Reduced intensity regimen for a second mismatched transplant

In this report we describe our experience with two patients in order to evaluate the clinical potential of a reduced intensity stem cell transplantation in a more difficult clinical setting, i.e. second transplant with a one- or two-antigen mismatched related donor for relapsed and refractory leukemia. Three benefits were hoped for: 1) reduced regimen-related toxicity, 2) potent engraftment facilitation, and 3) an intense anti-leukemia effect.

Reduced intensity stem cell transplantation (RIST) should be suitable for a second transplantation, since regimen-related toxicity (RRT) is one of the major causes of failure in a second transplant with conventional myeloablative regimens.[1-3] It was been reported that when two successive myeloablative transplants were performed on the same patient within one year, the transplant-related mortality was unacceptably high.[4] Using a RIST regimen, severe RRT in the second transplant can be avoided. We have explored the possibility of performing mismatched transplants from a related donor using a RIST regimen. So far, there has been extremely limited experience with RIST from a mismatched donor.[5]

Case #1. A 29-year old man was diagnosed as having acute myeloid leukemia (AML), which was refractory to various induction chemotherapies. Since he was much heavier than his one-locus mismatched mother, he was selected to undergo bone marrow transplantation (BMT) from a matched unrelated donor after a conditioning regimen of cyclophosphamide 60 mg/kg for two days and 12 Gy of total body irradiation (CY/TBI). His post-transplant course was uneventful with prompt engraftment, and no graft-versus-host disease (GVHD) was observed. However, a post-transplant echocardiogram revealed a decreased cardiac ejection fraction of 43%. Moreover, leukemic relapse was found on day 100. Re-induction chemotherapy with Ara-C (100 mg/m^2 for 6 days) was not effective in inducing complete remission (CR). We, therefore, decided to perform the second transplant using his mother as an alternative donor (Table 1). Six months after the first transplant, a second transplant was performed with a cladribine/busulfan/anti-thymocyte globulin (ATG) regimen.[6] The post-transplant course was uneventful, with evidence of engraftment on day 14 without significant RRT (Table 2). Grade II skin GVHD developed on day 55 after rapid tapering-off of cyclosporin A. The patient is still in complete remission with mild chronic GVHD more than 1 year after the second transplant.

Case #2. A 17-year old woman with primary refractory acute lymphoblastic leukemia (ALL) underwent bone marrow transplantation (BMT) from a matched unrelated donor using the CY/TBI regimen. The post-transplant course was uneventful without GVHD until 2 months after the transplant, when relapse of the ALL was confirmed. Standard-dose chemotherapy was started, and she then received donor lymphocyte infusion (DLI) from the original donor, which was followed by severe aplasia without GVHD. Remission was not induced and she continued to have fever and prolonged cytopenia, for which daily transfusion support was required. She then developed *Aspergillus* pneumonia. The decision was made to perform a second transplant using her two-loci mismatched father as an alternative donor after the lung lesion had subsided. Six months after the first transplant, she underwent a second transplant. She received the fludarabine/busulfan/ATG regimen. By day 15, her absolute neutrophil count exceeded 0.5×10^9/L without significant RRT. Karyotypic analysis of bone marrow on day 14 showed 86% donor-derived cells (Table 2). She subsequently died of exacerbation of pulmonary aspergillosis on day 26. An autopsy was performed; her bone marrow showed 100% donor cell engraftment without leukemic cells.

Once relapse or graft rejection occurs after unrelated transplantation, a second transplant becomes the only method for rescuing patients. Their prognosis is, however, still dismal, mainly because of organ dysfunction related to the first transplant. Thus, reducing the intensity of the conditioning regimen is beneficial in order to avoid RRT. Moreover, in the case of an unrelated transplant, donors are not necessarily available when the second transplant is urgently needed. If the second transplant using the RIST regimen can be done from a mismatched related donor, there may be more opportunity of those patients, who may not otherwise have a chance of cure, of receiving a transplant. However, engraftment is a major concern in mismatched transplants using less intensive regimens.[7-9] In this report, with a RIST regimen followed by a mismatched family donor transplant, RRT was manageable, and successful engraftment was achieved. Indeed, engraftment was achieved in case #2 even from a 2-antigen mismatched donor. This shows that the RIST regimen may have profound engraftment-facilitating capacity. The assumption that the direct cytoreductive potential of RIST regimens is inferior to that of conventional regimens has pre-

Table 2. HLA type of donors and recipients.

	Case#1			*Case#2*		
	A	*B*	*DRB1*	*A*	*B*	*DRB1*
Recipient	24, 33	44, 56	0901, 0303	11, 24	61, 62	0406, 1401
Donor	24, 33	44, 56	0901, 0803	2, 11	61, 62	0406, 0901

Table 1. Patients' characteristics, graft composition, and % donor chimerism.

Case	*Age/Sex*	*Disease*	*Interval before 2nd transplant*	*Conditioning regimen*	*HLA compatibility*	*Graft composition*		*% Donor chimerism*	
						Infused CD34 (×10^6/kg)	*Infused CD3 (×10^8/kg)*	*day 14 (%)*	*day 26 (%)*
1	29/M	AML	6 months	2-CdA/BU/ATG	5/6	3.7	6.8	100	100
2	17/F	ALL	6 months	Flu/BU/ATG	4/6	4.8	2.2	86	100

M; male, F; female, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, 2-CdA; cladribine, BU; busulfan, ATG; anti-thymocyte globulin, Flu; fludarabine, % donor chimerism was analyzed using cytogenetics and/or short tamdem repeat analysis methods.

vented the wider application of this procedure to those with refractory leukemia. However, as demonstrated by case #1, durable remission can be achieved with concomitant occurrence of GvHD even in a case of AML relapsed shortly after a myeloablative unrelated BMT procedure.[10] Thus RIST certainly has its role in second transplants if only mismatched family donors are available.

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