Journal of Stem Cell Research and Transplantation

Open Access

Austin Publishing Group

Case Report

A Case of Immune Checkpoint Inhibitor Use Following Allogeneic Stem Cell Transplant for Relapsed and Refractory Cutaneous T-Cell Lymphoma

Stephanie Franco, MD[1]; Megan Melody, MD, MS[2]; Jonathan Moreira MD[2*]

[1]Department of Internal Medicine, Northwestern Medicine, Chicago, Illinois, USA

[2]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

***Corresponding author:** **Jonathan Moreira, MD**
Northwestern Medicine, 676 N Saint Clair St, Suite 850, Chicago, IL 60611, USA.
Tel: 312-894-3121
Email: jonathan.moreira@northwestern.edu

Received: April 12, 2024
Accepted: May 06, 2024
Published: May 13, 2024

Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) following high-dose chemotherapy is an effective form of immunotherapy for the treatment of hematologic malignancies due to the Graft-Versus-Tumor (GVT) effect. Despite the efficacy of allo-HSCT, relapse is common and carries a poor prognosis. This has led to the use of Immune Checkpoint Inhibitors (ICI) and other novel immunotherapies following allo-HSCT to enhance the GVT effect in order to prevent relapse or re-induce remission. However, concerns have been raised regarding the safety of ICIs following allo-HSCT due to the potential increase in Graft-vs-Host Disease (GVHD) in addition to the desired GVT effect.

Although PD-1/PD-L1 inhibitors have been utilized for the treatment of Cutaneous T-Cell Lymphoma (CTCL), there is limited data regarding the use of ICIs following allo-HSCT for CTCL. Here we present a case of pembrolizumab use following allo-HSCT for relapsed and refractory CTCL resulting in long-term Complete Remission (CR) without significant adverse events, including GVHD. This case suggests that PD-1 inhibition following allo-HSCT may be a beneficial treatment option for a particular subset of patients. We propose that certain patient- and disease-specific characteristics, including the presence of a viable graft with 100% donor chimerism, absence of GVHD following allo-HSCT despite tapering of immune suppression, and good performance status, made this patient an ideal candidate for ICI following allo-HSCT. However, further studies are needed to evaluate ongoing risks of ICI in the post allo-HSCT setting and determine which patients are best suited for the use of ICIs following allo-HSCT.

Keywords: Allogeneic hematopoietic cell transplantation; Checkpoint inhibition; Immune checkpoint inhibitors; Relapsed/refractory disease; T-cell lymphoma

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) following high-dose chemotherapy was the first form of immunotherapy to demonstrate clinical efficacy and potential cure in many hematologic malignancies due to the Graft-Versus-Yumor (GVT) effect, in which donor T-cells and natural killer (NK) cells target recipient tumor cells [1,2]. Despite the efficacy of allo-HSCT in the treatment of hematologic malignancies, relapse is common (30-40%) and portends a poor prognosis [3]. A potential mechanism for relapse post-transplant includes tumor evasion of the immune system via expression of Cytotoxic T Lymphocyte-Associated Protein 4 (CTLA-4) and Programmed Death-1 (PD-1), preventing T-cell activation and proliferation [3]. This has led to the use of immune checkpoint inhibitors (ICI) and other novel immunotherapies including other monoclonal antibodies, bispecific T-cell engagers, donor lymphocyte infusion, and antibody-drug conjugates following allo-HSCT to enhance the GVT effect in order to prevent relapse or re-induce remission [1]. Concerns have been raised regarding the safety of ICIs following allo-HSCT due to the theoretical increase in Graft-Vs-Host Disease (GVHD) in addition to the desired GVT effect. A systematic review of the literature by Alkhaldi et al. reported the findings of various studies examining the use of the ICIs following allo-HSCT for the treatment of Hodgkin Lymphoma (HL) [4]. Small prospective studies considering the use

Citation: Franco S, Melody M, Moreira J. A Case of Immune Checkpoint Inhibitor Use Following Allogeneic Stem Cell Transplant for Relapsed and Refractory Cutaneous T-Cell Lymphoma. J Stem Cell Res Transplant. 2024; 11(1): 1046.

of CTLA-4 inhibitor ipilimumab for relapsed disease post-transplant have shown efficacy at higher doses, which induced Complete Remission (CR) in 5 of 22 patients (22.7%) [4]. GVHD and other immune-related adverse events (irAEs) were relatively infrequent (18% and 27% respectively) [4]. Additional case reports and case series have demonstrated the safety and efficacy of PD-1 inhibitors (nivolumab and pembrolizumab) following allo-HSCT for the treatment of HL [4]. CR was achieved in five of six patients included in these case reports. Of these six patients, three did not experience GVHD, one developed skin rash concerning for GVHD, and two developed grade IV acute GVHD (liver, skin) [4]. Three case series including 3, 20, and 31 patients treated with PD-1 inhibitors following allo-HSCT showed promising efficacy but rates of GVHD ranged from 30-55% [4]. Among the 60 patients included in these case reports and case series, there were 10 fatalities attributed to GVHD or other immune-related toxicities [4]. The use of ICIs following allo-HSCT for relapse or minimal residual disease has also been studied in other myeloid and lymphoid neoplasms with similar results. In one review including 176 patients with hematologic malignancies treated with ICIs following allo-HSCT, 14% developed acute GVHD and 9% developed chronic GVHD, with 7% dying of complications related to GVHD [3]. However, the overall response rate in this population was 54% and CR was 33% [3].

Although PD-1/PD-L1 inhibitors have been used as a novel treatment strategy for Cutaneous T-Cell Lymphoma (CTCL), there is a paucity of existing data regarding the use of ICIs following allo-HSCT for the treatment of CTCL [5,6]. Here we present a case of pembrolizumab use following allo-HSCT for relapsed and refractory CTCL resulting in long-term CR without significant adverse events.

Case Report

A 52-year-old man with past medical history of melanoma managed with surgical resection presented with 1-2 years of pruritus, left inguinal lymphadenopathy, and a developing facial plaque. Skin biopsy revealed mycosis fungoides, folliculotropic type, with lymph node biopsy revealing Peripheral T-Cell Lymphoma (PTCL), stage IVA2. Over the next several years, the patient was treated with bexarotene, Narrowband Ultraviolet B (NB-UVB), interferon, topical imiquimod, spot radiation therapy, as well as low dose Total Skin Electron Beam Therapy (TS-EBT). Except for bexarotene, which was initially discontinued due to tinnitus and later resumed at a lower dose, all other therapies were relatively well tolerated and resulted in partial remission but were eventually discontinued due to progression of disease. Five years from the time of diagnosis, while still taking bexarotene and interferon, the patient developed progressive right axillary lymphadenopathy. Biopsy revealed T-cell lymphoma with large cell transformation. The patient received one cycle of pralatrexate with progression of disease followed by five cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone). Despite these therapies, the patient developed a new parotid lesion as well as new-onset neurologic symptoms (sciatica, cranial nerve VII palsy). The patient was found to have leptomeningeal disease with lumbar spine involvement on magnetic resonance imaging and Cerebral Spinal Fluid (CSF) cytology was positive for a discrete abnormal T-cell population five days after completion of cycle 5 of CHOEP. He received five doses of intrathecal methotrexate with subsequent CSF cytology negative for residual disease. The patient then underwent myeloablative conditioning with busulfan, cyclophosphamide, mesna (sodium 2-mercaptoethane sulfonate), and etoposide followed by allo-HSCT with a matched unrelated donor (19-year-old male, 10/10 human leukocyte antigen allele match).

The patient's post-transplant course was uncomplicated, without infection or GVHD. Two months following allo-HSCT, surveillance PET-CT showed interval improvement of the pre-existing hypermetabolic lesions but was notable for a new hypermetabolic lesion of the distal right lower extremity. Biopsy confirmed recurrent mycosis fungoides with large cell transformation. Lumbar puncture revealed persistent low-level Central Nervous System (CNS) involvement of disease. CD3 and CD33 T-cells demonstrated 100% donor chimerism. Immunosuppression with cyclosporine was gradually tapered off in an effort to promote GVT effect. The patient was treated with intrathecal chemotherapy (cytarabine 100 mg plus hydrocortisone 100 mg alternating with cytarabine 100 mg, methotrexate 12.5 mg, and hydrocortisone 100 mg) for 8 doses, radiation therapy to the right lower extremity lesion, and lenalidomide 5 mg daily and later 10 mg daily. Five months following allo-HSCT, peripheral blood flow cytometry revealed atypical CD4 T-cells suspicious for blood involvement of Sezary cells. Lenalidomide was discontinued and the patient was started on interferon 3MU three times per week. The patient developed a new penile lesion, which was treated with radiation therapy. He also developed new tumoral plaques of the chin, bilateral upper extremities, and medial thighs.

The patient had no history of GVHD following allo-HSCT, even with titration off immunosuppression. Chimerism reports persistently demonstrated 100% donor engraftment. Given these findings and exhaustion of other treatment options, the decision was made to proceed with checkpoint inhibitor therapy to potentiate the GVT effect. Nine months following allo-HSCT, interferon was discontinued, and the patient was started on pembrolizumab 200 mg every 21 days. PET-CT performed after three doses of pembrolizumab showed FDG-avid skin lesions of the chin, lower abdomen, and medial thigh, which was used as his new baseline. Following FDA approval for extended-interval dosing of pembrolizumab, dosing was briefly extended to 400 mg every 6 weeks but was not tolerated due to diarrhea, thus the patient was eventually transitioned back to standard dosing with pembrolizumab 200 mg every 21 days. Twenty-two months following initiation of pembrolizumab, PET-CT revealed resolution of all previously seen lesions. More than 4.5 years since initiation of pembrolizumab monotherapy, the patient remains in CR. Furthermore, pembrolizumab has been well tolerated without evidence of GVHD or other irAEs aside from mild colitis, which markedly improved with resumption of standard dosing. Clonoseq testing has been performed to evaluate for the presence of minimal residual disease beginning in 2021, with the most recent testing not demonstrating evidence for presence of the original clone.

Discussion

Immune checkpoint inhibition offers a promising therapeutic option for those with relapsed or refractory disease or high risk of relapse following allo-HSCT. While ICIs have successfully been used to prevent relapse and re-induce remission post-transplant, the broader use of these agents has been limited due to the concerns for an increased risk of GVHD and other irAEs. However, due to promising efficacy in a patient population with difficult to control disease and limited available treatment options, ICIs remain a potential therapeutic option for those with relapsed refractory disease following allo-HSCT. While the use of ICIs after allo-HSCT has been studied across multiple hema-

tologic malignancies, there is limited existing data regarding the use of this treatment strategy in those with CTCL.

While the risks vs. benefits of checkpoint inhibition following allo-HSCT must be carefully considered, the increased risk of GVHD may not be as great as presumed. A comprehensive review of the literature reported fatalities in 10 of 60 (<17%) patients treated with PD-1/PD-L1 inhibitors following allo-HSCT [4]. Without the use of ICIs, mortality at 1 year following allo-HSCT has been reported at 24.4%, with 19% of deaths attributed to GVHD (acute or chronic) [7]. It is also worth noting that certain clinical factors may impact an individual's risk of developing GVHD with ICI use following allo-HSCT. A history of GVHD following allo-HSCT tends to increase an individual's risk of developing GVHD with the addition of immune ICI therapy, which can be helpful in weighing an individual's potential risk [4]. Additionally, risk of GVHD can be decreased with use of post-transplant cyclophosphamide as prophylaxis [4].

Aside from GVHD, there is also a potential increased risk of irAEs, however, the risk appears to be comparable to that of ICIs without preceding allo-HSCT. In a systematic review and meta-analysis conducted by Wang et al. including 125 clinical trials (n=20,128), the overall incidence of irAEs in patients treated with PD-1/PD-L1 inhibitors was approximately 66%, with 14% experiencing at least one grade III or higher adverse event [8]. While the exact incidence of irAEs in those treated with ICI therapy following allo-HSCT is not known, it does not appear significantly greater based on small retrospective studies.

In this case, we discuss the use of pembrolizumab following allo-HSCT for relapsed and refractory CTCL. This patient had heavily pre-treated disease with the best prior response being partial remission to multiple lines of therapy. Furthermore, mycosis fungoides with CNS involvement has been demonstrated to have a dismal prognosis, with a median overall survival of approximately 160 days from the time of CNS metastasis [9]. The addition of pembrolizumab following allo-HSCT has resulted in long-term CR without significant adverse events, including absence of GVHD. This case report suggests that PD-1 inhibition following allo-HSCT may be a potentially curative treatment option for some.

While further studies are needed to determine which patients are best suited for the use of ICIs following allo-HSCT, we hypothesize certain characteristics made this patient an ideal candidate. First, this patient had a viable graft with 100% donor chimerism making him more likely to mount a robust GVT effect with the addition of checkpoint inhibition and therefore more likely to experience a clinical response to therapy. Second, the patient did not have a history of GVHD following allo-HSCT, even after tapering of immune suppression, and therefore was lower risk for GVHD following addition of an ICI. Finally, the patient was otherwise healthy with good performance status making him better able to tolerate therapy and potential irAEs.

References

1. Sterling C, Webster J. Harnessing the immune system after allogeneic stem cell transplant in acute myeloid leukemia. American Journal of Hematology. 2020; 95: 529-547.
2. Oran B, Daver N. Check-Point Inhibitors before and after Allogeneic Hematopoietic Stem Cell Transplant: The Double-Edge Sword. Biology of Blood and Marrow Transplantation. 2019; 25: e1-e2.
3. Ijaz A, Khan AY, Malik SU, Faridi W, Fraz MA, Usman M, et al. Significant Risk of Graft-versus-Host Disease with Exposure to Checkpoint Inhibitors before and after Allogeneic Transplantation. Biology of Blood and Marrow Transplantation. 2019; 25: 94-99.
4. Alkhaldi H, Kharfan-Dabaja M, El Fakih R, Aljurf M. Safety and efficacy of immune checkpoint inhibitors after allogeneic hematopoietic cell transplantation. Bone Marrow Transplantation. 2023; 58: 1075-1083.
5. Khodadoust MS, Rook AH, Porcu P, Foss F, Moskowitz AJ, Shustov A, et al. Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study. JCO. 2020; 38: 20-28.
6. Sethi TK, Montanari F, Foss F, Reddy N. How we treat advanced stage cutaneous T-cell lymphoma – mycosis fungoides and Sézary syndrome. British Journal of Haematology. 2021; 195: 352-364.
7. Styczyński J, Tridello G, Koster L, Lacobelli S, Biezen AV, Werf SVD, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplantation. 2020; 55: 126-136.
8. Wang JH, Guo Q, Ma ZX, Ma QL, Yu MX, Yin XF, et al. Impact of Chemotherapy Delay on Overall Survival for AML with IDH1/2 Mutations: A Study in Adult Chinese Patients. PLoS One. 2015; 10: e0140622-e0140622.
9. Preston JD, Jansen CS, Kosaraju S, Niyogusaba T, Zhuang TZ, Iwamoto SW, et al. Cutaneous T-cell lymphoma with CNS involvement: a case series and review of the literature. CNS oncology. 2023; 12: CNS105.