Biol Blood Marrow Transplant 25 (2019) 94–99

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Allogeneic Adult

Significant Risk of Graft-versus-Host Disease with Exposure to Checkpoint Inhibitors before and after Allogeneic Transplantation

Awais Ijaz[1], Ali Younas Khan[1], Saad Ullah Malik[1], Warda Faridi[1], Muhammad Asad Fraz[1], Muhammad Usman[1], Muhammad Junaid Tariq[1], Seren Durer[1], Ceren Durer[1], Atlantis Russ[2], Nadia Nunes Cavalcante Parr[2], Zeeshan Baig[3], FNU Sagar[1], Zeeshan Ali[4], Ali McBride[5], Faiz Anwer[1,6,*]

[1] *Department of Medicine, Hematology/Oncology, Blood and Marrow Transplantation, The University of Arizona, Tucson, Arizona*
[2] *Internal Medicine Residency Program, College of Medicine, The University of Arizona, Tucson, Arizona*
[3] *Department of Internal Medicine, Hospital Medicine, Summit Medical Group, Summit, New Jersey*
[4] *Department of Internal Medicine, The University of Arizona, Tucson, Arizona*
[5] *Department of Pharmacy, The University of Arizona, Tucson, Arizona*
[6] *Department of Hematology, Medical Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio*

Article history:
Received 2 May 2018
Accepted 28 August 2018

Key Words:
Allogeneic hematopoietic stem cell transplantation
Graft-versus-host disease
Ipilimumab
Nivolumab
Pembrolizumab
Outcomes

A B S T R A C T

Investigators are using checkpoint inhibitors (CPIs) to treat aggressive hematologic malignancies in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) and in some patients with relapsed disease after allo-HSCT. CTLA-4 inhibitors and PD-1 inhibitors are 2 main types of CPIs, which work through activation of the immune system. On one hand, CPIs can achieve graft-versus-tumor effect, and on the other hand, there is a risk of graft-versus-host disease (GVHD). After a comprehensive literature review, we included data (n = 283) from 24 studies (11 original manuscripts and 13 case reports or case series) and evaluated the results to assess the safety and efficacy of CPI use in conjunction with allo-HSCT. Among the 283 patients, 107 received CPI before allo-HSCT, and 176 received CPI after allo-HSCT. The most common indication for CPI use was for Hodgkin lymphoma. The CPIs used in various studies included ipilimumab, nivolumab, and pembrolizumab. Among the patients exposed to CPI before allo-HSCT, 56% developed acute GVHD and 29% developed chronic GVHD. Investigators reported 20 deaths, 60% of which were GVHD-related. The overall mortality risk with GVHD is 11%. In this group, investigators noted an objective response rate (ORR) in 68% of patients, with complete remission (CR) in 47%, partial remission (PR) in 21%, and stable disease in 11%. Among the patients who received a CPI after allo-HSCT for disease relapse, 14% developed acute GVHD and 9% developed chronic GVHD. Investigators reported 40 deaths, 28% of which were GVHD-related. The mortality risk with GVHD is approximately 7%. Investigators reported ORR in 54% of patients, with CR in 33%, PR in 21%, and disease stabilization in 5%. After careful evaluation of collective data, we found that CPI use both before and after allo-HSCT can be highly effective, but exposure can lead to a significantly increased risk of GVHD-related morbidity and mortality in this patient population. Despite limited availability of data, there is need for extreme caution while making decisions regarding the use of CPIs. Detailed discussions and prospective well-designed clinical trials are needed to explore this issue further.

INTRODUCTION

The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in treating aggressive hematologic malignancies has potential for graft-versus-tumor (GVT) effect on one hand and the risk of graft-versus-host disease (GVHD) on the other hand. Despite the use of intensive conditioning followed by allo-HSCT, primary disease relapse remains a leading cause of death [1,2]. A summary report published by the Center for International Blood and Marrow Transplant Research shows that patients who received transplants from matched unrelated donors and HLA-matched siblings have relapse rates of 30% and 40%, respectively. The various postulated mechanisms of disease relapse after allo-HSCT include immune escape by the tumor, T cell anergy, down-regulation of regulatory T cells, and activation of immune checkpoints. The risk of relapse also may be greater with the use of nonablative conditioning regimens [3]. Tumors can use cytotoxic T Lymphocyte-Associated Protein 4 (CTLA-4) and Programmed Death-1 (PD-1) as

Financial disclosure: See Acknowledgments on page 98.

* Correspondence and reprint requests: Faiz Anwer, MD, The University of Arizona Cancer Center, Blood and Marrow Transplant Program, 1515 North Campbell Avenue, Room 2956, PO Box 245024, Tucson, AZ 85724.
E-mail address: anwerf@email.arizona.edu (F. Anwer).

https://doi.org/10.1016/j.bbmt.2018.08.028
1083-8791/

immune checkpoint escape mechanisms. The tumor antigens stimulate T lymphocytes to express receptors for immune checkpoints. The interaction between tumor cell ligands and checkpoint receptors prevents full activation and proliferation of T cells [2].

Recent developments in the field of immunotherapy have led to the discovery of numerous checkpoint inhibitors (CPIs), some of which are monoclonal antibodies directed against immune checkpoint pathways (CTLA-4 and PD-1) [4]. Examples of CPIs in clinical use include ipilimumab, pembrolizumab, and nivolumab. Ipilimumab blocks CTLA-4, whereas nivolumab and pembrolizumab block PD-1 receptors. Several CPI agents have received approval, and investigators are looking at additional agents as potential monotherapy or as combination regimens in clinical trials for the treatment of relapsed or refractory hematologic malignancies. These agents are being used either before or after allo-HSCT as salvage or rescue agents for the treatment of aggressive hematologic neoplasms. This CPI use has led to many serious immune-related side effects (ie, autoimmune diseases), and data are emerging on serious and potentially fatal GVHD in recipients of allo-HSCT [2,4,5]. Researchers have strongly recommended starting PD-1 blockers at low doses and closely monitoring for signs of GVHD when used in the pre- or post-allo-HSCT settings for patients with relapsed or refractory classical Hodgkin lymphoma [6]. There is a paucity of data on the safety and efficacy regarding the use of CPI in the peri-allo-HSCT setting. Here we report collective data with the aim of educating the transplantation community about the safety, efficacy, and risks related to CPI exposure in allo-HSCT recipients.

METHODS

We completed a comprehensive PubMed data search on March 28, 2018. Our search strategy included MeSH terms and key words for allo-HSCT, CPIs (including trade names and generic names), GVHD, safety, and efficacy. We found 123 articles, and after screening for duplicates, review articles, and nonrelevant studies, selected 24 articles (13 case reports and 11 original manuscripts) for data extraction. Our inclusion criteria included an analysis of CPIs used in hematologic malignancies either before or after allo-HSCT. We manually extracted data and summarized our results (Tables 1, 2, and 3) and divided the patients into 2 groups based on whether CPIs were used before or after allo-HSCT and then evaluated studies particularly for GVHD (acute and chronic), mortality data, and objective response rate.

RESULTS

We compiled data from 11 published original articles [1,2,5,7-14] and 13 case reports/case series [15-27] that included a total of 283 patients. The CPIs nivolumab, pembrolizumab, and ipilimumab were used either alone or in combination.

Indications

Hodgkin lymphoma (HL) was the most common indication (n = 93) in patients receiving a CPI before allo-HSCT. Other indications included non-Hodgkin lymphoma (NHL; n = 10), myelodysplastic syndrome (MDS; n = 3), and T cell lymphoma (n = 2).

The most common indication in patients receiving a CPI after allo-HSCT was HL (n = 89). Other indications included acute myelogenous leukemia (n = 28), NHL (n = 15), multiple myeloma (n = 9), chronic lymphocytic leukemia (n = 7), natural killer/T cell lymphoma (n = 7), MDS (n = 4), acute lymphoblastic leukemia (n = 4), chronic myelogenous leukemia (n = 2), chronic myelomonocytic leukemia (n = 2), *anaplastic large cell lymphoma* (n = 2), concurrent HL and NHL (n = 1), and 1 case each of myeloproliferative disorder, renal cell carcinoma, breast carcinoma, non-small cell lung carcinoma, mesothelioma, and desmoplastic small round cell carcinoma.

ORIGINAL ARTICLES

Pre-Allo-HSCT

CPIs and Doses

A total of 107 patients received a CPI before undergoing allo-HSCT. Ninety-one patients received nivolumab for a median of 4 to 11 cycles. Among these 91 patients, 37 received nivolumab at a dose of 3 mg/kg; dosage information is not available for the others. Pembrolizumab was given to 11 patients for 8 cycles; no information about dosage was mentioned. A median of 4 cycles of ipilimumab were administered in 8 patients; no dose was mentioned.

Efficacy and Safety

Investigators noted ORR in 42 of 62 patients (68%), with CR in 29 patients (47%) and PR in 13 patients (21%). Investigators noted stable disease (SD) in 7 patients (11%) and progressive

Table 1
Case Reports of CPI Use after Allo-HSCT

Study	CPI	Dose, mg/kg	Primary Disease (n)	Response (n)	GVHD (grade)	Other Outcomes (n)
Onizuka et al, 2016 [18]	NV	0.5-2	HL (1)	PR (1)	GVHD worsened	NA
Angenendt et al, 2016 [24]	NV	3	HL (1)	CR (1)	None	NA
Villasboas et al, 2016 [16]	PZ	2	HL (2)	CR (1) PR (1)	None	NA
Chan et al, 2016 [21]	PZ	2	ALCL (1)	PR (1)	None	NA
Yared et al, 2016 [15]	NV	0.5-3	HL (1)	PR (1)	None	Pneumonitis, hepatitis
Shad et al, 2016 [23]	NV	3	HL (1)	CR (1)	None	NA
Albringet al, 2017 [25]	NV†		AML (3)	CR (1) SD (1) PD (1)	GVHD (2)*	Myalgias
Singh et al, 2017 [17]	PZ	NA	HL (1)	CR (1)	GVHD (4)	Death due to pneumonia
Kwong et al, 2017 [19]	PZ	2	NK/T cell lymphoma (7)	CR (5) PR (1)	GVHD (2)*	NA
Godfrey et al, 2017 [20]	NV	3	HL (3)	PR (3)	none	Arthralgias, conjunctivitis, and rash (2)
Cheikhet al, 2017 [27]	NV	3	HL (2)	CR (2)	GVHD (3)*	Death due to fungal infection (1)
Boekstegers et al, 2017 [22]	PZ	3.3	ALL (1)	CR	GVHD (4)	Death
Covut et al, 2017 [26]	NV	NA	HL (2)	CR	none	Death due to hepatic failure

AML indicates acute myelogenous leukemia; ALL, acute lymphocytic lymphoma; ALCL, anaplastic large cell lymphoma; allo-HSCT, allogenic hematopoietic stem cell transplantation; CPI, checkpoint inhibitor; CR, complete remission; GVHD, graft-versus-host disease; HL, classical Hodgkin lymphoma; NV, nivolumab; PD, progressive disease; PR, partial remission; PZ, pembrolizumab; SD, stable disease; NK, natural killer; NA, not available.

* Only 1 patient had GVHD.

† One patient received single dose of 100 mg, 1 received a repetitive regimen of 0.3 to 1 mg/kg weekly for 5 infusions, and 1 received 2 injections (100 mg each).

Table 2
Safety and Efficacy of CPI Therapy after Allo-HSCT

Article	N	n	mFU, mo	CPI	Dose, mg/kg	Interval, mo	ORR, %	Response (%)	aGVHD, %	cGVHD, %	Deaths, %
Bashey et al, 2009 [1]	29	18*	12	IP	0.1-3†	12.5	17	CR (11) PR (6)	0	0	NA
Schoch et al, 2016 [12]	9	NA	24	NV, IP, PZ	NA	14.4	NA	NA	11	0	44
Davids et al, 2016 [2]	6	6	15	IP	3	22.5	0	0	0	17	0
Herbaux et al, 2017 [8]	20	19	12	NV	3	23	95	CR (42) PR (53)	30‡	0	20
Davids et al, 2017 [13]	22	22	15	IP	10	22.5	32	CR (27) PR (5)	5	9	59
Davids et al, 2017 [13]	15	13	9	IP	5	NA	23	PR (23)	7	33	13
Davids et al, 2017 [13]	8	6	8	NV	1; 0.5§	NA	17	PR (17)	0	13	13
Haverkos et al, 2017	31	30	14	NV, PZ	3,200	26.4	77	CR (50) PR (27)	32‖,¶	23	32
Khouri et al, 2018	10	9	20.5	IP + LN**	3††	29; 52‡‡	44	CR (33) PR (11)	0	0	10

CPI indicates checkpoint inhibitor; CR, complete remission; PR, partial remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation; interval, median interval between allo-HSCT and CPI administration; IP, ipilimumab; mFU, median follow-up; N, total number of patients; n, evaluable patients for response; NV, nivolumab; PZ, pembrolizumab; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; ORR, objective response rate; NA, not available.
* Evaluable patients for response receiving >1 mg/kg in the study.
† Dose escalation study; single infusion, starting with 0.1 mg/kg and increased to 0.33, 0.66, 1.0, and 3.0 mg/kg.
‡ 25% had severe GVHD.
§ Six patients received 1 mg/kg, and 2 patients received 0.5 mg/kg.
‖ 19% had severe (grade III-IV) GVHD.
¶ Four patients had overlap GVHD.
** Lenalidomide given in combination with ipilumumab; GVHD after lenalidomide administration.
†† Ipilimumab given for a total of 2 doses at 3 mg/kg alternating with lenalidomide.
‡‡ Patients with aggressive histology; patients with indolent histology.

disease (PD) in 12 patients (19%). In this group, in which patients received CPI before allo-HSCT, 8 patients (7%) developed hyperacute GVHD, 60 (56%) developed acute GVHD, and 20 (29%) developed chronic GVHD. Investigators reported 20 deaths, 12 of which were GVHD-related (60%).

Post-Allo-HSCT

CPIs and Doses

A total of 150 patients received a CPI after undergoing allo-HSCT. Sixty-two patients received nivolumab therapy with a dose of 3 mg/kg every 2 weeks in 2 studies, for 8 cycles in 1 study [8] and 2 cycles in the other study [7], and 1 mg/kg every 2 weeks for 8 cycles in the third study [13]. Eighty-five patients received ipilimumab therapy. In 1 study, single infusions were given to 29 patients, starting at a dose of 0.1 mg/kg and increasing to 0.33, 0.66, 1.0, and 3.0 mg/kg [1]. In another study, 6 patients received a dose of 3.0 mg/kg and 22 patients received a dose of 10 mg/kg for 4 cycles, followed by maintenance therapy every 12 weeks for 1 year. Another cohort of 15 patients received ipilimumab at a dose of 5 mg/kg [2,13]. Ipilimumab was given to 10 patients at 3 mg/kg for a total of 2 doses, alternating with lenalidomide [9]. In another study, 3 patients received ipilimumab for 5 cycles, with no information on dose available [12]. In 2 studies, a total of 4 patients received pembrolizumab, with a dose of 200 mg/kg every 3 weeks for a median of 2 cycles in 3 patients [7] and 5 cycles of administration with no information on dosage in 1 patient [12].

Efficacy and Safety

A total of 19 patients who received CPI post-allo-HSCT developed acute GVHD (13%), and 11% developed chronic GVHD. Out of a total of 123 evaluable patients, ORR was seen in 59 patients (48%), with 34 patients (28%) achieving CR and 25 (20%) achieving PR. SD was reported in 7 patients (6 %), and 4 patients (3%) showed disease progression. Investigators reported 35 deaths, 10 of which (28%) were GVHD-related. Nine studies reported a previous history of GVHD in 49% of patients [1,7-9, 13,16,20,26,27]. Complications other than GVHD included hematologic side effects (22%), most notably

Table 3
Safety and Efficacy of CPI Therapy before Allo-HSCT

Study	N	mFU, mo	CPI	Median Cycles	Interval, d	ORR, %	Response, %	aGVHD,* %	Deaths, %	cGVHD, %
Schoch et al, 2016 [12]	11	8.0	NV/IP	4	43	NA	NA	36	00	0
Armand et al, 2016 [14]	17	8.7	NV	9	29	NA	NA	82	35	NA
Kasamon et al, 2017 [11]	17	4.6	NV	9†	28	NA	NA	65	35	NA
Merrymen et al, 2017 [5]	39	12	NV/PZ	8	62	62	CR (36) PR (26)	44	10	41
Beköz et al, 2017 [10]	11	2	NV	9†	30	73	CR (45) PR (27)	36	18	9
Cheikh et al, 2017 [27]	9	10	NV	8†	44	78	CR (78)	100	11	33
Covut et al, 2017 [26]	3	4.7	NV	11	NA	100	CR (100)	33	33	NA

aGVHD indicates acute graft-versus-host disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation; cGVHD, chronic graft-versus-host disease; CPI, checkpoint inhibitor; CR, complete remission; interval, median interval between CPI administration and allo-HSCT; IP, ipilimumab; mFU, median follow-up; NV, nivolumab; ORR, objective response rate; PR, partial remission; PZ, pembrolizumab; NA, not available.
* 7% of patients had hyperacute GVHD, and 20% of patients had grade III-IV GVHD.
† Nivolumab was given at a dose of 3 mg/kg; dose not mentioned in the other studies.

neutropenia, along with respiratory and hepatic complications (16% and 14%, respectively).

CASE REPORTS AND CASE SERIES

Post-Allo-HSCT

CPIs and Doses

A total of 26 patients received CPI therapy after allo-HSCT as salvage therapy for various hematologic malignancies. Twelve patients (46%) were treated with pembrolizumab (PD-1 blockade), 3 patients with a dose of 2.0 mg/kg every 3 weeks and 2 patients with a single dose (3.3 mg/kg; not mentioned). The other 14 patients (54%) were treated with nivolumab (PD-1 blockade), 2 with a single infusion at 3 mg/kg [27], 1 with 6 cycles, and 1 with 4 cycles (dose not mentioned) [26]. Two patients received a single dose of 100 mg [25] and 200 mg [24], 2 patients were treated with a single 3 mg/kg dose, 1 with 2 doses of 100 mg [25] given 2 weeks apart, 2 patients with 13 [23] and 16 [20] cycles of 3 mg/kg every 2 weeks, 1 patient with 7 cycles of 2 mg/kg every 2 weeks [16], and 2 patients with 7 cycles [19] and 16 cycles [16] of 2 mg/kg every 3 weeks. One patient was treated with 5 weekly doses of 0.3 to 1.0 mg/kg [25] and 2 patients received escalating dosages of 0.5 to 3 mg/kg [15] and 0.5 to 2.0 mg/kg [18] for up to 6 doses.

Efficacy and Safety

At the time of observation of the respective cases, investigators recorded an ongoing response in 15 patients (58%) with CR, 7 patients (30%) with PR, 1 patient (4%) with SD, and 1 patient (4%) with PD. One patient (4%) could not be evaluated for an outcome. Five patients (19%) developed acute GVHD, and 1 patient (4%) had a flare of existing GVHD. Total mortality was 15%; 1 patient (4%) died due to GVHD, and the other 3 deaths were attributed to pneumonia, hepatic failure, and fungal infection, respectively. The most common adverse reactions noted were related to the gastrointestinal tract, most notably hepatitis (32%), followed by skin (25%) and pulmonary-related problems (25%).

DISCUSSION

Analysis of 107 patients from 7 studies [5,10-12,14,26,27] revealed a high rate of acute GVHD (56%) among patients who were exposed to CPI therapy before receiving allo-HSCT. This rate is higher than the historical rates, which range between 26% and 50% [28,29]. Most previous studies used nivolumab, with only 1 study administering pembrolizumab in 11 patients [5] and 1 study administering ipilimumab in 8 patients [12]. Twelve of the 20 (60%) deceased patients died due to GVHD, and the aggregated mortality risk attributed to GVHD was 11%, which may be higher than the historically reported incidence (8% to 10%), but statistical significance is not proven [30]. Hyperacute GVHD (diagnosed within 14 days after transplantation) occurred in 8 patients (7%), suggesting a higher risk of hyperacute GVHD with the use of CPI therapy before allo-HSCT. The median interval between the last dose of CPI and allo-HSCT was variable, ranging between 28 and 62 days. The half-life of nivolumab is approximately 1 month.

The high incidence (56%) of GVHD across the studies is likely secondary to donor-derived lymphocyte activation, with residual CPI lasting in the body after allo-HSCT resulting in higher incidences of hyperacute, atypical noninfectious febrile syndrome, and acute GVHD. Decreased PD-1 expression on T cells persists for at least 10 months following CPI therapy, confirming long-term immune activation beyond many half-lives [5]. Owing to the long-lasting effects of CPI on immune activation, the time for GVHD risk to return to baseline is unknown in this patient population. We compared the studies with shortest median intervals (28 days [11], 29 days [14], and 30 days [10]) and longest median intervals (43 days [12], 44 days [27], and 62 days [5]) between the last dose of CPI and allo-HSCT. We found that the incidence of GVHD was 60% in the former versus 70% in the latter, but the numbers of patients in each group were very limited. An increased rate of efficacy with a GVT effect correlated positively with an increasing risk of GVHD activity (grade II to IV) in 3 studies [5,10,27], complementing the association between GVT and GVHD, as previously reported in animal studies that tested PD-1 blockade [31,32]. The US Food and Drug Administration has issued label warnings for the use of HSCT after previous PD-1 blockade. Immunosuppressive $CD4^+$ T regulatory cells with CTLA-4 expression have been found in markedly high proportions surrounding malignant tissues [33]. This may explain the increased efficacy, as well as the high incidence of GVHD associated with CPI use, as PD-1 blockade depletes the PD-1^+ T cell and Treg populations. CD62L is a lymph node "homing receptor" that is down-regulated during T cell response that allows for the escape of T lymphocytes from lymph nodes. Ipilimumab indirectly increases the number of $CD62L^-$ regulatory $CD4^+$ cells [2]. PD-1 blockade may alter post-allo-HSCT immune reconstitution through its effects on antigen-presenting cells and cytokines [5]. Three of the studies reported increased numbers of circulating activated $CD8^+$ and $CD4^+$ cells but a decreased $CD4^+$ Treg-to-effector T cell (Teff) ratio [2,5,33]. A $CD4^+$ Treg:Teff ratio $<9\%$ is associated with increased incidence and severity of GVHD. In one study in which CPI was used, this ratio was found to be in the range of 3% to 5% [5].

Various salvage therapies are used for patients with hematologic malignancies who relapse after allo-HSCT, including the use of donor lymphocyte infusion (DLI), conventional chemotherapy, immunotherapy, and CAR T cell therapy, and second allo-HSCT is considered in selected patients. CPI administration as salvage therapy after allo-HSCT can restore T cell function, activate lymphocytes, and induce a strong GVT effect. On the other hand, it can also cause serious immune-related adverse events, including serious GVHD. Aggregated data from studies of CPI use after an allo-HSCT relapse disease show that it is possible to achieve CR in 28% of relapse cases, with PR noted in an additional 19% of patients and SD seen in 7% of patients.

Depending on the nature of malignancy, other than its use in CML, the efficacy of DLI is limited, with a significant risk of GVHD. Compared with the low efficacy historically reported with DLI use, it may become possible to appropriately time the exposure and manipulate immune activation with a safe CPI dose in this difficult-to-treat population. The risk of GVHD with CPI exposure is approximately 23% in the post-allo-HSCT population, including 14% with acute GVHD and 9% with chronic GVHD. Whether a particular dosage or proper timing of CPI exposure may be safer with good efficacy and low risk of GVHD is a matter of debate. In a phase 1 clinical trial, no cases of GVHD were reported in 29 patients given ipilimumab at doses of up to 3 mg/kg (low dose) [1]. Four patients developed immune adverse events, including polyarthropathy, hyperthyroidism, and grade IV pneumonitis. ORR was reported to be 17%, with a median overall survival of 24.7 months even in the low-dose group [1].

In a study reported by Davids et al. [2], 6 patients received ipilimumab at a dose of 3 mg/kg and showed no objective response, with 1 patient developing chronic GVHD of the liver.

Other patients (n = 22) who received a higher dose (10 mg/kg) showed an ORR of 32%, with a median overall survival of 28.2 months. Investigators reported chronic GVHD of the liver in 2 patients while one patient developed grade II acute GVHD of the gut [2]. In 2017, Davids et al. [13] administered ipilimumab to another cohort of 15 patients at a dose of 5 mg/kg. ORR was reported to be 23%, and GVHD developed in 6 patients (1 acute and 5 chronic). These limited results indicated to investigators that they could administer ipilimumab safely at doses up to 3 mg/kg in relapsed allo-HSCT recipients; however, the efficacy is low at this dose. Increasing the dose of the antibody increases the efficacy but also increases the risk of GVHD. The median time of drug administration after allo-HSCT was 12.2 months in the study by Bashey et al. [1] and 22.5 months in the study of Davids et al. [2]. The lower incidence of GVHD at a lower dose (3 mg/kg) reported by Bashey et al. and Davids et al. could be due to the extended interval between transplantation and ipilimumab administration. In another study reported by Herbaux et al. [8], the patients who developed GVHD after CPI exposure were then given nivolumab relatively early after allo-HSCT, at the median interval of 8.5 months. The patients who received nivolumab late after transplantation at a median interval of 28.5 months did not experience GVHD [8]. Most studies administered CPI at least 3 months after allo-HSCT, and thus the investigators could draw no conclusions regarding its safety and efficacy when used sooner than 3 months post-transplantation. Available limited data suggest that investigators could minimize the risk of GVHD if they could increase the interval between allo-HSCT and CPI exposure.

Previous history of GVHD appears to have a positive correlation with an increased risk of GVHD in patients treated with PD-1 blockers after experiencing disease relapse. In the study by Herbaux et al. [8], nivolumab was administered to 20 patients at a dose of 3 mg/kg, and the ORR was 95%. Six patients developed acute GVHD, but none developed chronic GVHD [8]. In another study reported by Haverkos et al. [7], 28 patients received nivolumab at a dose of 3 mg/kg and 3 patients received pembrolizumab at a dose of 200 mg/kg. Out of 31 patients, 17 developed GVHD (10 with acute GVHD and 7 with chronic GVHD). It is noteworthy that in both of the foregoing studies, the majority of patients who developed CPI-related GVHD had a previous history of GVHD (12 of 17 cases reported by Haverkos et al. [7] and all 6 cases reported by Herbaux et al. [8]).

Evaluation of the collective data reveals high incidences of hyperacute, acute, and chronic GVHD associated with previous CPI exposure in patients who later underwent allo-HSCT. CPI use after allo-HSCT for post-transplantation relapse has higher efficacy, but the risk of GVHD is significant. Investigators found that higher drug doses, shorter intervals between CPI exposure and allo-HSCT, and previous history of GVHD had positive correlations with patient response and the risk of GVHD. In addition, CPI use causes long-lasting immune activation, with an elevated risk of GVHD for many months. GVHD-related mortality was higher in patients who received a CPI before undergoing allo-HSCT. Owing to the limited available data, we suggest that future clinical trials should assess the safety and efficacy of CPI use in association with allo-HSCT. This study has some limitations, including heterogeneity of the patient population, the possibility of double-counting of some patients, inconsistent nonstandardized GVHD scoring reported in many of the available trials, the possibility of incorrect categorization of GVHD versus other immune-mediated toxicities, a lack of autopsy data to confirm exact cause of mortality, and potential reporting biases.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported in part by National Cancer Institute Grant P30 CA023074.

Conflict of interest statement: There are no conflicts of interest to report. with this manuscript.

REFERENCES

1. Bashey A, Medina B, Corringham S, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood*. 2009;113:1581–1588.
2. Davids MS, Kim HT, Bachireddy P, et al. Ipilimumab for patients with relapse after allogeneic transplantation. *N Engl J Med*. 2016;375:143–153.
3. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol*. 2010;3:429–441.
4. Merryman RW, Armand P. Immune checkpoint blockade and hematopoietic stem cell transplant. *Curr Hematol Malig Rep*. 2017;12:44–50.
5. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood*. 2017;129:1380–1388.
6. Herbaux C, Merryman R, Devine S, et al. Recommendations for managing PD-1 blockade in the context of allogeneic HCT in Hodgkin lymphoma: taming a necessary evil. *Blood*. 2018;132:9–16.
7. Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood*. 2017;130:221–228.
8. Herbaux C, Gauthier J, Brice P, et al. Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma. *Blood*. 2017;129:2471–2478.
9. Khouri IF, Fernandez Curbelo I, Turturro F, et al. Ipilimumab plus lenalidomide after allogeneic and autologous stem cell transplantation for patients with lymphoid malignancies. *Clin Cancer Res*. 2018;24:1011–1018.
10. Beköz H, Karadurmuş N, Paydaş S, et al. Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience. *Ann Oncol*. 2017;28:2496–2502.
11. Kasamon YL, de Claro RA, Wang Y, Shen YL, Farrell AT, Pazdur R. FDA approval summary: nivolumab for the treatment of relapsed or progressive classical Hodgkin lymphoma. *Oncologist*. 2017;22:585–591.
12. Schoch LK, Borrello I, Fuchs EJ, et al. Checkpoint inhibitor therapy and graft versus host disease in allogeneic bone marrow transplant recipients of haploidentical and matched products with post-transplant cyclophosphamide. *Blood*.. 2016;128:4571.
13. Davids MS, Kim HT, Costello C, et al. Optimizing checkpoint blockade as a treatment for relapsed hematologic malignancies after allogeneic hematopoietic cell transplantation. *Blood*.. 2017;130:275.
14. Armand P, Zinzani PL, Collins GP, et al. Outcomes of allogeneic hematopoietic stem cell transplantation (HSCT) after treatment with nivolumab for relapsed/refractory Hodgkin lymphoma. *Blood*. 2016;128:3502.
15. 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;51:850–852.
16. Villasboas JC, Ansell SM, Witzig TE. Targeting the PD-1 pathway in patients with relapsed classic Hodgkin lymphoma following allogeneic stem cell transplant is safe and effective. *Oncotarget*. 2016;7:13260–13264.
17. Singh AK, Porrata LF, Aljitawi O, et al. Fatal GvHD induced by PD-1 inhibitor pembrolizumab in a patient with Hodgkin's lymphoma. *Bone Marrow Transplant*. 2016;51:1268–1270.
18. Onizuka M, Kojima M, Matsui K, et al. Successful treatment with low-dose nivolumab in refractory Hodgkin lymphoma after allogeneic stem cell transplantation. *Int J Hematol*. 2017;106:141–145.
19. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood*. 2017;129:2437–2442.
20. Godfrey J, Bishop MR, Syed S, Hyjek E, Kline J. PD-1 blockade induces remissions in relapsed classical Hodgkin lymphoma following allogeneic hematopoietic stem cell transplantation. *J Immunother Cancer*. 2017;5:11.
21. Chan TS, Khong PL, Kwong YL. Pembrolizumab for relapsed anaplastic large cell lymphoma after allogeneic haematopoietic stem cell transplantation: efficacy and safety. *Ann Hematol*. 2016;95:1913–1915.
22. Boekstegers AM, Blaeschke F, Schmid I, et al. MRD response in a refractory paediatric T-ALL patient through anti-programmed cell death 1 (PD-1) Ab treatment associated with induction of fatal GvHD. *Bone Marrow Transplant*. 2017;52:1221–1224.
23. Shad AT, Huo JS, Darcy C, et al. Tolerance and effectiveness of nivolumab after pediatric T–cell replete, haploidentical, bone marrow transplantation: a case report. *Pediatr Blood Cancer*. 2017;64.
24. 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*. 2016;51:443–445.
25. Albring JC, Inselmann S, Sauer T, et al. PD-1 checkpoint blockade in patients with relapsed AML after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2017;52:317–320.

26. Covut F, Pinto R, Cooper BW, et al. Nivolumab before and after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2017;52:1054–1056.
27. El Cheikh J, Massoud R, Abudalle I, et al. Nivolumab salvage therapy before or after allogeneic stem cell transplantation in Hodgkin lymphoma. *Bone Marrow Transplant*. 2017;52:1074–1077.
28. Ringdén O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009;113:3110–3118.
29. Center for International Blood and Marrow Transplant Research (CIBMTR). Progress report January–December 2008. Available at: https://www.cibmtr.org/About/AdminReports/Documents/2008_CIBMTR_Annual_R.pdf. Accessed April 14, 2018.
30. DSouza A, Fretham C. Current uses and outcomes of hematopoietic cell transplantation (HCT): CIBMTR Summary Slides, 2017. Available at: http://www.cibmtr.org. Accessed April 18, 2018.
31. 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;122:3062–3073.
32. 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;171:1272–1277.
33. Zhou J, Bashey A, Zhong R, et al. CTLA-4 blockade following relapse of malignancy after allogeneic stem cell transplantation is associated with T cell activation but not with increased levels of T regulatory cells. *Biol Blood Marrow Transplant*. 2011;17:682–692.