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HLA-mismatched bone marrow transplantation in severe aplastic anemia

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To the Editor:

Hematopoietic stem cell transplantation (SCT) can be curative for patients with severe aplastic anemia (SAA)[1, 2]. Concerns with graft failure and graft-versus-host disease (GVHD), more so for human leucocyte antigen (HLA) -mismatched donors have impeded the utility of SCT for these patients. The introduction of post-SCT cyclophosphamide (PTCy) has been shown to decrease alloreactivity in the host-versus-graft and graft versus-host directions and could be particularly well suited for SAA patients[3]. Only a few patients in two recent reports have documented outcomes of patients with SAA treated with a haploidentical transplant and PTCy-based GVHD prophylaxis, both using non-myeloablative (NMA) conditioning with fludarabine, cyclophosphamide and 2Gy total body irradiation (TBI)[4, 5]. Concern for higher rejection rate, both primary and secondary; have prompted us to use a more intense conditioning regimen, as previously described[6]. Here we report clinical outcomes in transfusion dependent (n-6, 5 were refractory to first line immunosuppressive therapy, 1 patient received hypomethylating agent for hypoplastic MDS but was subsequently managed as AA) SAA patients who underwent HLA-mismatched bone marrow SCT from haploidentical (n=2) and a 9/10 matched unrelated donors (n=4) at our center between 01/2010 and 5/2013. Conditioning regimen consisted of melphalan (140mg/m2) on day-8, thiotepa (5mg/kg) on day-7 and fludarabine (160mg/m2) on days-6 to −3, followed by cyclophosphamide (50mg/kg) on days +3 and +4, tacrolimus and mycophenolate mofetil. Median age of patients at the time of SCT was 37 years (range 21–50), median Karnofsky performance score was 90 (range 80–100) and median time from diagnosis to transplant was 9 months (range 2–15 months). Of the 6 patients, 2 of them had a concomitant PNH clone > 20% prior to SCT. All patients engrafted the donor cells with 100% chimerism noted for both myeloid and T-cell lineage at day + 30 post-SCT. Of the 4 long term survivors 100% donor chimerism data was available at 1 year post SCT for 3 patients and for up to 6 months for 1 patient. However the patient on whom we had chimerism information till 6 months was disease free at 1 year post SCT and was followed

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elsewhere for routine care. Median time to neutrophil and platelet engraftment was 16 and 13 days, respectively (Table1). Acute GVHD was seen in 3 patients (grades-1, 2 and 4 each) and led to death in 1 patient who had a 9/10 MUD SCT (Table1). No chronic GVHD (cGVHD) or disease relapse was noted. After a median follow-up of 949 days (range 735–1617), 4/6 (66.6%) patients (two haploidentical and two 9/10 MUD) were alive, fully engrafted without cGVHD.

Only about 25–30% of SAA patients have an HLA-identical related donor, and the probability of finding a fully HLA matched unrelated donor for patients with hematologic disorders needing SCT varies substantially based on their ethnicity[7]. Hence, when a fully HLA matched unrelated donor is not identified, HLA mismatched transplantation provides an option with curative potential otherwise not available to many patients. More recently, introduction of PTCy prophylaxis has shown encouraging results in patients with hematologic malignancies receiving SCT from haploidentical and 9/10 MUD donors[8, 9]. Concerns remain, however, with the low intensity NMA conditioning regimen especially for patients with non-malignant diseases regarding a higher rate of primary or secondary graft rejection, and the need to re-transplant a subgroup of these patients[4]. Here we report our experience with a more intense, melphalan-based conditioning regimen for SAA patients, in which all patients achieved prompt engraftment with no mixed chimerism post-SCT, alleviating the concern for secondary graft failure. Acute GVHD incidence appears well controlled with PTCy-based GVHD prophylaxis and no cGVHD was observed. Our results show that application of a more intense conditioning is feasible and could be used for counseling patients who express concerns of secondary graft failure with NMA options. Our experience also adds to the growing body of evidence that supports the use of PTCy for HLA mismatched SCT recipients and increase the donor pool for SAA patients.

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Table1.

Characteristics and outcomes of patients with SAA treated with PTCy-based GVHD prophylaxis and a mismatched graft.

Disease	KPS	Age	Time from Diagnosis to SCT (months)	Donor	Time to ANC 500	Time to Platelet count 20K	Donor Chimerism (D+30)	Acute GVHD (Max Grade)	Chronic GVHD	Follow-up (Days) from SCT	Cause of Death
SAA	90	21	12	9/10 MUD (HLA-B Mismatch)	20		Y (100%)	No	N/A	33 (D)	Infection (Bacterial)
SAA	80	44	6	9/10 MUD (HLA-DRB1 Mismatch)	17	23	Y (100%)	No	None	1617 (A)	N/A
SAA+ PNH	90	50	15	9/10 MUD (HLA-A Mismatch)	13	11	Y (100%)	Yes (1)	None	848 (A)	N/A
SAA	NA	30	2	HAPLO	18	40	Y (100%)	No	None	1050 (A)	N/A
SAA	90	50	12	9/10 MUD (HLA-DQB1 Mismatch)	14	13	Y (100%)	Yes (4)	None	131(D)	Acute GVHD
SAA	100	23	5	HAPLO	15	0	Y (100%)	Yes (2)	None	735 (A)	N/A

SCT – Stem Cell Transplant; HLA- Human Leucocyte Antigen, SAA- Severe Aplastic Anemia, PNH- Paroxysmal Nocturnal Hemoglobinuria, KPS- Karnofsky Performance Scale, PTCy- Post Transplant Cyclophosphamide, MUD- Matched Unrelated Donor, Haplo- Haploidentical, ANC- Absolute Neutrophil Count, GVHD- Graft Versus Host Disease, Max-Maximum, A- Alive, D- Dead; N/A – not applicable.