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ORIGINAL ARTICLE

Second allogeneic hematopoietic SCT for relapsed ALL in children

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A second SCT is generally accepted as the only potentially curative approach for ALL patients that relapse after SCT, but the role of second SCT for pediatric ALL is not fully understood. We performed a retrospective analysis of 171 pediatric patients who received a second allo-SCT for relapsed ALL after allo-SCT. OS at 2 years was 29.4 ± 3.7%, the cumulative incidence of relapse was 44.1 ± 4.0% and non-relapse mortality was 18.8 ± 3.5%. Relapse occurred faster after the second SCT than after the first SCT (117 days vs 164 days, $P=0.04$). Younger age (9 years or less), late relapse (180 days or more after first SCT), CR at the second SCT, and myeloablative conditioning were found to be related to longer survival. Neither acute GVHD nor the type of donor influenced the outcome of second SCT. Multivariate analysis showed that younger age and late relapse were associated with better outcomes. Our analysis suggests that second SCT for relapsed pediatric ALL is an appropriate treatment option for patients that have achieved CR, which is associated with late relapse after the first SCT.

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Keywords: second transplantation; relapse; ALL; children

INTRODUCTION

SCT is the most effective treatment for high-risk and refractory leukemia, but relapse is still a major event of allo-SCT. It is generally accepted that a second SCT is the only potentially curative approach for patients who relapse after allo-SCT, but only some patients are eligible for a second SCT because of the high mortality and morbidity associated with repeated allo-SCT. In addition, high relapse rates occur because of the resistance of leukemic cells that have not been eliminated by the first SCT. Some previous studies have examined the role of second SCT,[1–10] but because of the small number of patients in these studies, the efficacy and safety of second allo-SCT for pediatric ALL patients that have relapsed after SCT remains unclear.

In this study, to investigate the prognostic factors of second SCT and identify subgroups for whom second SCT is effective, we performed a retrospective analysis of 171 patients who received a second SCT for relapsed ALL after allo-SCT.

PATIENTS AND METHODS

Patients and transplantations

This study was approved by the institutional ethics committee of Saitama Children's Medical Center. A total of 171 patients were analyzed based on data reported to the Japan Society for Stem Cell Transplantation registry (Table 1). The patients were selected according to the following criteria: (1) children with a diagnosis of ALL who were aged 18 years or younger at the second SCT; (2) second allo-SCT was performed for ALL that relapsed after allo-SCT; and (3) both the first and second SCT were performed between 1983 and 2009.

Myeloablative conditioning was defined as TBI of >8 Gy or the administration of >8 mg/kg BU. All other regimens were analyzed as reduced intensity conditioning SCT (RIST), including low-dose TBI (8 Gy or less) and low-dose BU (8 mg/kg or less).

Statistical analysis

OS probabilities were calculated using Kaplan–Meier estimates. Non-relapse mortality (NRM) and the incidence of relapse were expressed as cumulative incidence curves to adjust the analysis for competing risks. Univariate analyses were performed using the log-rank test, and multivariate analysis was performed using the Cox proportional hazard regression model. The following variables were examined in the univariate analysis: patient age, timing of relapse after first SCT, disease status at second SCT, conditioning regimens used for first and second SCT, severity of acute GVHD, type of donor and stem cell source. The factors that were found to be significant at $P<0.2$ were entered into the multivariate analysis. All statistical analyses were performed with the statistical software 'R' (The R Foundation for Statistical Computing, Vienna, Austria, version 2.9.1). A two-sided P-level of <0.05 was considered statistically significant for all analyses.

RESULTS

The patients' characteristics are listed in Table 1. The median follow-up duration of the survivors was 776 days (range, 62–5021). In all, 45 out of 171 patients were alive at the time of our analysis,

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Table 1. Clinical characteristics of patients and transplantations

Characteristics	*No. of patients (%)*	
	1st HSCT	*2nd HSCT*
Total no. of patients	171	
Age at 2nd HSCT, years		
Median	8	10
Range	0–18	1–18
Gender		
Male	113 (66)	
Female	58 (34)	
Disease status at HSCT		
CR	112 (65)	77 (45)
Non-CR	43 (25)	80 (47)
Unknown	16 (9)	14 (8)
Time to relapse from 1st HSCT, days		
<180	93 (54)	
⩾180	78 (46)	
Conditioning regimen		
Myeloablative	151 (88)	97 (57)
TBI	118	34
BU	26	43
Missing values	7	20
Reduced intensity	15 (9)	72 (42)
Unknown	5 (3)	2 (1)
Donor and stem cell source[a]		
Related		
BM	88 (51)	69 (40)
HLA-match	61	34
HLA-mismatch	15	25
Missing values	12	10
PBSC	24 (14)	45 (26)
HLA-match	17	20
HLA-mismatch	5	20
Missing values	2	5
Unrelated BM[b]	32 (19)	27 (16)
HLA-match	28	24
HLA-mismatch	4	3
Cord blood	24 (14)	30 (18)
HLA-match	9	9
HLA-mismatch	15	21
Donor of 1st and 2nd HSCT		
Same donor	33 (19.3)	
Different donors	105 (61.4)	
Unknown	33 (19.3)	

Abbreviation: HSCT = hematopoietic SCT.
[a]HLA disparity is based on serological typing result.
[b]There was no SCT of PBSC from unrelated donor.

and the estimated OS probability (±s.e.) at 2 years was 29.4 ± 3.7%. The cumulative incidence of relapse at 2 years was 44.1 ± 4.0%, and NRM was 18.8 ± 3.5% (Figure 1). In 34 out of 45 survivors (75.6%), the duration of remission was longer than the time to relapse after the first SCT. We identified 83 patients who relapsed after the second SCT, and remission period after the second SCT was shorter compared with that after the first SCT (median remission period was 164 days for first SCT, and 117 days for second SCT, $P = 0.04$).

The associations between outcome and various clinical characteristics are shown in Table 2. Young patient age at the second SCT (9 years or younger) was a prognostic factor for a good outcome. Although the difference was small, younger age was also found to be associated with better outcomes by multivariate analysis (Table 3). Early relapse (at 180 days or earlier

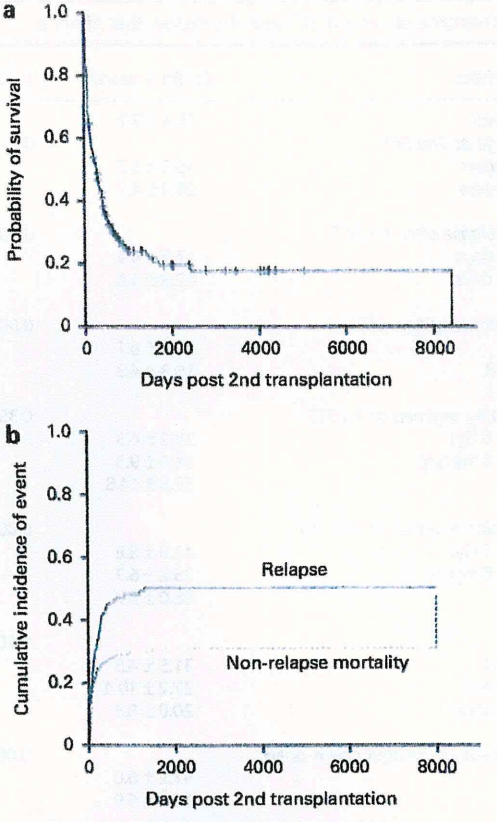

Figure 1. Outcome after second allo-SCT. (a) OS of all 171 patients. (b) Cumulative incidence of events.

after the first SCT) was associated with a worse outcome (OS at 2 years; 17.7 ± 4.4%) than late relapse (180 days or more after the first SCT; 42.3 ± 5.8%) (Figure 2a). The inferior outcomes of the patients who relapsed early after the first SCT were due to their high rate of subsequent relapse. Disease status at the second SCT was also strongly correlated with prognosis. OS at 2 years was 47.9 ± 6.1% for patients who had achieved CR before the second SCT, whereas it was 15.3 ± 4.3% for those that had not ($P = 0.0003$) (Figure 2b). The timing of relapse after the first SCT (<180 days or ⩾180 days) and disease status at the second SCT (CR or non-CR) were correlated with each other ($P = 0.0001$), but multivariate analysis showed that both of these factors were independently correlated with survival (Table 3).

OS at 2 years was 41.9 ± 8.8% in the patients that had undergone myeloablative TBI as part of the second SCT, 25.2 ± 6.7 in those that underwent myeloablative BU and 28.0 ± 5.7% in those that underwent RIST (Figure 2c). The difference between these conditioning regimens was statistically significant ($P = 0.003$). The low OS of RIST was mainly due to the high relapse rate associated with RIST (53.2 ± 6.3% at 2 years). The conditioning regimen of the first SCT was not related to survival after the second SCT. However, the patients for whom RIST was performed during the first SCT had a tendency to achieve a better outcome. In particular, nine patients underwent RIST as part of their first SCT and myeloablative conditioning during their second SCT. These nine patients included four patients younger than 1-year old, but the detailed reason for the selection of RIST as the first SCT is unclear. Although relapse after the first SCT was occurred earlier than 180 days in six patients out of the nine patients, CR was achieved in seven out of the nine patients, and six of the seven CR patients were alive at the time of our analysis.

Table 2. Outcome of second SCT and the factors that affect it

Characteristics	*OS (at 2 years)*	*P-value*	*Relapse (at 2 years)*	*P-value*	*NRM (at 2 years)*	*P-value*
All patients	29.4 ± 3.7		44.1 ± 4.0		18.8 ± 3.5	
Patient age at 2nd SCT		0.03		0.09		0.5
<10 years	35.9 ± 5.7		43.5 ± 6.0		27.8 ± 5.3	
⩾10 years	23.4 ± 4.7		52.2 ± 5.5		31.0 ± 5.0	
Time to relapse after 1st SCT		0.00002		0.01		0.93
⩽180 days	17.7 ± 4.4		56.9 ± 5.6		30.2 ± 5.1	
>180 days	42.3 ± 5.8		38.3 ± 5.7		29.0 ± 5.3	
Disease status at 2nd SCT		0.0003		0.00015		0.66
CR	47.9 ± 6.1		33.4 ± 5.7		30.2 ± 5.4	
Non-CR	15.3 ± 4.3		61.4 ± 5.5		28.6 ± 5.0	
Conditioning regimen of 1st SCT		0.35		0.46		0.85
TBI (>8 Gy)	26.2 ± 4.3		50.2 ± 4.8		30.1 ± 4.4	
BU (>8 mg/kg)	34.6 ± 9.3		42.3 ± 10.1		30.8 ± 9.3	
RIST	52.5 ± 14.8		35.3 ± 13.5		21.9 ± 12.0	
Conditioning regimen of 2nd SCT		0.003		0.87		0.52
TBI (>8 Gy)	41.9 ± 8.8		33.3 ± 8.4		30.3 ± 8.3	
BU (>8 mg/kg)	25.2 ± 6.7		39.5 ± 7.6		37.4 ± 7.6	
RIST	28.0 ± 5.7		59.6 ± 6.5		25.1 ± 5.4	
Donor		0.108		0.15		0.12
Related	31.5 ± 4.5		53.5 ± 4.8		24.1 ± 4.1	
Unrelated	27.2 ± 10.4		35.2 ± 13.0		46.2 ± 12.0	
Cord blood	20.0 ± 8.3		37.9 ± 9.3		40.0 ± 10.1	
Stem cell source (related donor only)		0.0003		0.002		0.37
BM	41.2 ± 6.0		43.6 ± 6.2		26.6 ± 5.4	
PBSC	15.2 ± 5.9		68.6 ± 7.4		20.3 ± 6.2	
Donor of 1st and 2nd HSCT		0.01		0.70		0.73
Same donor	36.1 ± 8.4		46.9 ± 9.1		25.0 ± 7.9	
Different donors	25.3 ± 4.8		51.1 ± 5.3		31.3 ± 4.9	
Acute GVHD		0.81		0.30		0.18
0 to I	31.5 ± 4.7		51.0 ± 5.0		24.3 ± 4.2	
II to IV	25.9 ± 6.3		44.2 ± 7.0		37.7 ± 7.0	

Abbreviations: NRM = non-relapse mortality; RIST = reduced intensity SCT.
OS, relapse incidence and NRM of second SCT are shown as the mean + s.e.

In all six patients, the remission period after the second SCT was longer than that after the first SCT.

Receiving a second SCT from a related donor was associated with similar outcomes to unrelated and cord blood SCT. Receiving an SCT from a related donor was associated with low NRM, although the relapse incidence of this group tended to be higher than those of the unrelated and cord blood SCT groups. In our cohort, PBSCT was associated with worse survival than BMT ($P = 0.0003$). No such difference was detected by multivariate analysis because there was a high proportion of non-CR patients in the PBSCT group (79.5% of patients were classified as non-CR) whereas 39.1% of BMT patients were classified as non-CR.

For the second SCT, a different donor from the first SCT was selected in 105 patients, but the second SCT using a different donor was associated with a trend toward a higher NRM and it failed to provide improvement in survival (Tables 2 and 3). There were 10 patients for whom SCT was performed from another HLA-matched related donor who was different from the first SCT donor, and there were 26 patients for whom SCT was performed from the same HLA-matched related donor. OS at 2 years of these two groups was similar, 37.5 ± 16.1% for different donor group and 38.5 ± 9.5% for same donor group, respectively ($P = 0.47$).

The severity of acute GVHD did not influence survival (Figure 2d and Tables 2 and 3).

DISCUSSION

Relapse is the most frequent event of SCT for hematologic malignancies, and the prognosis of relapsed leukemia is dismal. In this study, relapse was also the most frequent event after second allo-SCT. In our cohort, most post-second SCT relapses occurred earlier than the post-first SCT relapses, indicating that the leukemia cells that were not eradicated by the first SCT were highly resistant to treatment. Consequently, we should identify prognostic factors that are useful for establishing a standard treatment strategy (move to second SCT for long-term survival or palliative treatment).

Several studies of leukemia patients who relapsed after SCT have been reported.[2,3,5,11] These studies demonstrated that the duration of remission after the first SCT, conditioning regimens including TBI, and acute GVHD were prognostic factors, although most of these studies included both ALL and AML patients. A few reports included pediatric patients, and these studies showed that the outcomes and prognostic factors of second SCT were similar to those for adults. In these reports, the OS of second SCT was reported to be around 30%.[3,9] However, the number of pediatric patients included in these previous studies was small, thus the role of second SCT remains unclear.

Our analysis revealed that pediatric ALL patients that suffer a late relapse (>180 days) after their first SCT and those who

Table 3. Multivariate analysis of the risk factors for overall mortality

Characteristics	*HR*	*95% CI*	*P-value*
Patient age at 2nd SCT			
<10 years	1		
⩾10 years	2.17	1.34–3.50	0.002
Time to relapse after 1st SCT			
⩽180 days	1		
>180 days	0.59	0.36–0.98	0.04
Disease status at 2nd SCT			
CR	1		
Non-CR	1.59	0.97–2.62	0.07
Conditioning regimen of 2nd SCT			
TBI	1		
BU	0.87	0.45–1.71	0.69
RIST	1.12	0.61–2.05	0.72
Donor of 2nd SCT			
Related	1		
Unrelated	0.76	0.40–1.47	0.42
Cord blood	1.43	0.70–2.62	0.26
Donor of 1st and 2nd HSCT			
Same donor	1		
Different donors	1.10	0.59–2.03	0.77
Stem cell source of 2nd SCT (related donor only)			
BM	1		
PBSC	0.74	0.32–1.69	0.47

Abbreviations: CI = confidence interval; HR = hazard risk of death; RIST = reduced intensity SCT.

achieve CR might be able to achieve long-term survival by undergoing a second allo-SCT. Although the interval between the two SCT procedures was short in the early relapse patients, NRM was similar between the early and late relapse patients. These two factors were well correlated, and the proportion of patients that achieved CR among the patients that suffered late relapse was 64.5%, while that of the patients that suffered early relapse was 34.6%.

RIST was not found to be advantageous in our analysis. It is assumed that most of the RIST patients could not undergo myeloablative conditioning because of their poor condition. Accordingly, the reduction in NRM was not sufficient to overcome their high relapse rate after RIST. Our data suggest that it is important to maintain a good performance status and organ function in order to allow the use of myeloablative conditioning regimens. In particular, SCT with myeloablative conditioning could offer a better prognosis to patients in whom RIST was performed as part of the first transplant. A previous report suggested that TBI provides better outcomes than BU, and our results showed a similar tendency, although the difference was not significant. However, it should be noted that most of the patients in whom the BU regimen was used during the second SCT suffered relapsed leukemia after SCT involving TBI. TBI is thought to be a more potent therapeutic regimen than BU, and thus leukemic cells that endure TBI are more likely to become resistant. In other words, patients who relapsed after SCT involving BU have a greater chance of being cured, especially when they have achieved CR.

Acute GVHD did not influence survival after second SCT. Severe GVHD resulted in a high NRM for patients who underwent allo-SCT twice. This result differs from those of previous studies on adult leukemia[3] and might have arisen from the fact that most of the patients in the previous studies had AML, which is known to be relatively sensitive to GVL effects.

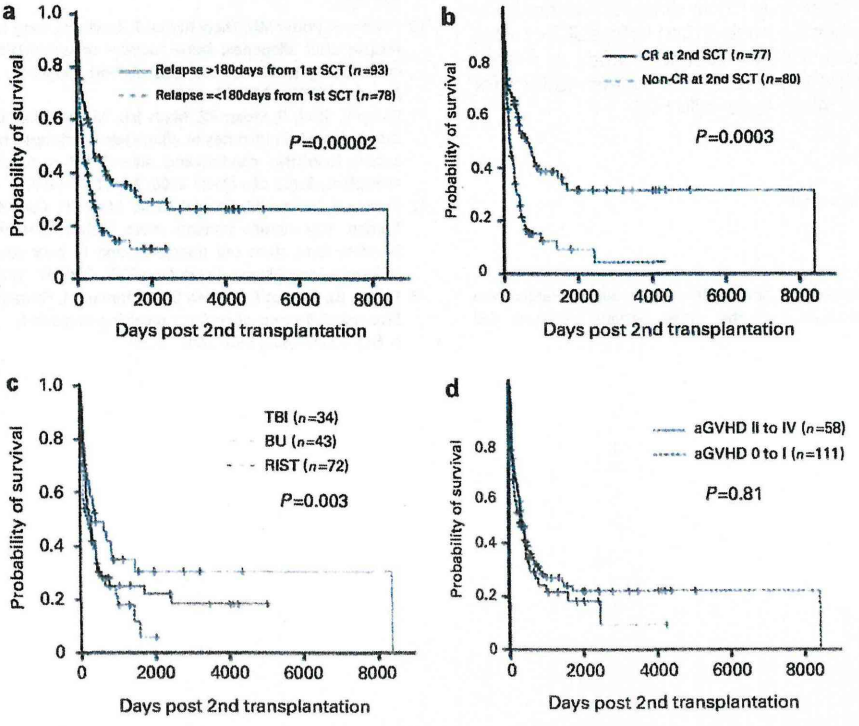

Figure 2. Variables and OS after second SCT. OS is shown according to the following characteristics: (**a**) early vs late relapse, (**b**) disease status at second SCT, (**c**) conditioning regimen for second SCT and (**d**) severity of acute GVHD.

There are no confirmatory data about an advantage for the selection of a different donor for the second SCT, although there are some reports[4] about this selection, including a study showing that different donor has a trend toward better survival.[12] Our analysis did not provide evidence supporting the use of a different donor. Different donor for the second SCT included unfavorable donor, such as a haploidentical parent, and these high-risk donors might cause the inferior outcome of the different donor SCT. However, our result did not show advantage for the second SCT from a different donor, even in SCT from another HLA-matched related donor.

In our study, the type of donor did not influence the survival rate after second SCT. However, those who received an SCT from a related donor displayed a trend toward a higher incidence of relapse. This might have occurred because the related SCT group included patients who could not wait for unrelated donor coordination because of their highly aggressive disease or poor performance status. The second SCT from related donor included 25 SCT from two or three Ag HLA-mismatched donor, while only 6 SCT was performed as for the first SCT from two or three Ag mismatched related donor.

Multivariate analysis showed that older age, earlier relapse after first SCT and non-remission at second SCT were prognostic factors for a worse outcome. The inferior outcomes of the high-risk group were mainly caused by the high incidence of relapse. This result suggested that the poor prognosis of second SCT was dependent on the resistance of leukemic cells. Thus, novel therapeutic strategies, such as small molecule targeting therapies,[13] are required to improve the outcome of second SCT. The OS at 2 years for younger patients (9 years old or younger) that suffered a late relapse (>180 days from first SCT) and had achieved CR at the second SCT was 55.3 ± 11.4%. Patients in this most favorable group have a greater chance of long-term survival, even those with relapsed ALL.

Our study provides important information about the role of second SCT in pediatric ALL, although it is essential to pay attention to late complications caused by allogeneic second SCT. However, this was a retrospective and uncontrolled study, and therefore, there are some limitations to our data. For example, our analysis did not include patients who had died before SCT or were too ill to undergo a second SCT. A prospective study in a large cohort is required to further improve the treatment options for pediatric ALL patients that relapse after allo-SCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Author contributions: MK, YH, YO, YT, DH and KK designed the research; K Koh, JT, MI, HK, AO, YS, K Kawa, HY, HS and RS collected the data; and MK analyzed the data and wrote the paper. All authors discussed the results and commented on the paper.

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bjh research paper

Stem cell transplantation for paediatric patients with non-anaplastic peripheral T-cell lymphoma in Japan

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Summary

Reports of non-anaplastic peripheral T-cell lymphoma (PTCL) in paediatric patients, especially results of stem cell transplantation (SCT), are relatively rare. We herein report the results of SCT using the Transplant Registry Unified Management Program system of the Japanese Society of Stem Cell Transplantation in paediatric patients with non-anaplastic PTCL. We analysed 26 patients (13 females and 13 males) aged ≤18 years with non-anaplastic PTCL who underwent a total of 28 SCT. Median age at transplantation was 13·5 years (range: 0–18 years). PTCL not otherwise specified was diagnosed in 17 patients; extranodal Natural Killer (NK)/T cell lymphoma, nasal type in nine; and subcutaneous panniculitis-like T-cell lymphoma in two. Transplantation was with syngeneic donor in one, related donor in 10; unrelated donor in 10; and auto transplantation in 7. Five-year overall survival rate and event-free survival rate was 62·96% and 55·56%, respectively. Male gender, chronic graft-*versus*-host disease (GVHD), and reduced intensity conditioning were good prognostic factors in all patients. In 20 patients with refractory or relapsed disease, male gender and chronic GVHD were also good prognostic factors. This study is the first report concerning transplantation in children with non-anaplastic PTCL, although the number of patients was small. Larger studies are needed to confirm these findings.

Keywords: peripheral T-cell lymphoma, stem cell transplantation, children.

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare malignancies that usually demonstrate clinical aggressiveness (International T-Cell Lymphoma Project, 2008). Reports of non-anaplastic PTCL in paediatric patients are relatively rare (Brodkin *et al*, 2008; Hutchison *et al*, 2008; Medhi *et al*, 2008; Windsor *et al*, 2008; Lim *et al*, 2009). We previously reported this malignancy in Japanese paediatric patients; although five of the 21 patients relapsed, 17 were alive without disease at last follow-up, giving an overall 5-year survival rate of 85·2% (Kobayashi *et al*, 2010). This survival rate is much better than that reported previously in both adults and children (International T-Cell Lymphoma Project, 2008; Windsor *et al*, 2008; Hutchison *et al*, 2008). Stem cell transplantation (SCT) early in the disease course appears to have contributed to this excellent result. SCT does not tend to improve the prognosis for adults with non-anaplastic PTCL, and the literature contains few reports of the results of this therapy in paediatric patients with this disease. Herein, we report the results of SCT performed using the Transplant Registry Unified Management Program (TRUMP) system of the Japanese Society of Stem Cell Transplantation in paediatric patients with non-anaplastic PTCL.

Methods

Between 1996 and 2010, 26 patients (28 transplantations) aged $\leq$18 years who received SCT for non-anaplastic PTCL were registered according to the TRUMP system of the Japanese Society of Stem Cell Transplantation. Thirteen of the patients were male (14 transplantations) and 13 (14 transplantations) were female; median age was 13·5 years (range: 0–18 years). Histological diagnosis was as follows: PTCL not otherwise specified (PTCL-NOS), n = 17; extra-nodal NK/T cell lymphoma, nasal type, n = 9; and subcutaneous panniculitis-like T-cell lymphoma, n = 2. Stage at initial diagnosis was: I, n = 7; II, n = 4; III, n = 2; IV, n = 11, and unknown (n = 4). Status of disease at transplantation was first complete remission (CR) n = 6; second CR, n = 4; first partial remission (PR), n = 2; second PR, n = 1; no response after treatment, n = 7; first relapse, n = 5; and second relapse, n = 3. Median interval from diagnosis to transplantation was 11·5 months (range: 3·6–46·4 months). Ten patients underwent bone marrow transplantation (BMT), 12 patients had peripheral blood stem cell transplantation (PBSCT), and six patients underwent cord blood transplantation (CBT). A syngeneic donor was used in one patient, related donor in 10, unrelated donor in 10, and auto transplantation in 7. The conditioning regimens contained busulfan (n = 7 patients), melphalan (n = 14), cyclophosphamide (n = 13), etoposide (n = 12), carboplatin (n = 2), cytosine arabinoside (n = 8), fludarabine (n = 5), and methyl chloroethyl nitroso urea (n = 6); 15 patients received total body irradiation. Reduced-intensity conditioning stem cell transplantation (RIST) was performed in five patients. Two patients received a second transplantation because of relapse in both cases: one received a related-donor PBSCT 3 months after the first SCT (autologous BMT); the other received an unrelated-donor BMT 18 months after the first SCT (autologous PBSCT).

One patient was excluded from the survival analysis because of insufficient data. The two instances of second transplantation were analysed as separate transplantations. Median follow-up time was 32·3 months. Data was analysed as of September 2011.

Statistical analysis

Overall survival and event-free survival were analysed using the Kaplan–Meier method, with differences compared by log-rank test. Events were defined as relapse, second malignancy, and death for any reason. Statistical analyses were performed using Dr. SPSS II for Windows (release 11·0·1J, IBM Japan, Tokyo, Japan). P values < 0·05 were considered statistically significant.

Results

The 5-year overall survival rate was 62·96%. Although the 5-year event-free survival was 55·56%, one patient relapsed about 10 years after transplantation (Fig 1). Five-year relapse rate and transplant-related mortality was 14·25% and 19·81%, respectively. Overall survival and event-free survival in male patients was 85·71% and 78·57%, respectively, which was significantly better than in female patients (38·46%, 30·77%) (Table I). Survival rates did not differ with respect to age (>10 years vs. $\leq$10 years) or type of SCT (autologous *versus* allogeneic). However, in patients who had undergone allogeneic transplantation, there was a non-significant tendency towards better survival rates in those transplanted from an unrelated donor than in those transplanted from a related donor. Moreover, in terms of histological diagnosis, status at transplantation and type of conditioning regimen, survival rates were superior for extranodal NK/T lymphoma, nasal type histology; status at transplantation of CR and conditioning regimen not involving TBI, but these differences were not significant. Survival rates were also better for patients who developed acute graft-*versus*-host disease (GVHD) than those who did not, but this difference also failed to reach statistical significance. Of those who underwent allogeneic SCT, only five patients had RIST. However, overall survival and event-free survival rates in these patients were both 100%, significantly better than in those who did not undergo RIST. Moreover, in the five patients who received allogeneic SCT, those who developed chronic GVHD also had overall survival and event-free survival rates of 100%, significantly better than in those who did not develop this complication.

In addition, we divided the patients into two groups for further analysis: first CR or PR *versus* refractory or relapsed patients (Table II). Five-year overall survival and event-free

survival rates in patients with first CR or PR were 87·50% and 75·00%, respectively. While these were superior to survival rates in refractory or relapsed patients (52·63%, 47·37%), the differences did not reach significance. Although relapse rates did not differ between the two groups (12·50% vs. 14·77%), transplant-related mortality in patients with first CR or PR was lower than in refractory or relapsed patients (0% vs. 29·16%, $P = 0·1032$). All four patients who received allogeneic transplants in first CR or PR were alive and disease-free at last follow-up. In refractory or relapsed patients, survival rates did not differ between those who received autologous SCT and those who had allogeneic SCT. In this group, male gender and chronic GVHD were also associated with significantly enhanced prognosis.

Discussion

The literature contains several reports of autologous SCT in adults with non-anaplastic PTCL in first CR. Further, several groups have examined the role of dose-escalated chemotherapy with auto-SCT support as consolidation therapy for PTCL (Mounier *et al*, 2004; Corradini *et al*, 2006; Feyler *et al*, 2007; Rodríguez *et al*, 2007a). However, reports that solely concern non-anaplastic PTCL are rare. In these reports, first-line therapy produced disease-free survival rates with long follow-up of 30–40% (Mercadal *et al*, 2008; Reimer *et al*, 2009). Progression-free survival rates for auto-SCT in patients with second remission or refractory disease were reported to be 0% and 15–20% (Rodríguez *et al*, 2007b; Chen *et al*, 2008). Reports of experience with allogeneic SCT in non-anaplastic PTCL are similarly limited. Other than case reports, five retrospective series with at least 10 patients have been reported in patients with relapsed and refractory PTCL (Murashige *et al*, 2005; Feyler *et al*, 2007; Hamadani *et al*, 2008; Le Gouill *et al*, 2008; Kyriakou *et al*, 2009). The largest series was published by the Société Francaise de Greffe de Moëlle et de Thérapie Cellulaire (Le Gouill *et al*, 2008). In 77 pretreated patients, most of whom received a myeloablative conditioning regimen, the 5-year overall survival and progression-free survival rates were 57% and 53%, respectively, after a median follow up of 43 months. The treatment-related mortality (TRM) was 33% at 5 years. In a multivariate analysis, chemotherapy-resistant disease at transplantation and grade 3/4 acute GVHD were the strongest adverse prognostic factors for overall survival (Le Gouill *et al*, 2008). Most of these studies revealed a graft-*versus*-lymphoma (GVL) effect (Hamadani *et al*, 2008; Le Gouill *et al*, 2008; Kyriakou *et al*, 2009). However, TRM had a relevant impact on outcome and increased over time up to 69% at 3 years in the series by Hamadani *et al* (2008). The overall survival rates ranged from 40% at 2 years to 57% at 5 years. On the other hand, other than case reports, we could find no studies concerning transplantation for patients with paediatric PTCL. The present report therefore appears to be the first to document the outcomes of

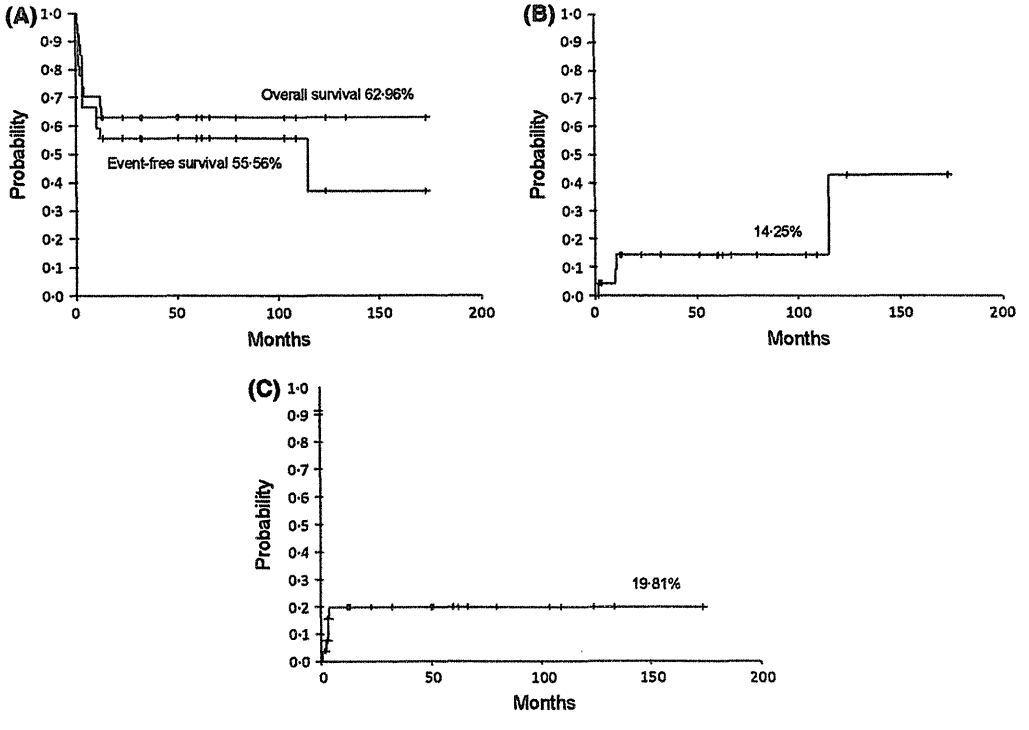

Fig 1. (A) Overall survival and event-free survival rate for all analysed patients. (B) Relapse rate for all analysed patients. (C) Transplant-related mortality rate for all analysed patients.

Table I. Five-year overall survival rate and 5-year event-free survival rate in all analysed patients.

	N	5-year OS (%)	P	5-year EFS (%)	P
Gender					
Male	14	85·71	0·0136	78·57	0·0059
Female	13	38·46		30·77	
Age					
≤ 10 years	6	66·67	0·6379	66·67	0·3929
>10 years	21	61·90		52·38	
Donor					
Autologous	7	71·43	0·5738	42·86	0·5899
Syngeneic	1	100		100	
Allogeneic	19	60·00		60·00	
Related	9	40·00	0·0704	45·45	0·1598
Unrelated	10	77·78		77·78	
Histology					
PTCL-NOS	16	56·25	0·6344	56·25	0·3133
Extra nodal NK/T lymphoma, nasal type	9	77·78		66·67	
Subcutaneous panniculitis-like T cell lymphoma	2	50·00		0	
Status of disease at transplantation					
Complete remission	10	80·00	0·4721	70·00	0·6489
Partial remission	3	66·67		66·67	
Relapse	7	57·14		42·86	
Induction failure	7	42·86		42·86	
Conditioning					
TBI regimen	13	50·00	0·1173	50·00	0·6151
Non-TBI regimen	14	76·92		61·54	
Acute GVHD in allogeneic SCT patients					
Yes	10	70·00	0·1330	70·00	0·1819
No	9	44·44		44·44	
Chronic GVHD in allogeneic SCT patients					
Yes	5	100	0·0459	100	0·0443
No	14	42·86		42·86	
Conditioning regimen in allogeneic SCT patients					
RIST	5	100	0·0459	100	0·0443
MAST	14	42·86		42·86	

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TBI, total body irradiation; GVHD, graft *versus* host disease; SCT, stem cell transplantation; RIST, reduced intensity transplantation; MAST, myeloablative stem cell transplantation; OAS, overall survival; EFS, event event-free survival.

Table II. Five-year overall survival rate and 5-year event-free survival rate in patients with first CR or PR and in those with refractory disease or relapse.

	CR1/PR1 (n = 8)			Induction failure/relapse (n = 19)		
	N	5-year OS (%)	5-year EFS (%)	N	5-year OS (%)	5-year EFS (%)
Gender						
Male	4	100	100	10	80·00*	70·00*
Female	4	75·00	50·00	9	22·22*	22·22*
Age						
≤ 10 years	3	66·67	66·67	3	66·67	66·67
>10 years	5	100	80·00	16	50·00	43·75
Donor						
Autologous	4	75·00	50·00	3	66·67	33·33
Syngeneic	0	–		1	100	100
Allogeneic	4	100	100	15	46·67	46·67
Related	1	100	100	9	33·33	33·33
Unrelated	3	100	100	6	66·67	66·67
Histology						
PTCL-NOS	4	75·00	75·00	12	50·00	50·00
Extra nodal NK/T lymphoma, nasal type	3	100	100	6	66·67	50·00
Subcutaneous panniculitis like T cell lymphoma	1	100	0	1	0	0
Conditioning regimen						
TBI regimen	2	100	100	12	41·67	41·67
Non-TBI regimen	6	83·33	66·67	7	71·43	57·14
Acute GVHD in patients with allogeneic transplantation						
Yes	3	100	100	7	57·14	57·14
No	1	100	100	8	37·50	37·50
Chronic GVHD in patients with allogeneic transplantation						
Yes	1	100	100	4	100*	100*
No	3	100	100	11	27·27*	27·27*
Conditioning regimen in patients with allogeneic transplantation						
RIST	2	100	100	3	100	100
MAST	2	100	100	12	33·33	33·33

*$P < 0·05$.

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; CR1, first complete remission; PR1, first partial remission; TBI, total body irradiation; GVHD, graft-*versus*-host disease; SCT, stem cell transplantation; RIST, reduced intensity transplantation; MAST, myeloablative stem cell transplantation; OS, overall survival; EFS, event-free survival.

transplantation in non-anaplastic PTCL in a series of paediatric patients.

We analysed the results of 26 non-anaplastic PTCL patients with 28 transplantations in terms of factors related to prognosis. Although the overall survival rate was 62·96%, that in first CR and first PR patients was much better, at 87·5%. Moreover, male patients had better prognosis than female patients. In the two patients who received a second transplantation, the male patient survived and the female patient died. However, if each of these patients was counted as one transplantation, the survival rate by gender did not change (male 84·62% vs. female 41·67%, $P = 0·0340$). The reason for this is not clear. On the other hand, all patients who underwent RIST and those who had chronic GVHD survived and were free of disease at last

follow-up, and these factors were more common in male patients than in female patients. Although it was generally difficult to judge influence on the prognosis of chronic GVHD, analysis of patients who survived more than 100 d after allogeneic transplantation revealed a 5 year-survival rate of 100% in patients with chronic GVHD and 85·7% in those without chronic GVHD. This suggests that chronic GVHD and RIST are good prognostic factors in patients with paediatric non-anaplastic PCTL.

In addition, we conducted further analysis after dividing the patients into two groups: first CR or PR ($n = 8$) and refractory or relapsed ($n = 19$) patients. Half of the patients with first CR or PR underwent allogeneic transplantation. The histological subtype of this group of patients was PTCL-NOS in 4, extranodal NK/T lymphoma, nasal type in three and subcutaneous panniculitis-like T-cell lymphoma in 1. Stage at initial diagnosis was I in two patients, II in two patients, III in one patient, and IV in three patients. Of the four patients who received allogeneic SCT, two were in PR and two were in CR. On the other hand, all four patients who received autologous SCT were in CR. Prognostic factors in this group were unclear because of the high survival rate. However, all patients who received allogeneic transplantation survived and were free of disease at final follow-up. In patients with refractory or relapsed disease, 16 of 20 transplants were allogeneic. Although the overall survival rate was higher in those patients with refractory disease or relapse who received autologous transplantation, the event-free survival rate was higher in those who received allogeneic transplantation. Male gender and chronic GVHD were also good prognostic factors in refractory or relapsed patients. Although very few of these patients received RIST, their event-free survival rate was 100%.

The literature contains few studies of RIST in T-cell lymphoma. A pilot study of 17 patients (which comprised nine with PTCL-NOS, four with angioimmunoblastic T-cell lymphoma, and four with ALK-positive anaplastic large cell lymphoma) reported a 2-year non-relapse mortality of only 6% following a conditioning regimen that incorporated thiotepa, fludarabine, and cyclophosphamide (Corradini *et al*, 2004). Severe acute or chronic extensive GVHD was reported in three patients, and 12 patients were in CR after a median follow-up of 28 months. Recently, the same group reported a 50% survival rate in 52 patients with relapsed or refractory PTCLs including anaplastic large cell lymphoma (Dodero *et al*, 2012). Eight of 12 patients who received donor lymphocyte infusions for disease progression responded, and the authors confirmed a GVL effect. In our study, patients who had undergone RIST and developed chronic GVHD were all surviving without relapse at final follow-up. In particular, one patient who received CBT during relapse was alive without relapse at last follow-up. Moreover, the survival rate in patients who underwent transplantation from unrelated donors was superior to those transplanted from related donors. These circumstances demonstrate a GVL effect in patients with paediatric non-anaplastic PTCL.

It is very difficult to determine the indications for SCT in paediatric patients with non-anaplastic PTCL. All patients with refractory or relapsed status met the requirements for allogeneic SCT rather than autologous SCT because TRM was low compared with adult patients and GVL was anticipated. On the other hand, allogeneic SCT may be appropriate in patients with progressive PTCL and a clinical option in patients with early-stage disease. However, given the reports of good results with chemotherapy in early-stage paediatric patients, chemotherapy or autologous SCT may be able to serve as a choice in these patients (Hutchison *et al*, 2008; Windsor *et al*, 2008). As non-anaplastic PTCL is very rare in paediatric patients, further prospective trials are warranted.

Author contributions

R.Kobayashi designed the research, analysed data and wrote the paper. N. Fujita, T. Mitsui, F.Iwasaki and J. Suzumiya designed the research. H. Kuroda, R. Nishimura, Y. Sasahara, Y. Takeshita and K.Kato treated patients and sent data. H. Sakamaki, H. Yabe, K. Kawa, K. Kato and R. Suzuki analysed data.

Conflict of interest

The authors have declared there is no conflict of interest to disclose.

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