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Toxicity associated with PD-1 blockade after allogeneic haematopoietic cell transplantation

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Summary

Cancer immunotherapy with immune checkpoint inhibitors (ICIs) such as programmed death ligand-1 (PD-L1) blockers offers pronounced clinical benefit with durable responses and a manageable safety profile. Patients with a high risk of immune-related adverse events are generally excluded from clinical trials testing ICI therapy. Thus, only a little information on the safety and clinical outcome of patients treated with an ICI after allogeneic haematopoietic cell transplantation (HCT) is currently available. Here, we report the characteristics and outcomes of six patients with, respectively, clear cell renal carcinoma, diffuse large cell B-cell lymphoma, Hodgkin lymphoma, a microsatellite instable colorectal cancer and melanoma who were treated with PD-1 blocking antibodies. All patients had previously undergone allogeneic HCT. Severe grade 3–5 immune-related adverse events were observed in three of five patients who received full-dose ICI therapy. One patient received a lower dose of PD-1 blocking antibody. Only one patient had an objective response, whereas all the other patients had progressive disease. The high toxicity of a full- dose anti-PD-1 treatment regimen suggests that other treatment approaches for patients after allogeneic HCT are needed outside of the context of relapsed Hodgkin disease. In cases where ICI therapy is the only treatment option, reduced dosing should be explored.

Keywords: *graft-versus-host disease (GvHD), PD-1, CTLA-4, immune-related adverse event (irAE), immunotherapy*

Introduction

The enthusiasm for cancer immunotherapy with immune checkpoint inhibitors (ICIs) is fuelled by studies showing meaningful responses in many different solid cancers and some lymphomas [1–3]. The programmed death-1 (PD-1) pathway serves as a checkpoint to limit T-cell mediated immune responses. Blocking the PD-1 receptor on T cells with monoclonal antibodies results in T-cell activation and proliferation and can induce a potent immunotherapeutic antitumour effect. Over recent years, objective response and survival benefit has been demonstrated in patients with, for example, melanoma, and lung, renal and bladder cancer patients. Among lymphoid tumours, classical Hodgkin lymphoma (cHL) has demonstrated remarkable responsiveness to PD-1 blockade, probably due to overexpression of programmed death ligand-L1 (PD-L1) and PD-L2 by Hodgkin and Reed Sternberg cells, driven by genetic alterations and deregulated signalling pathways [4–6].

In lymphoma models, preclinical studies showed that PD-1 blockade can augment the graft-versus-tumour (GVT) effect when given in the posttransplant setting [7]. As treatment options are scarce, many clinicians are therefore considering off-label use of ICIs in relapse after allogeneic haematopoietic cell transplantation (HCT) [8–10]. These reports describe the use of PD-1 blocking agents in cHL, but it remains unclear how patients with other post-HCT malignancies and a potential indication for ICI therapy should be treated. The best established PD-1 blocking antibodies used in clinics are nivolumab and pembrolizumab. Here, we describe the treatment and outcomes of six patients treated at our centre with PD-1 blocking agents. The patients suffered from different cancers

ABBREVIATIONS:

AML	acute myeloid leukaemia
cHL	classic Hodgin lymphoma
CLL	chronic lymphatic leukaemia
CT	computed tomography
CTL4	cytotoxic T-lymphocyte antigen-4
DLBCL	diffuse large B cell lymphoma
FDG	fluorodeoxyglucose
GvHD	graft-versus-host disease
GvT	graft-versus-tumour
HL	Hodgkin lymphoma
HCT	haematopoietic stem cell transplantation
ICI	immune checkpoint inhibitor
PD-1	programmed death 1
PD-L1	programmed death ligand-1
PET	positron emission tomography

Author contributions
GOS, SG JP, FS, AZ, JH and HL treated the patients and wrote the case reports. SD performed the histopathological analysis. All authors read and approved the final manuscript.

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Methods

Patient data and characteristics were collected from patients treated at the University Hospital Basel in Switzerland. Patients that had previously received allogeneic HCT and were undergoing ICI therapy with a PD-1/PD-L1 blocking agent were retrospectively analysed. All the patients had consented to the retrospective analysis of their anonymised data.

Case descriptions

The characteristics of all six patients are summarised in table 1.

Patient 1

This was a 43-year-old female with the diagnosis of acute myeloid leukaemia (AML) at the age of 17. She underwent allogeneic HCT from her HLA-matched brother in March 1990 and achieved complete remission. No manifestations of graft-versus-host disease (GvHD) occurred and immunosuppression with ciclosporin was successfully tapered over 6 months. On February 2008, a clear cell renal carcinoma was diagnosed and a nephrectomy was performed (pT3b pN2 M0). She received adjuvant systemic therapy with the oral multitargeted tyrosine kinase inhibitor sunitinib. One year later, disease progression with multiple lymph node metastases (supraclavicular, hilar, mesenteric and para-aortic) was diagnosed. First-line palliative treatment with sunitinib was given between March and September 2009. Upon progression, from December 2009- to 2010, second-line therapy with the mTOR (mammalian target of rapamycin) inhibitor temsirolimus was started, which resulted in partial remission. In March 2012, abdominal sonography revealed again tumour progression in retroperitoneal lymph nodes. A lymph node biopsy confirmed a metastasis of the clear cell renal carcinoma. Temsirolimus was restarted until December 2013. After 18 months on therapy tumour progression was confirmed. Chimerism analysis on T cells and neutrophils confirmed 100% donor type. Immunotherapy with nivolumab (3 mg/kg every second week, q2w) was initiated, and she received eight doses with no signs of GvHD. Six months later a computed tomography (CT) scan showed progressive disease with new metastasis in the liver, lungs and peritoneal cavity, and therapy with the multireceptor tyrosine kinase inhibitor axitinib was initiated. Clinical and radiographic disease progression was evident after 2 months on treatment. There was no evidence of GvHD. The patient received symptom-oriented therapy and died as a result of disease progression.

Patient 2

This was a 34-year-old female with a diagnosis of acute lymphoblastic leukaemia (ALL) at the age of 19, who underwent allogeneic HCT from an unrelated donor in 2002. The immune suppression was tapered within the first year after transplantation. In 2016, the patient presented with a complete large bowel obstruction due to adenocarcinoma of the sigmoid colon. The pathological work-up showed a microsatellite instable tumour with a KRAS-mutation (typical mutation in colorectal cancer in the *KRAS* gene), KRAS G13D (24%). A fluorodeoxyglucose-positron emission tomography (FDG-PET) / CT scan revealed multiple liver metastases in segment IV and in the right lobe of the liver and para-aortic lymph node metastasis. Neo-adjuvant chemotherapy with six cycles of FOLFOXIRI (5-fluorouracil, oxaliplatin, irinotecan, leucovorin) resulted in partial remission. Radiofrequency thermal ablation of liver segment VIII and resection of segments IV and V were performed, but there was early relapse. Immunotherapy with pembrolizumab (2 mg/kg, q3w) was started. After the second infusion of pembrolizumab, clinical and radiographic disease progression was evident with new liver and lymph node metastasis, ascites and a metastasis in the right adrenal gland and clinical signs of hepatic encephalopathy. There were no immune-related complications, her disease continued to progress and she died as a result of liver failure.

Patient 3

A 47-year-old man with chronic lymphatic leukaemia (CLL) and Richter syndrome, diffuse large B-cell lymphoma (DLBCL)-type, in first relapse, underwent non-myeloablative HCT from an HLA-matched unrelated donor in April 2015 without complications. Immune suppression consisted of tacrolimus and mycophenolic acid. Acute grade 2 GvHD of the skin developed and was controlled by steroids; immunosuppressive treatment was tapered and stopped in October 2015. In December 2015, an early lesion of posttransplant lymphoproliferative disorder, plasmacytic hyperplasia, was diagnosed and subsequently treated with four cycles of rituximab. Three months later the patient developed biopsy-proven relapse of his disease in the right external iliac artery. The pathology revealed a CLL infiltration with high proliferation rate. FDG-PET/CT showed new lymphoma manifestations in the right sciatic foramen, around the left side of the infrarenal aorta and both aortoiliac arteries. Treatment with the phosphinosi-

Table 1: Patient characteristics.

Patients	Indication for HCT; remission status	Disease warranting ICI therapy	Best response to ICI therapy	ICI treatment details, dose
1. 43-year-old female patient	AML; CR	Clear cell renal carcinoma	PD	Nivolumab 3 mg/kg
2. 34-year-old female patient	ALL; CR	MSI adenocarcinoma of colon sigmoid	PD	Pembrolizumab 2 mg/kg
3. 47-year-old male patient	DLBCL; CR	DLBCL	SD	Pembrolizumab 2 mg/kg
4. 41-year-old male patient	HL; PD	HL	CR	Nivolumab 3 mg/kg
5. 68-year-old male patient	Myelodysplastic neoplasm; CR	BRAF neg. melanoma	PD	Pembrolizumab 2 mg/kg Pembrolizumab 1 mg/kg
6. 72-year-old female patient	Primary myelofibrosis; CR	Mucosal melanoma	PD	Nivolumab 0.5 mg/kg

AML = acute myeloid leukaemia; CR = complete response; DLBCL = diffuse large B-cell lymphoma; HCT = haematopoietic cell transplantation; HL = Hodgkin lymphoma; ICI = immune checkpoint inhibitor; MSI = microsatellite instable; PD = progressive disease; SD = stable disease

tol-3-kinase inhibitor idelalisib and rituximab was started. Six months later FDG-PET/CT revealed progressive disease on the right sciatic foramen. Stereotactic radiotherapy of this soft tissue lesion was performed. Subsequently, treatment with the BCL2 inhibitor venetoclax was initiated. Two months later a Richter transformation (DLBCL) was again confirmed. Lenalidomide and rituximab were started. After 2 cycles, the treatment was stopped due to infection. In August 2017, therapy with blinatumomab was attempted, as well as donor lymphocyte infusion, in escalating dose. Follow-up imaging in January 2018 demonstrated progression of the lymphoma with new infiltration of the gluteal muscles, and lymph node enlargement in the retrocrural space and through the dorsal intrathoracic wall. Blinatumomab was stopped and pembrolizumab (2 mg/kg q3w) was started in February 2018. Three weeks later he presented with cough, shortness of breath and fever. A chest CT scan demonstrated bilateral pleural effusions. Microbial tests were positive for rhinovirus/enterovirus and he received broad-spectrum antibiotic therapy. His performance status worsened, with dyspnoea and delirium. Empirical therapy with corticosteroids was initiated for a presumed pembrolizumab-related adverse event. The patient did not respond to intravenous corticosteroids and was transferred to the intensive care unit for mechanical ventilation. A CT scan revealed bilateral pulmonary infiltrates, and acute respiratory distress syndrome was diagnosed. Bronchoscopy did not show any bacterial or fungal infection. Liver biopsy showed hepatic GvHD and sepsis-associated cholestasis. An abdominal CT scan revealed dilated intestinal loops. Treatment with high-dose corticosteroids and tacrolimus was initiated. In the absence of an improvement within 3 days the patient received one dose of alemtuzumab. His performance status declined and a CT scan showed a haemoperitoneum and a subcapsular liver haematoma with an active bleeding in the Morrison-Pouch. An angiographic approach to stop the bleeding was not possible and a surgical approach was rejected. The patient died as a result of multiorgan failure. All CT scans after pembrolizumab showed a slight decrease of the lymphoma manifestations.

Patient 4

A 41-year-old patient with cHL of the nodular sclerosis type in third relapse underwent allogeneic HCT from an HLA-matched unrelated donor after conditioning with a BEAM-Flu regimen (carmustine, cytarabine, fludarabine, etoposide, melphalan). His posttransplant course was complicated by chronic GvHD overlap syndrome involving the eyes and oral mucosa; it was treated with ciclosporin and corticosteroids which were subsequently tapered. By January 2013, an FDG-PET/CT scan showed a relapse of the HL. Immune suppression was stopped and radiotherapy with 40 Gy to the right cervical region and mediastinum was given. In addition, donor lymphocyte infusions were applied. New manifestations of chronic GvHD of the skin, eye and mouth developed. In July 2013, new hypermetabolic right hilar and left precarinal lymph nodes were identified. Radiotherapy of these regions was performed and metabolic complete remission was achieved. His chronic GvHD progressed with new manifestations of fasciitis and sclerodermiform skin manifestations. GemOx (gemcitabine, oxaliplatin) chemotherapy for 12 months was started 6 months later because of another relapse of the HL that was ultimately progressive. In November 2015, immunotherapy with nivolumab (3 mg/kg, q2w) was started. At the time of initiation of therapy, he had no evidence of active GvHD and immune suppression was maintained with low-dose prednisone only. After one dose of nivolumab, the patient developed an immune-related meningoencephalitis, and a grade 3 GvHD of the skin and the liver, which responded promptly to oral prednisone, 2 mg/kg per day for 1 week and tapered over 4 weeks to 10 mg/day. Nivolumab was permanently stopped. FDG-PET/CT showed complete remission up to 7 months later. Subsequently, three local relapses were diagnosed in the following 2 years, all of which were treated with stereotactic radiotherapy until 2018. Since then, the patient remains in remission.

Patient 5

This was a 68-year-old man diagnosed in 2001 with a JAK2 V617F-positive myelodysplastic/myeloproliferative neoplasm (unclassifiable myelodysplastic syndrome / myeloproliferative neoplasm [MPN]-U). His disease continued to progress to AML in March 2016. Induction chemotherapy with idarubicin, cytarabine and cladribine was started. The patient underwent allogeneic HCT from an HLA-haploidentical related donor in June 2016 after conditioning with fludarabine/cyclophosphamide, and posttransplant GvHD prophylaxis consisting of mycophenolic acid and ciclosporin, achieving complete remission. His posttransplant course was complicated by acute grade 3 GvHD involving the skin, which was well controlled with systemic corticosteroids.

Two years before the allogeneic HCT, a stage IIIc (American Joint Committee on Cancer, Version 7.0) melanoma of the left cheek had been diagnosed and resected completely (R0). No mutation in *BRAF* was detected. One year later, a biopsy-proven local relapse was found. A parotidectomy and cervical neck dissection was performed. In November 2015, multiple satellite metastases on the left cheek were detected. Excision and adjuvant radiotherapy with 52 Gy were performed. Shortly after the allogeneic HCT in November 2016, mediastinal lymph node and multiple pulmonary metastases of the melanoma were detected. Steroid dose was lowered and ICI therapy with pembrolizumab (2 mg/kg, q3w) was initiated. After the first dose, an acute grade 2 GvHD-like reaction involving eyes and skin developed, which was well controlled with a short course of systemic corticosteroids. Further treatment with a second dose of pembrolizumab at a reduced dose (1 mg/kg) was given. In April 2017, biopsy proven pulmonary GvHD was diagnosed, which was treated with an intensification of immunosuppression including tacrolimus, mycophenolic acid and steroids. Four weeks later, progressive melanoma with new liver and lung metastases was diagnosed. The clinical course was complicated by worsening of the respiratory distress and clostridium enterocolitis. The patient died as a result of the infection.

Patient 6

This patient was a72-year-old woman, diagnosed with primary, JAK2 V617F-positive myelofibrosis in 2013. The patient had received multiple lines of therapy due to hepatosplenomegaly and clinical symptoms; these included

hydroxyurea, ruxolitinib and cladribine. In March 2015, with DIPPS (Dynamic International Prognostic Scoring System) intermediate-2, she underwent allogeneic HCT from a HLA-identical unrelated donor after non-myeloablative conditioning with fludarabine/busulfan (FluBu) and GvHD prophylaxis with anti-thymocyte globulin, ciclosporin and methotrexate, reaching a complete remission. In November 2015, bone marrow biopsy revealed a refractory cytopenia with multilineage dysplasia (RCMD), which was interpreted as a relapse of the original myeloid neoplasia transformed to myelodysplastic syndrome, although a therapy-associated myeloid neoplasia was also possible. A second allogeneic HCT after conditioning with fludarabine/busulfan and GvHD prophylaxis with ciclosporin and methotrexate was performed in May 2016. Her posttransplant course was complicated by acute grade 3 GvHD involving the liver und upper gastrointestinal tract, which was successfully treated with the addition of systemic corticosteroids. In April 2018, a primary mucosal melanoma without *BRAF* mutation was found in her intestinal tract. In addition, hepatic metastases were found. Immunotherapy with nivolumab with dose adjustment (15% of nivolumab dose) was started and a low dose of ciclosporin with subtherapeutic levels was maintained. At the time of initiation of therapy with nivolumab she had no evidence of active GvHD. The patient died after 6 weeks owing to rapid melanoma progression.

An overview of the cases of ICI-induced GvHD is presented in table 2.

Discussion

Here we report on our experience with regard to efficacy and toxicity of PD-L1 blockade after allogeneic HCT in six patients in our centre. Several important observations were made. Patients treated with a PD-1 blocking ICI had severe immune-related adverse events due to reactivation of GvHD (cases 3–5). Importantly, these immune adverse events were difficult to control with standard immune suppressive therapy including high-dose corticosteroids normally used for treatment of GvHD.

The interval between allogeneic HCT and ICI treatment was long, and withdrawal of immunosuppression had been completed. This experience prompted us to use a lower dose in patient 6. Use of lower starting doses has previously been described in some case reports [11, 12]. No severe side effects were seen in this patient with melanoma, but unfortunately she died as a result of disease progression.

The observed efficacy of ICI treatment in this small patient cohort was limited (one patient with cHL, overall response rate 16.7%). Previous publications of larger case series have focused on the treatment of Hodgkin lymphoma (HL) after allogeneic HCT [8–10]. Treatment of HL with ICIs targeting PD-1/PD-L1 has been shown to be effective in several trials in patients prior to allogeneic HCT [4, 13–16]. Haverkos and colleagues conducted a multicentre retrospective analysis to better characterise the risks and benefits of PD-1 blockade after allogeneic HCT [8]. They analysed 31 lymphoma patients receiving an anti-PD-1 antibody for relapse after allogeneic HCT. Twenty-nine (94%) patients had cHL and 27 had ≥1 salvage therapy after the allogeneic HCT and prior to anti-PD-1 treatment. Median follow-up was 428 days after the first dose of anti-PD-1 therapy. Overall response rate was 77% (15 complete and 8 partial responses) in 30 evaluable patients. At last follow-up, 11 of 31 patients had disease progression and 21 of 31 (68%) remained alive, with 8 (26%) deaths related to new-onset GvHD after anti-PD-1. Seventeen (55%) patients developed GvHD after initiation of anti-PD-1 treatment (six acute, four overlap and seven chronic), with onset after a median of 1, 2 and 2 doses, respectively. GvHD severity was grade 3 to 4 acute or severe chronic in nine patients. Only 2 of these 17 patients achieved a complete response of GvHD with treatment, and 14 of 17 required ≥2 systemic therapies [8]. Herbaux and colleagues analysed a cohort of 20 patients with relapsed HL after allogeneic HCT treated with nivolumab [9]. Whereas the efficacy was very encouraging with a 95% overall response rate, six patients (30%) had induction or worsening of GvHD. The authors concluded that nivolumab is a treatment option for patients with HL after allogeneic HCT [9]. Another study investigated the use of ICI therapy targeting cytotoxic T-lymphocyte antigen-4 (CTLA4) in 29 patients with mainly haematological malignancies [17]. Bashey et al assessed the safety and preliminary efficacy of a neutralising human anti-CTLA4 monoclonal antibody, ipilimumab, in stimulating the GVT effect after allogeneic HCT [17]. Ipilimumab did not exacerbate acute or chronic GvHD in these patients. The eligibility criteria of the trial may have limited the risk of severe GvHD: only patients without prior grade 3 or 4 acute GvHD and with discontinuation of all immunosuppressive medications for a minimum of 4 to 6 weeks were eligible. Thus, it is unclear whether ipilimumab would also not induce or exacerbate GvHD in patients who had experienced prior severe acute GvHD or who were still on immunosuppressive therapy at the time of treatment [17]. Twenty-eight patients with relapse of the malignancy that led to the transplantation were

Table 2: Overview of ICI-induced GvHD.

Patients	New onset GvHD After anti-PD-1, grade	Type	Treatment
1. 43-year-old female patient	None	NA	NA
2. 34-year-old female patient	None	NA	NA
3. 47-year-old male patient	5	Pneumonitis GvHD	Corticosteroids 2mg/kg, tacrolimus
4. 41-year-old male patient	4	Encephalitis GvHD	Corticosteroids 2 mg/kg
5. 68-year-old male patient	3	GvHD	Corticosteroids 2 mg/kg
6. 72-year-old female patient	None	NA	NA

GvHD = graft versus host disease; ICI = immune checkpoint inhibitor; NA = not applicable; PD-1 = programmed death-1

treated with ipilimumab [18]. Six patients (21%) had severe toxicity and a worsening of their GvHD [18]. Four patients had a complete response [18]. A meta-analysis of all published studies of patients treated with an ICI after allogeneic HCT revealed a very high toxicity of ICI therapy in this patient population [10]. In this meta-analysis the main indication was HL and only limited conclusions can be drawn for other diseases [10].

Preclinical studies show that PD-1 blockade can augment the GVT effect when given after transplantation by remodelling the tumour microenvironment [7]. In particular, the PD-1 axis was more active in lymphoid organs and the GVT effect could be enhanced by the addition of PD-1 blocking agents [7]. In addition, no increase in GvHD frequency was observed in this model [7]. However, in other experimental models blockade of PD-1 resulted in an increase in GvHD [19]. Other studies have shown that PD-1/PD-L1 critically regulates the strength of GvHD effects [20, 21]. A recent analysis has demonstrated a role in GvHD of the heart [22]. Another study showed a function of PD-1 interaction with PD-L1 in inhibition a Th1/Th17-mediated graft-versus-host immune reaction [23]. Given the multiple roles of PD-1 in protection from GvHD, it is not surprising that PD-1/PD-L1 blockade induced strong allo-immune reactions in some of our patients.

The main limitation of our report is the low number of patients, the heterogeneity of the diseases and the time between the allogeneic HCT and the start of the ICI therapy. These limitations prevent general conclusions from this report. The toxicity profile, however, warrants the consideration of alternative treatment options, if available: for example, BRAF and MEK inhibitors in melanoma. In the case of no other treatment options, risk assessment should include the previous grade of GvHD, the time since transplantation and level of immune suppression when the ICI therapy is planned. Reducing the starting dose of PD-1 blocking antibodies should be explored (starting dose 15–20% of standard dosing), although there are only case reports supporting this approach [11, 12].

The strength of our report is its reflection of a real-world scenario. Not only patients with HL will relapse after allogeneic HCT but also patients with secondary solid tumours after HCT. Patients who underwent allogeneic HCT are more likely to develop second cancers [24, 25], some of which are highly responsive to ICI treatment. Evidence of the response and the toxicity as described in this report will help to support clinical treatment decisions and develop internal guidelines.

To conclude, blockade of the PD-1/PD-L1 immune checkpoint for cancer therapy is associated with high toxicity in our experience. In particular, patients still receiving immunosuppressive therapy and with recent allogeneic HCT are at very high risk for severe complications. In these patients, alternative treatment options if available or lower dosing regimens should be considered.

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