

Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: the Japan Marrow Donor Program

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We retrospectively analyzed results for 154 patients with acquired severe aplastic anemia who received bone marrow transplants between 1993 and 2000 from unrelated donors identified through the Japan Marrow Donor Program. Patients were aged between 1 and 46 years (median, 17 years). Seventy-nine donor-patient pairs matched at HLA-A, -B, and -DRB1 loci, as shown by DNA typing. Among the 75 mismatched pairs, DNA typing of 63 pairs showed that 51 were mismatched at 1 HLA locus (18 HLA-A, 11 HLA-B, 22 HLA-DRB1) and 12 were mis-

matched at 2 or more loci. Seventeen patients (11%) experienced either early or late graft rejection. The incidence of grade III/IV acute graft versus host disease and chronic graft versus host disease was 20% (range, 7%-33%) and 30% (range, 12%-48%), respectively. Currently, 99 patients are alive, having survived for 3 to 82 months (median, 29 months) after their transplantations. The probability of overall survival at 5 years was 56% (95% confidence interval, 34%-78%). Multivariate analysis revealed the following unfavorable factors: transplantation more than

3 years after diagnosis (relative risk [RR], 1.86; $P = .02$), patients older than 20 years (RR, 2.27; $P = .03$), preconditioning regimen without antithymocyte globulin (RR 2.28; $P = .04$), and HLA-A or -B locus mismatching as determined by DNA typing. Matching of HLA class I alleles and improvement of preparative regimens should result in improved outcomes in patients with severe aplastic anemia who receive transplants from unrelated donors. (Blood. 2002;100:799-803)

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Introduction

Bone marrow transplantation (BMT) from an HLA-matched family donor is the treatment of choice for children and young adults with severe aplastic anemia (SAA).¹ However, this approach is limited by the availability of HLA-matched donors. Immunosuppressive therapy (IST) with a combination of antithymocyte globulin (ATG) and cyclosporine has been an alternative treatment for patients without a suitable related donor.²⁻⁴ BMT from a phenotypically HLA-matched unrelated donor is indicated as salvage therapy for patients who fail to respond to one or more courses of IST and patients who experience relapse of disease.^{5,6} Initial attempts to use unrelated donor BMT for patients with SAA were hampered by the high incidence of graft failure and graft versus host disease (GVHD); survival rates ranged from 20% to 54%.⁷⁻¹⁰

An optimum conditioning regimen, GVHD prophylaxis, and better donor selection are considered to be indispensable for improving outcomes for patients who receive unrelated donor BMT. Here we report a detailed analysis of outcomes for 154 SAA patients who underwent BMT from an unrelated donor identified through the Japan Marrow Donor Program (JMDP). This report represents one of the largest series of unrelated donor BMT for SAA. Moreover, results of high-resolution HLA typing were available for more than 90% of the recipient-donor pairs in this study. We attempted to clarify the effect of HLA mismatching as determined by high-resolution DNA typing. Our results suggest that higher survival rates are attained when recipients are young, transplantation is performed soon after diagnosis, an ATG-containing regimen is used, and HLA-A or -B locus-mismatched donors are not used.

Patients, materials, and methods

Patients

From February 1993 to April 2000, 154 consecutive patients with acquired SAA received bone marrow transplants from unrelated donors at 68 centers in Japan. All donors were identified through the JMDP.¹¹ Characteristics of patients and donors are summarized in Table 1. Disease was considered severe if at least 2 of the following were noted: neutrophil count less than $0.5 \times 10^9/L$, platelet count less than $20 \times 10^9/L$, or reticulocyte count less than $20 \times 10^9/L$ with a hypocellular marrow.⁴ Patients were aged between 1 and 46 years (median 17 years). Most of the patients failed to respond to conventional ISTs and had been dependent on transfusions of red blood cells or platelets. All patients or their guardians gave informed consent for transplantation and submission of data to the JMDP.

Transplantation procedure

Characteristics of the transplantation procedures are listed in Table 1. The various preconditioning regimens used by individual centers classified into 5 categories: total body irradiation (TBI; 2-10 Gy) plus cyclophosphamide (CY; 120-200 mg/kg) plus ATG ($n = 56$);¹² limited field irradiation (LFI; 5-8 Gy) plus CY plus ATG ($n = 26$); TBI plus CY ($n = 51$); LFI plus CY ($n = 13$); and others ($n = 8$). In 113 patients (73%), cyclosporine (CSA) and methotrexate (MTX) were used for prophylaxis against GVHD according to the Seattle protocol. Twenty-one patients (14%) received tacrolimus instead of CSA. Ex vivo T-cell depletion was not used for any of the patients. All but 5 patients received recombinant human granulocyte colony-stimulating factor to facilitate recovery of neutrophils.

From the Japan Marrow Donor Program. Participating centers are listed in an appendix at the end of this article.

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Table 1. Patient, donor, and transplantation characteristics

Characteristic	No. of patients
No. of patients	154
Median patient age, y (range)	17 (1-46)
Median donor age, y (range)	33 (21-53)
Sex (male/female)	
Patient	86/68
Donor	93/61
Patient/donor sex	
Male/male	58
Female/female	33
Male/female	28
Female/male	35
Etiology of aplastic anemia	
Idiopathic	147
Hepatitis	6
Drug	1
Disease duration before BMT	
1 y or less	26
1-3 y	52
3 y or more	73
Unknown	3
RBC transfusions before BMT	
Less than 20	30
20 or more	112
Unknown	12
Platelet transfusions before BMT	
Less than 20	31
20 or more	109
Unknown	14
GVHD prophylaxis	
CSA/MTX	113
Tacrolimus/MTX	21
Others	20
Marrow cell dose	
Less than $3 \times 10^8/\text{kg}$	36
$3 \times 10^8/\text{kg}$ or more	78
Unknown	40
Conditioning regimen	
TBI + CY + ATG	56
LFI + CY + ATG	26
TBI + CY	51
LFI + CY	13
Others	8

RBC indicates red blood cell.

Recipient-donor HLA matching

The HLA matching between recipient and donor was based on HLA serotyping according to the standard technique. Until 1997, the JMJD approved serologically determined 6 of 6 matched donors as suitable for corresponding patients. Since 1998, 5 patients have received transplants from donors serologically determined to be mismatched at 1 antigen. In 142 (92%) of the present 154 recipient-donor pairs, molecular analyses of HLA-A, -B, and -DRB1 loci were performed by DNA-based methods either prior to transplantation or afterward using pretransplantation samples.¹³

Data collection and statistical analysis

Transplantation data were collected using standardized forms provided by the JMJD. Patient baseline information and follow-up report were submitted at 100 days, 6 months, 1 year, and annually after transplantation. Analysis of patient outcome was performed using the date of last reported follow-up or the date of death. The median length of follow-up was 29 months (range, 3-82 months). Data were analyzed as of July 1, 2000.

In evaluation of engraftment, patients who died before day +22 without engraftment were not considered evaluable. Patients who failed to engraft were

excluded from analyses of acute and chronic GVHD. Probability of overall survival and acute and chronic GVHD was estimated from the time of transplantation according to the Kaplan-Meier product-limit method.¹⁴ In univariate analysis, the χ^2 test and log-rank statistics were used to assess significance of differences in outcome among various groups. In multivariate regression analysis of risk factors for graft rejection, acute and chronic GVHD, and 5-year survival, the Cox proportional hazards model was used. Conditioning regimens and HLA matching were each classified into 2 major categories. The following variables were evaluated: donor and recipient age, sex, disease duration before BMT, number of pretransplantation transfusions, marrow cell doses, methods of prophylaxis against GVHD, ATG-containing regimen (yes/no), TBI-containing regimen (yes/no), HLA-A or -B locus matching (yes/no), and HLA-DRB1 locus matching (yes/no). In analysis of chronic GVHD, history of grade II-IV acute GVHD was included as an additional variable.

Results

HLA matching by DNA typing

Of the 142 recipient-donor pairs evaluated by DNA typing in this study, 79 were found to be matched at HLA-A, -B, and -DRB1 loci. Among

Table 2. Outcome following unrelated donor BMT for SAA: univariate analysis

Covariates	Graft failure,		Grade III/IV acute		Chronic GVHD,		5-year survival,	
	%	P	GVHD, %	P	%	P	%	P
Recipient age								
Less than 20 y	8		78		27		69	
20 y or more	19	.05	19	.94	29	.85	45	.005
Donor age								
Less than 35 y	10		16		26		66	
35 y or more	16	.29	21	.52	29	.69	51	.02
Recipient sex								
Male	16		16		24		57	
Female	9	.17	20	.55	32	.32	56	.70
Donor sex								
Male	13		22		26		49	
Female	11	.79	12	.14	29	.69	69	.02
Recipient/donor sex								
Male/male	13		22		21		51	
Female/female	21		19		31		69	
Male/female	0		22		28		71	
Female/male	13	.14	22	.23	33	.71	50	.02
Disease duration before BMT								
1 y or less	13		16		40		65	
More than 1 y to less than 3 y	8		23		29		69	
3 y or more	14	.68	16	.58	23	.35	51	.04
RBC transfusions before BMT								
Less than 20	13		23		32		79	
20 or more	12	.85	16	.33	27	.59	49	.06
Platelet transfusions before BMT								
Less than 20	10		21		35		66	
20 or more	13	.64	16	.54	25	.37	52	.08
GVHD prophylaxis								
CSA/MTX	13		18		28		59	
Tacrolimus/MTX	0		18		13		51*	
Others	10	.22	22	.89	43	.18	19	.29
Marrow cell dose								
Less than $3 \times 10^8/\text{kg}$	20		9		17		68	
$3 \times 10^8/\text{kg}$ or more	10	.15	17	.25	27	.33	53	.28

*3-year survival.

Table 3. Outcome following unrelated donor BMT for SAA: univariate analysis

Covariates	Graft failure, %	P	Grade III/IV acute GVHD, %	P	Chronic GVHD, %	P	5-year survival, %	P
Conditioning regimen								
TBI + CY + ATG	2		10		22		75	
LFI + CY + ATG	25		15		23		61	
TBI + CY	13		29		34		53	
LFI + CY	21	.02	18	.09	35	.50	24	.10
HLA matching by DNA typing								
HLA-A, -B, -DRB1 matched	8		12		26		60	
A locus mismatched	24		22		13		46	
B locus mismatched	11		30		29		32	
DRB1 locus mismatched	14		29		39		71	
2 or more loci mismatched	20	.42	27	.25	67	.28	30	.009

the 63 mismatched pairs, 51 were mismatched at 1 HLA locus (18 HLA-A locus, 11 HLA-B locus, 22 HLA-DRB1 locus), 11 were mismatched at 2 HLA loci, and 1 was mismatched at 3 HLA loci.

Engraftment and late graft rejection

Engraftment was defined as achievement of a peripheral blood absolute neutrophil count of more than $0.5 \times 10^9/L$ for 3 consecutive days. The median time to engraftment was 18 days, ranging from 10 to 70 days. Seven (5%) of the 144 evaluable patients failed to engraft. Late graft rejection was defined as development of sustained severe neutropenia (absolute neutrophil count $< 0.5 \times 10^9/L$) and hypocellular bone marrow in patients who had previously engrafted. Late graft rejection occurred in 10 (8%) of the 137 engrafted patients; thus, 17 patients (11%) experienced either early or late graft rejection. In univariate analysis, 2 variables were associated with graft failure: recipient age and conditioning regimen (Tables 2 and 3). In multivariate regression analysis, relative risk was much higher in patients conditioned with non-TBI regimens than in patients conditioned with TBI-containing regimens (relative risk, 3.84; 95% confidence interval [CI], 1.26-12.4; $P = .01$).

Acute GVHD

Figure 1 shows the incidence at 100 days of grade II-IV acute GVHD (29%, range 14%-44%) and grade III/IV acute GVHD (20%, range 7%-33%). In univariate analysis, none of the covariates were statistically significant. Multivariate analysis revealed that significantly higher incidence of grade III/IV acute GVHD was

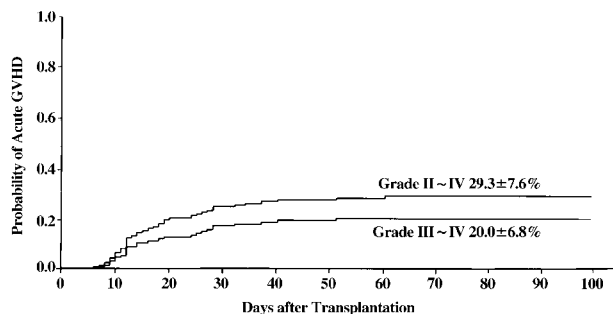


Figure 1. Incidence of acute GVHD in patients with SAA who received transplants from unrelated donors.

Table 4. Outcome following unrelated donor BMT for SAA: multivariate analysis

Covariates	Relative risk (95% CI)	P
Graft failure		
Recipient 20 y or more	2.86 (0.94-8.44)	.06
Non-TBI regimen	3.94 (1.26-12.4)	.01
HLA-A or -B locus mismatching	2.43 (0.78-7.46)	.12
Grade III/IV acute GVHD		
Male donor	3.45 (0.95-12.5)	.06
Non-ATG regimen	4.21 (1.36-13.1)	.01
HLA-A or -B locus mismatching	3.32 (1.09-10.1)	.03
Chronic GVHD		
HLA-A or -B locus mismatching	6.62 (1.76-25.0)	.005
Grade II-IV acute GVHD	6.29 (1.55-25.5)	.01
5-year survival		
Recipient 20 y or more	2.27 (1.08-4.81)	.03
Male donor	2.81 (0.94-5.63)	.07
Disease duration 3 y or more	1.86 (1.11-3.14)	.02
Non-ATG regimen	2.28 (1.06-4.91)	.03
HLA-A or -B locus mismatching	2.28 (1.04-5.02)	.04

associated with conditioning regimens without ATG and use of an HLA-A or -B locus-mismatched donor (Table 4).

Chronic GVHD

At 2 years after BMT, overall incidence of chronic GVHD was 30% (range, 12%-48%) (Figure 2). Of the patients with chronic GVHD, 51% had extensive type. In univariate analysis, a history of prior grade II-IV acute GVHD was associated with higher incidence of chronic GVHD (53% vs 18%, $P = .001$). This finding was confirmed by multivariate analysis. Mismatch at the HLA-A or -B locus was another statistically significant risk factor (Table 4).

Survival

Of the 154 patients, 99 are presently alive, 3 to 82 months (median 29 months) after transplantation. The probability of overall survival at 5 years was 56% (Figure 3; 95% CI, 34%-78%). Univariate analysis revealed the following statistically significant variables: recipient and donor age, donor sex, recipient/donor sex, disease duration before BMT, and HLA matching (Tables 2 and 3). The conditioning regimen that included CY, ATG, and TBI resulted in the highest probability of survival (Figure 4). Probability of survival did not differ between recipients of transplants from donors that matched at HLA-A, -B, and -DRB1 loci and those who received transplants from HLA-DRB1-mismatched donors (Figure 5). Multivariate analysis revealed the following unfavorable variables: older recipient, late BMT, non-ATG-containing regimen, and HLA-A or -B locus mismatching, as determined by DNA typing (Table 4). Mismatching of HLA-DRB1 did not result in increased mortality.

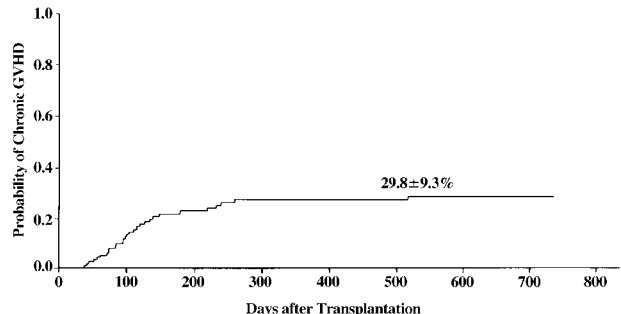


Figure 2. Incidence of chronic GVHD in patients with SAA who received transplants from unrelated donors.

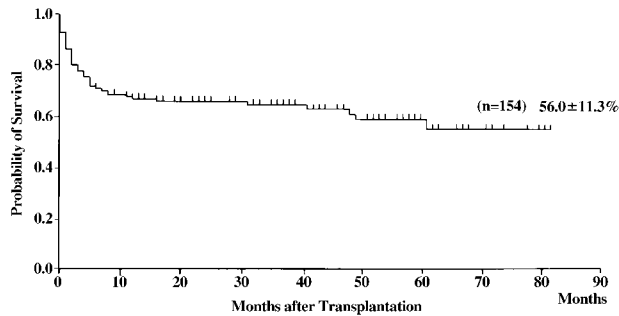


Figure 3. Probability of survival in patients with SAA who received transplants from unrelated donors.

Causes of death are summarized in Table 5. Graft failure, bacterial/fungal infections, and acute GVHD were major causes of death. The performance status at the time of the last follow-up was measured using the Karnofsky activity score. Of the 94 evaluable patients, 85 (90%) had a normal or nearly normal activity score (Karnofsky assessment, 90%-100%). The scores of the remaining 9 patients ranged from 40% to 80%.

Discussion

The survival rate for BMT from an HLA-matched sibling has increased substantially over the past 20 years for patients with SAA. Five-year survival rates as high as 90% have recently been reported.¹⁵⁻¹⁷ In contrast, results of unrelated donor BMT have generally been unsatisfactory for SAA.⁷⁻¹⁰

In this large series of unrelated donor BMT for SAA, we attempted to identify prognostic factors that may be useful for improving outcomes of patients. Better donor selection based on molecular HLA typing appears to be one of the most important variables for improvement of survival rate.¹⁸⁻¹⁹ HLA-A, -B, and -DRB1 genotypic mismatches were found in 63 (44%) of the 142 donor-recipient pairs that were matched for HLA-A, -B, and -DR by serology in our series. The results of the current study are consistent with those of a previous JMJD study in which only 10% of the patients had SAA. In the latter study, mismatching of class I HLA alleles between donor and recipient was found to be a strong risk factor for GVHD and survival,¹³ whereas mismatching of HLA class II alleles did not have a significant effect on outcomes of the patients. In the National Marrow Donor Program (NMDP) study, mismatching of HLA-DRB1 was found to be the most crucial risk factor for survival.^{20,21} Patients who received transplants from donors with matching DRB1 alleles had significantly better outcomes than DRB1-mismatched patients: 60% versus 15% survival at 3 years. In the current JMJD study, the 5-year survival rate was 56% for the 79 patients who

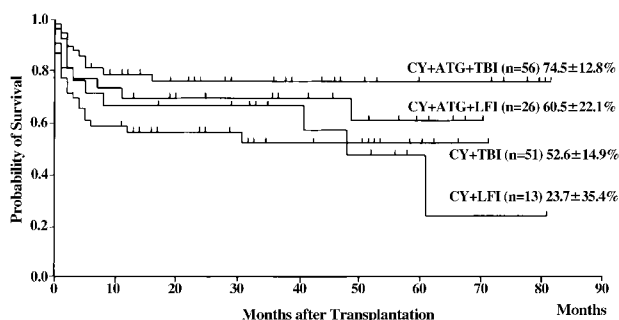


Figure 4. Probability of survival for various conditioning regimens in patients with SAA who received transplants from unrelated donors.

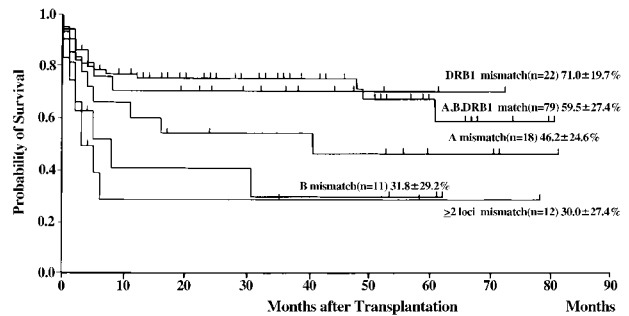


Figure 5. Probability of survival according to HLA matching on the basis of DNA typing in patients with SAA who received transplants from unrelated donors.

received transplants from HLA-A-, -B-, and -DRB1-matched donors, compared with 71% for the 22 patients who received transplants from donors matched at HLA-A and -B and mismatched at HLA-DRB1 ($P = .95$). The differences between the results of the JMJD study and those of the NMDP study may be due to differences in the roles of individual HLA loci in unrelated donor BMT in different ethnic groups.²² Restricting BMT to donor-recipient pairs perfectly matched at molecular levels will exclude many patients from candidacy for unrelated donor BMT. The current study demonstrated that mismatching of DRB1 alleles is acceptable for Japanese patients, and this finding could increase the number of possible unrelated BMT donor-recipient pairs.

Large registration studies have shown that the inclusion of irradiation in preparative conditioning can reduce graft rejection.²³ Both LFI and TBI are used for patients with SAA. Our results clearly show a lower risk of graft rejection for transplantation patients who received a TBI regimen, compared with those who received a non-TBI regimen. In the present study, CY (120 mg/kg) plus TBI (10 Gy) plus ATG and, also, CY (200 mg/kg) plus LFI (7.5 Gy) plus ATG were the most frequently used regimens, although other doses were also used. Only 1 (3%) of the 30 patients (17 HLA-matched, 13 HLA-mismatched) experienced graft rejection in the CY/TBI/ATG group, whereas 5 (21%) of the 24 patients in the CY/LFI/ATG group (15 HLA-matched, 6 HLA-mismatched, 3 HLA not tested by molecular techniques) failed to engraft. A high-dose TBI-containing regimen is effective in ensuring engraftment, but there is growing concern about regimen-related morbidity and mortality. Moreover, long-term complications such as cataracts and endocrine dysfunction are frequent in patients who received TBI.²⁴ In light of these concerns, the NMDP conducted a prospective study to determine the minimal dose of TBI sufficient to achieve sustained engraftment when it was used in combination with CY (200 mg/kg) and ATG.²⁵ The doses of TBI were as follows: first cohort of patients, 2 Gy \times 3; second cohort, 2 Gy \times 2; subsequent cohorts, 2 Gy \times 1. All 30 patients who received 6 Gy or 4 Gy of TBI achieved engraftment, and 17 of those patients are presently alive. Of the 13 patients who received 2 Gy of TBI, 1 failed to engraft and 8 are presently alive. Pulmonary toxicity occurred in 8 of the 30 patients who received 6 Gy or 4 Gy of TBI and 2 of the 13 patients who received 2 Gy of TBI. The authors of the NMDP study concluded that a TBI dose of 2 Gy was sufficient to allow engraftment without increasing toxicities for perfectly HLA-matched pairs.

In evaluating the effects and toxicities of TBI, we must be mindful that observed effects and toxicities could be related to interactions among CY, TBI, and ATG. In our study, 2 of the 3 patients (2 HLA-matched, 1 HLA-mismatched) who were conditioned with CY (120 mg/kg) plus low-dose TBI (5 or 8 Gy) failed to engraft, and 3

Table 5. Causes of death following unrelated donor BMT for SAA

Cause of death	No. of patients
Graft failure	10
Bacterial/fungal infection	9
Acute GVHD	6
Hemorrhage	5
Interstitial pneumonitis	5
Chronic GVHD	3
Venoocclusive disease	2
Renal toxicity	2
Hepatic toxicity	2
Others	11

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Appendix

The following centers participated in the bone marrow transplantations for SAA facilitated by the JMDFP: Hokkaido University School of Medicine; Sapporo Medical University; Sapporo Hokuyu Hospital; Tohoku University School of Medicine; Hirosaki University School of Medicine; Iwate Medical University School of Medicine; Yamagata University Hospital; Akita University School of Medicine; Fukushima Medical College; Toho University School of Medicine, Omori Hospital; Tokyo University Hospital; Tokyo Metropolitan Komagome Hospital; Nihon University School of Medicine, Itabashi Hospital; Keio University; Tokyo Medical College Hospital; Tokyo Medical and Dental University Hospital, Faculty of Medicine; Yokohama City University Hospital; Kanagawa Children's Medical Center; Tokai University Hospital; Chiba University School of Medicine; Chiba Municipal Hospital; Chiba Children's Hospital; Saitama Children's Medical Center; Saitama Cancer Center Hospital; Saitama Medical School; Ibaraki Children's Hospital; Saiseikai Maebashi Hospital; Shinshu University School of Medicine; Saku Central Hospital; Shizuoka General

patients died. In contrast, 10 patients (6 HLA-matched, 4 HLA-mismatched) who were conditioned with (200 mg/kg) plus low-dose TBI (2 to 5 Gy) plus ATG engrafted, and 9 are presently alive. These results extended the findings of the NMDP TBI study by demonstrating that low-dose TBI can be sufficient to allow engraftment in patients who receive a transplant even from an HLA-nonidentical donor.

The combined effects of these favorable prognostic factors result in a 5-year survival rate of 88%, which is comparable to the best results achieved by SAA patients who received transplants from HLA-matched siblings. Given the present encouraging results, we recommend unrelated donor transplantation as a salvage therapy in nonresponders to IST in children and young adults.

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