent GVHD, nivolumab was well tolerated and efficacious, allowing our patient to achieve a CR. More systematic clinical trials and dissection of the molecular mechanisms underlying its tolerance, tolerability, and efficacy are required.

### ACKNOWLEDGMENTS

J.S.H. is a recipient of a Young Investigator Award from the Alex's Lemonade Stand Foundation and was supported by NIH T32 CA60441. This work was supported by National Institutes of Health, National Cancer Institute grant P30 CA006973 (Kimmel Cancer Center Core grant).

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

### REFERENCES

1. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. *Nat Rev Clin Oncol*. 2016;13(1):10–24.
2. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose post-transplantation cyclophosphamide. *Blood*. 2015;125(19):3024–3031.
3. Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118(2):282–288.
4. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 2015;27(4):450–461.
5. Saha A, Aoyama K, Taylor PA, et al. Host programmed death ligand 1 is dominant over programmed death ligand 2 expression in regulating graft-versus-host disease lethality. *Blood*. 2013;122(17):3062–3073.
6. Blazar BR, Carreno BM, Panoskaltsis-Mortari A, et al. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-gamma-dependent mechanism. *J Immunol*. 2003;171(3):1272–1277.

7. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651–3658.
8. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood*. 2008;111(1):109–111.
9. Janku F, Oki Y, Falchook GS, et al. Activity of the mTOR inhibitor sirolimus and HDAC inhibitor vorinostat in heavily pretreated refractory Hodgkin lymphoma patients. *J Clin Oncol (ASCO Annu Meet Abstr)*. 2014;32(15 Suppl):8508.
10. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311–319.
11. Angenendt L, Schliemann C, Lutz M, et al. Nivolumab in a patient with refractory Hodgkin's lymphoma after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2015;51:443–445.
12. Herbaux C, Morschhauser MD. Nivolumab is effective and reasonably safe in relapsed or refractory Hodgkin's lymphoma after allogeneic hematopoietic cell transplantation: a study from the Lysa and SFGM-TC. *Blood*. 2015;126(23):3979.
13. Yared JA, Hardy N, Singh Z, et al. Major clinical response to nivolumab in relapsed/refractory Hodgkin lymphoma after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2016;51(6):850–852.