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Allogeneic Stem Cell Transplantation for HIV-positive Patients with Hematologic Malignancies

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Abstract

Objective—HIV-positive patients with hematologic malignancies are frequently not considered for treatment with allogeneic hematopoietic stem cell transplantation (alloHSCT) because of reported high morbidity and mortality with this procedure and scant published experience. Advances in HIV care and supportive care for alloHSCT prompted us to review our experience since 2010, after we instituted multidisciplinary management of HIV-infected patients during the peri-transplant period.

Methods—We retrospectively reviewed the records of all HIV-positive patients who received alloHSCT at our institution since 2010.

Results—Five patients with various hematologic malignancies received alloHSCT from matched related (2) or unrelated (3) donors since 2010. All patients received tenofovir (TDF)/emtricitabine in combination with either efavirenz (1) or raltegravir (4) and engrafted a median of 17 days post-transplant. The most common infection was CMV viremia, 6 episodes in 4 patients, controlled with antivirals. There was no transplant-related mortality. Three patients relapsed 6, 7 and 13 months post-transplant, two were alive and well after 42 and 55 months. HIV viral load remained undetectable and CD4+ cell count increased progressively. One patient had acute renal failure (ARF) and improved with hydration and replacement of TDF with abacavir.

Conclusions—Our patients received alloHSCT without transplant-related mortality or major infectious complications. Their HIV viral load remained undetectable without the use of protease inhibitors or need to discontinue antiretroviral therapy. One patient had ARF that resolved after discontinuation of TDF. Our findings support considering selected HIV-infected patients for alloHSCT when indicated for the management of their hematologic malignancies.

Keywords

HIV; Hematopoietic stem cell transplantation; Opportunistic infections; Antiretroviral Therapy; Highly Active; Cytomegalovirus; Hematologic Neoplasms

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a well-established treatment option for hematologic malignancies such as Hodgkin and non-Hodgkin lymphomas, acute and chronic leukemias, and other hematologic conditions in HIV-negative patients. In HIV-positive patients, alloHSCT is often not considered an option due to multiple challenges, in particular their history of opportunistic infections and malignancies, concomitant infections, complex drug interactions between antiretroviral therapy (ART) and medications used in transplantation as well as the effects of HIV on T cells and the bone marrow environment and cytokine milieu that may affect engraftment, lead to an increase in conditioning regimen-related toxicity, graft-versus-host disease (GVHD), and infection risk, thus leading to increased transplant-related mortality (TRM) [1]. In addition, there is little published experience.

Recent advances in HIV management, particularly the ability to suppress viral replication during the set-up for alloHSCT utilizing new agents with a low side effect profile, few if any drug interactions and good oral tolerability offer the possibility of protecting the newly transplanted immune system from the effects of the virus [2]. Participation of Infectious Disease consultants with experience in the management of HIV as well as infections in alloHSCT has been proposed in order to optimize outcomes [3]. Additionally, newer approaches to alloHSCT, including the use of less toxic conditioning chemo-radiotherapy, including non-myeloablative (reduced intensity) regimens to decrease the risk of toxic effects and transplant-related mortality while preserving the graft-versus-tumor effect, as well as improved supportive care, including the prevention of infections and the use of immunosuppressive agents to avoid GVHD [4], prompted us to look at our experience over the last 5 years. During this time, our institution developed a coordinated approach for the management of these patients, with participation of experienced Infectious Diseases physicians, starting before transplant and including the optimization of ART and prophylaxis regimens, the treatment, suppression or prophylaxis of prior or concomitant infections, and follow up during the peri- and post-transplant periods, maintaining control of HIV replication. Here we present our experience.

METHODS

This retrospective study was approved by the Institutional Review Board of MD Anderson Cancer Center. Five patients with HIV infection underwent alloHSCT from January 1st of 2010 until January 31, 2015. We retrospectively reviewed their medical records. Endpoints included duration, interruption, and adverse effects of ART, post-alloHSCT CD4+ cell count and maintenance of an undetectable viral load, engraftment, defined as the first of 3 consecutive post-alloHCT days on which the absolute neutrophil count exceeded 500/mm³; occurrence of acute and chronic GVHD, episodes of CMV reactivation, defined as CMV antigenemia ≥ 5 cells/million white blood cells (WBC) or <5 cells/million WBC if the patient received therapy or developed end-organ disease (retinitis, pneumonia, gastrointestinal disease or other), and other infection episodes. TRM was defined as death from any cause without malignancy relapse in the first 100 days after alloHSCT and overall survival (OS)

was measured from date of alloHSCT to the date of last visit or death. End point follow up was stopped upon diagnosis of disease relapse or death.

RESULTS

The baseline characteristics of our 5 patients are summarized in Table 1. They were all male; the median age was 55 years (range 38 to 62). The indications for transplantation included acute myeloid leukemia (AML) in 2 patients, Burkitt lymphoma (BL) in one, large granular lymphocytic leukemia in one, and myelodysplastic syndrome (MDS) in one. Two of patients had secondary malignancies, patient 1 had AML after therapy for BL, and patient 5 had therapy-related MDS after chemotherapy for anal squamous cell carcinoma. Three patients were in remission at the time of alloHSCT.

HIV disease and ART

Patients were diagnosed with HIV infection and received ART for a median of 5 years prior to alloHSCT. Patient 1 received tenofovir (TDF)/emtricitabine (FTC)/efavirenz (EFV) for 5 years before alloHSCT and continued until 169 days post-alloHSCT, when EFV was changed to raltegravir (RAL) because of a drug interaction. Patient 2 received TDF/FTC-RAL as his first ART starting one month before alloHSCT and the remaining patients were switched to TDF/FTC-RAL a median of 83 days before transplantation. Patient 3 had hepatitis that resolved after lopinavir/ritonavir (LPV/r) was replaced with RAL prior to alloHSCT. Except for patient 3, all others had an undetectable pre-transplant HIV viral load. The median pre-alloHSCT CD4+ cell count was 208 cells/ μ L (range 33 to 1661 cells/ μ L). Four patients had history of pre-transplant infections or comorbidities related to HIV infection.

Transplantation

Two patients received grafts from matched related and 3 from matched unrelated donors. All 5 received standard GVHD prophylaxis with tacrolimus and methotrexate. Infection prophylaxis included levofloxacin while neutropenic, valacyclovir for the first 90 days, an azole or echinocandin and either trimethoprim/sulfamethoxazole or intravenous pentamidine. They were monitored for CMV reactivation with twice weekly measurement of CMV antigenemia for the first 90 days and while receiving systemic therapy for GVHD, if applicable, and were treated preemptively for reactivations with ganciclovir or foscarnet under the same protocol followed for HIV-negative alloHSCT recipients. These were the same prophylactic measures we used on our HIV-negative patients. In addition, two patients received weekly azithromycin prophylaxis.

Transplant outcomes

All patients engrafted a median of 17 days post-alloHSCT (range: 13 to 19 days) and there was no transplant-related mortality. Patients 1 and 4 relapsed after 3 months and patient 5 relapsed 9 months post-transplant. Their OS was 6, 7 and 13 months post-transplant, respectively. Patients 2 and 3 were alive and in remission on last follow up 55 and 42 months post-transplant, respectively. Two patients had acute GVHD grades 1 and 2, and one had chronic GVHD of the skin, oral mucosa and liver.

Infection episodes

Patients 1, 2 and 5 had neutropenic fever treated successfully with empiric antibiotics, their blood cultures were negative. One or two episodes of CMV reactivation, without end-organ disease, occurred in 4 patients and were controlled with ganciclovir or foscarnet. Only 2 other post-transplant infections were diagnosed in the first 100 days post-alloHSCT: rectal herpes in patient 1 and acute cholecystitis in patient 2, both resolved.

Post-transplant monitoring of HIV infection

We performed a total of 27 post-transplant HIV PCR quantitative viral load measurements, a median of 3 per patient (range 2 to 11), all were undetectable except one in patient 3: 138copies/mL, the following viral load was undetectable. We had 31 CD4+ cell count values, a median of 5 per patient (range 2 to 11). Patients 2 and 3, who achieved complete remission and had the longest follow ups, had the highest post-alloHSCT CD4+ counts, which peaked 600 and 880 days post-alloHSCT, respectively.

Adverse effects of ART

Patient 3 developed acute kidney injury, presenting 218 days post-transplant with nausea, vomiting and hyperkalemia. He was dehydrated and his creatinine was 7.3 mg/dL. He responded to supportive measures. TDF/FTC and RAL were held for 7 days, and then replaced with abacavir/lamivudine (ABC/3TC), RAL was restarted. His HIV viral load remained undetectable and his creatinine was 0.9mg/dL on last follow up.

ART interruptions and substitutions

There were no other documented interruptions, and only one additional substitution: Patient 1 had EFV replaced for RAL 169 days post alloHSCT, to avoid a drug interaction with voriconazole. All patients continued on ART until their last follow up, except patient 5, who discontinued ART when he was transferred to hospice.

DISCUSSION

Five HIV-infected patients underwent alloHSCT for different hematologic malignancies and received different myeloablative and nonmyeloablative conditioning regimens in a single institution after 2010. The conditioning regimens were those used in HIV-negative patients with a similar indication for transplantation. The previous practice of scheduled ART interruption during the peri-transplant period [1, 5], when mucositis makes oral intake difficult and drug interactions with the conditioning regimen may increase drug toxicity, was not necessary due to the use of well tolerated, low pill burden regimens with little or no drug interactions. Standard anti-infectious and GVHD prophylaxis regimens were used. Before transplant, they had well controlled HIV infection, a good performance status and protease inhibitor-free ART regimens.

Compared to patients reported previously, our patients were older, with a mean age of 55 years compared to 37 and 34 years in two previous reviews [1, 4]. All patients engrafted within the expected time and were alive at 100 days post-transplant. This is in contrast with very high transplant-related mortality at day 100 in previous reports, affecting 10 of 23

(43%) patients reported to the Center for International Blood and Bone Marrow Transplant Research between 1987 and 2003[1], and attributed mainly to treatment-related toxicities and infection. In a more recent review of published cases reported in the literature between 2000 and 2009 totaling 17 patients, it decreased to 18%, and total non-relapse mortality was 29%. [4]. However, a review of published reports is susceptible to publication bias.

Only one of our patients had ART-related toxicity, with acute kidney injury that was probably multifactorial, as the patient was acutely dehydrated and receiving tacrolimus, TDF, and trimethoprim/sulfamethoxazole. He improved with supportive care and TDF was replaced with ABC. TDF is reported to cause acute tubular necrosis and Fanconi syndrome in HIV-infected patients with complete or partial improvement in renal function in most cases after discontinuation [6]. A new formulation, tenofovir alafenamide, has been shown to lead to improved renal function when replacing the current tenofovir disoproxil fumarate in ART regimens and, once available, may be a better alternative for transplanted patients, who already have a high risk of nephrotoxicity [7, 8].

Our patients were able to continue on their ART without programmed or documented interruptions, which led to excellent viral control post-transplant, with all of them having undetectable viral loads in the first 90 days post-HSCT and subsequently. They had good recovery of their CD4+ cell counts, which continued to rise, in the two long term survivors, for up to 3 years. Peri-transplant treatment interruptions may cause rebound viremia and an acute febrile illness similar to primary HIV, along with infection of donor T cells. There is also the risk of developing ART resistance, thus, they should be avoided if possible [9].

The most common post-transplant infection was CMV viremia in 4 patients, followed by neutropenic fever in 3, similar to what is seen in HIV-negative transplant recipients. The primary cause of death was malignancy relapse in 3 patients, with 2 alive and in remission after prolonged follow up. Chemotherapy-related toxicities and infection were the most frequent causes of death post alloHSCT in patients receiving ART in a previous review of reported cases [1] and single institution case series [10], while relapse-related mortality was uncommon, presumably because of the short survival.

Our case series shows that advances in the management of HIV infection allowed us to treat our patients' hematologic malignancies as we would in HIV-negative patients with other comorbidities, such as diabetes or heart disease: by providing state of the art multidisciplinary management and supportive therapy through the peri-transplant period.

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P. Desai: Designed collection form, reviewed charts, limited participation in writing manuscript and reviewed and approved the article.

U. Popat: Designed study, IRB approval, obtained patients from transplant registry and reviewed and approved the article.

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References

1. Gupta V, Tomblyn M, Pedersen TL, Atkins HL, Battiwalla M, Gress RE, et al. Allogeneic hematopoietic cell transplantation in human immunodeficiency virus-positive patients with hematologic disorders: a report from the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2009; 15:864–871. [PubMed: 19539219]
2. Hutter G, Zaia JA. Allogeneic haematopoietic stem cell transplantation in patients with human immunodeficiency virus: the experiences of more than 25 years. *Clin Exp Immunol*. 2011; 163:284–295. [PubMed: 21303358]
3. Durand CM, Ambinder RF. Hematopoietic stem cell transplantation in HIV-1-infected individuals: clinical challenges and the potential for viral eradication. *Curr Opin Oncol*. 2013; 25:180–186. [PubMed: 23385862]
4. Serrano D, Miralles P, Balsalobre P, Diez-Martin JL, Berenguer J. Hematopoietic stem cell transplantation in patients infected with HIV. *Curr HIV/AIDS Rep*. 2010; 7:175–184. [PubMed: 20549392]
5. Kang EM, de Witte M, Malech H, Morgan RA, Phang S, Carter C, et al. Nonmyeloablative conditioning followed by transplantation of genetically modified HLA-matched peripheral blood progenitor cells for hematologic malignancies in patients with acquired immunodeficiency syndrome. *Blood*. 2002; 99:698–701. [PubMed: 11781257]
6. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. 2006; 42:283–290. [PubMed: 16355343]
7. Dhanireddy S, Baeten JM. Tenofovir alafenamide for HIV: time to switch? *Lancet Infect Dis*. 2016; 16:3–5. [PubMed: 26538524]
8. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016; 16:43–52. [PubMed: 26538525]
9. Echenique IA, Nelson GE, Stosor V, Durand CM. HIV and Stem Cell Transplantation. *Curr Infect Dis Rep*. 2014; 16:424. [PubMed: 25120135]
10. Serrano D, Miralles P, Balsalobre P, Kwon M, Rodriguez-Macias G, Gayoso J, et al. Graft-versus-tumor effect after allogeneic stem cell transplantation in HIV-positive patients with high-risk hematologic malignancies. *AIDS Res Hum Retroviruses*. 2013; 29:1340–1345. [PubMed: 23800257]

Table 1

Baseline characteristics of the 5 transplanted patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at SCT	57	51	38	55	62
Malignancy	AML	BL	LGL	AML	MDS
Remission at SCT	Yes	Yes		Yes	
HIV Dx to SCT date (in months)	59	5	36	125	191
ART start to SCT (in months)	57	1	35	125	83
Pre-SCT ART	TDF/FTC/EFV	TDF/FTC/RAL	TDF/FTC/EFV; TDF/FTC/LPV/r; TDF/FTC/RAL	Unknown; TDF/FTC/EFV; TDF/FTC/RAL	Unknown; TDF/FTC/RAL
HIV-related pre-SCT morbidity	KS, BL, ITP, syphilis	Herpes zoster	Splenectomy Hepatitis due to LPV/r		Anal squamous cell carcinoma Hepatitis C
Pre-SCT CD4 count (%)	95 (32%)	33 (5%)	1661 (19%)	208 (29%)	155 (15%)
HIV viral load pre-SCT (copies/mL)	<48	146	<20	<20	<20
TDF/FTC/RAL initiation to SCT		35	63	81	683
Performance Status	90	90	90	100	100
Donor type	MUD	MRD	MUD	MUD	MRD
Myeloablative	N	Y	N	Y	Y
Conditioning	FLU-MEL-ATG	BEAM-R	FLU-MEL-ATG	FLU-BU	FLU-BU

SCT, stem cell transplant; Dx, diagnosis; ART, antiretroviral therapy; AML, acute myeloid leukemia; BL, Burkitt lymphoma; LGL, large granular leukemia; MDS, myelodysplastic syndrome; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; RAL, raltegravir; KS, Kaposi's sarcoma; MUD, matched unrelated donor; MRD, matched related donor; FLU, fludarabine; MEL, melphalan; ATG, anti-thymocyte globulin; BEAM, carmustine, etoposide, cytarabine, melphalan; R, rituximab; BU, busulfan

Table 2

Outcomes of the 5 transplanted patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Disease-free survival (months)	3	55	42	3	9
Overall survival (months)	6	55	42	7	13
Current disease state	Relapsed, died	CR, alive	CR, alive	Relapsed, died	Relapsed, died
Days to neutrophil engraftment (days)	18	17	13	19	13
Acute GVHD	No	GI grade 1	No	Skin grade 2	No
Chronic GVHD	No	Skin, mucosal, liver	No	No	No
CMV antigenemia episodes	1	2	2	1	0
Other post-SCT infections (days post-SCT)	rectal HSV (30)	Acute cholecystitis (93)	None	None	None
		PJP (1898)			
Duration of TDF/FTC/RAL post- SCT (days)		1643	218	132	386
HAART interruption	No	No	7 days	No	No
Reason for interruption or discontinuation of HAART			AKI		Hospice
CD4 count (%) first 90 days	31 (6%)	119 (30%)	157 (10%)	107 (33%)	159 (16%)
Peak CD4 count (%) post-SCT	40 (9%)	513 (22%)	1503 (14%)	269 (40%)	172 (28%)
Peak CD4 count post-SCT day	137	600	880	27	41
HIV viral load first 90 days	<48	<20	<20	<20	<20
Copies/mL					

AKI, acute kidney injury; CR, complete remission; FTC, emtricitabine; GI, gastrointestinal; GVHD, graft-versus-host disease; PJP, *Pneumocystis jiroveci* pneumonia; RAL, raltegravir; SCT, stem cell transplant; TDF, tenofovir