Equivalent Outcome of Autologous Stem Cell Transplantation and Reduced Intensity Conditioning Stem Cell Transplantation in Acute Myeloid Leukemia Patients with t(8;21)

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For editorial comment see p. 264

Key Words

Acute myeloid leukemia · t(8;21) · Reduced intensity conditioning · Autologous stem cell transplantation

Abstract

We analyzed the outcome of stem cell transplantation (SCT) for 59 acute myeloid leukemia (AML) patients with t(8;21). The 5-year overall and disease-free survival (OS and DFS) were 70.2 and 68.4%, respectively. The 5-year cumulative incidence of relapse (CIR) and nonrelapse mortality were 16.9 and 13.6%, respectively. OS and DFS in the reduced-intensity conditioning (RIC)-SCT group (70.4%) were not different from in the autologous SCT (ASCT) group (72.4 and 69.0%, respectively). Age was a factor affecting OS ($p = 0.007$) and DFS ($p = 0.008$) in the ASCT group, but not in the RIC-SCT group. In the ASCT group, lack of the X chromosome (–X) and an age of >50 years were associated with inferior survival; however, these differences disappeared in the RIC-SCT

group. CIR was significantly higher in patients with –X than in those without –X only in the ASCT group ($p = 0.038$), i.e. not in the RIC-SCT group. ASCT and RIC-SCT are equally effective for the intensification of postremission treatment of AML patients with t(8;21). The subgroups with advanced age or –X should be preferentially considered for RIC-SCT, rather than ASCT. Further investigations with randomized prospective trials of a sizeable study population are warranted.

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Introduction

Translocation (8;21) (q22;q22) [t(8;21)] along with inversion 16 [inv(16)] is associated with mutations in the core-binding factor, which are found in approximately 1/3 karyotypically abnormal patients and in approximately 8% of all patients with acute myeloid leukemia (AML) [1, 2]. Patients with these mutations generally have a fa-

favorable prognosis with a higher first complete remission (CR1) rate and a higher cure rate with high-dose cytarabine (HDARA-C), which precludes these patients from undergoing stem cell transplantation (SCT). In previous studies, patients with t(8;21) AML were reported to have a significantly shorter overall survival (OS) than patients with inv(16) [3, 4]. Several studies reported that t(8;21) AML patients have significantly shorter survival times after relapse than inv(16) AML patients [5, 6], suggesting that the difference in OS between patients with t(8;21) AML and those with inv(16) AML might be related to the inferior response to salvage treatment in the former group. AML patients with t(8;21) are expected to benefit more from intensive postremission treatment such as allogeneic (allo)-SCT or autologous SCT (ASCT) than those with inv(16). No available randomized study discusses whether several HDARA-C cycles yield better results than other intensive postremission approaches like SCT.

The role of SCT has not yet been settled in this subgroup of patients with favorable cytogenetics. ASCT is generally associated with lower procedure-related toxicity and mortality than conventional allo-SCT, but the relapse incidence is a major concern. Although allo-SCT following myeloablative conditioning (MC) is known to decrease the risk of relapse, this benefit is partially offset by the toxicity associated with the procedure; current practice therefore does not support the use of this treatment modality for t(8;21) AML in CR1. Recently, reduced-intensity conditioning (RIC)-SCT is being increasingly used for patients with myeloid malignancies, especially those who would otherwise not be considered candidates for conventional allo-SCT. RIC-SCT is associated with a clearly lower nonrelapse mortality (NRM) than MC-SCT while preserving the graft-versus-leukemia (GVL) effect, so this modality could be a reasonable alternative to conventional SCT, especially for patients with favorable-risk AML but, so far, there is no adequate information regarding this subgroup of patients. Although several papers have reported the results of RIC-SCT in AML patients with t(8;21), the data analyzed have been heterogeneous in terms of conditioning regimen intensity, inclusion criteria, disease status at transplant and cytogenetics [previous studies included core-binding factor leukemia as a whole, rather than only t(8;21)], making it difficult to discern the definite role of SCT in this patient population. To date, to our knowledge, few papers have evaluated the role of RIC-SCT and ASCT specifically for the intensification of postremission treatment in AML patients with t(8;21) after CR1 has been achieved. From this point of view, we analyzed the outcomes of SCT

to evaluate the safety and efficacy of RIC-SCT and ASCT in these patients who were treated at our institution during the same period.

Patients and Methods

Eligibility Criteria

We included adult AML patients between the age of 16 and 64 years who had t(8;21) with or without additional aberrations at the time of diagnosis. Patients in whom CR1 had been achieved on our institutional protocol were recommended ASCT or RIC-SCT after 1 or 2 cycles of consolidation chemotherapy according to donor availability. Patients who were able to find a suitable stem cell donor (HLA-matched sibling, matched unrelated or ≤ 2 -allele mismatched unrelated) received RIC-SCT. If they failed to find a suitable donor, they were recommended ASCT or RIC-SCT from a haploidentical familial donor (HFD); the decision to pursue RIC-SCT from an HFD as opposed to ASCT was based on both the patient's and physician's preference. Patients who had a status of advanced pretransplant disease ($\geq$ second CR, relapsed or refractory disease) were not considered for this study. Patients with inadequate organ function and Eastern Cooperative Oncology Group performance status of >2 were excluded from receiving ASCT. The patients preferentially received RIC-SCT rather than ASCT if they were ≥ 50 years or if they had comorbidities. The International System for Cytogenetic Nomenclature [7] was used as a guideline for classification, and cytogenetic risk groups were classified using the guidelines of the Southwest Oncology Group trial [2]. Patients who had t(8;21) with or without secondary aberrations were included; however those with del(9q) and complex karyotype (≥ 3 unrelated abnormalities) were excluded. All patients provided written informed consent, and the study protocol was approved by the institutional review board of the Catholic University of Korea.

Treatment before Transplantation

All of the patients were treated according to our standard protocol [8], which consists of induction chemotherapy with '3 + 7' idarubicin (IDA) plus N⁴-behenoyl-1- β -D-arabinofuranosylcytosine (BH-AC). Briefly, IDA was administered daily at a dose of 12 mg/m² for 30 min intravenously (i.v.) for 3 consecutive days. BH-AC is known to be active regardless of treatment schedules, mainly due to its resistance to cytidine deaminase and high affinity for lipids which allow its prolonged retention in blood and tissue [9, 10], so it was administered daily at a dose of 300 mg/m² over a period of 4 h for 7 consecutive days rather than as a continuous infusion. Patients who were recommended RIC-SCT received 1 course of consolidation chemotherapy, which consisted of '3 + 5' IDA plus BH-AC, and then SCT after RIC. Patients who were recommended ASCT received SCT after completing the second consolidation chemotherapy consisting of a combination of mitoxantrone (12 mg/m² i.v. for 3 days) and etoposide (100 mg/m² i.v. for 5 days).

Transplantation

Patients assigned to the ASCT group were prepared by means of our modified transplant-associated microangiopathy regimen [11], which consisted of fractionated total body irradiation (10 Gy, 5 fractions in 3 days) from day -8 to -6, followed by intermediate-

Table 1. Pretransplantation patient characteristics

Variables	Overall (n = 59)	SCT group		p
		ASCT (n = 29)	RIC-SCT (n = 30)	
Male/female, n	43/16	21/8	22/8	0.937
Median age, years (range)	36.0 (16–64)	28.0 (16–64)	40.0 (17–62)	0.023
Median white blood cell count, $\times 10^9/l$ (range)	8.6 (0.7–116.9)	8.8 (0.7–29.6)	7.6 (1.2–116.9)	0.898
Median LDH, IU/l (range)	765 (322–16,468)	984 (385–2,943)	667 (322–16,468)	0.089
Additional cytogenetic abnormalities, n (%)				
None	17 (28.8)	9 (31.0)	8 (26.7)	0.938
–Y $\pm$ others	19 (16.9)	14 (46.7)	5 (16.7)	
–X $\pm$ others	20 (49.2)	5 (16.7)	15 (50.0)	
Others	3 (5.1)	1 (3.4)	2 (6.7)	
Median time to CR, days (range)	29.0 (20–50)	29.0 (26–36)	28.0 (20–50)	0.208
Median time to SCT, days (range)	183 (65–261)	206.0 (152–261)	147.0 (65–216)	<0.001

Bold values indicate statistical significance.

dose Ara-C (6 doses of 1.5 g/m² over 3 h every 12 h) from day –5 to –3 and melphalan (100 mg/m² over 30 min) on day –2 only.

Patients in the RIC-SCT group were given a RIC regimen consisting of fludarabine (30 mg/m²/day) on days –6, –5, –4, –3, and –2 and busulfan (3.2 mg/kg/day) on days –6 and –5. Grat-versus-host disease (GVHD) prophylaxis was undertaken by administering calcineurin inhibitors plus methotrexate (5 mg/m²) on days 1, 3, 6 and 11. Calcineurin inhibitors were administered (i.v. cyclosporine 3 mg/kg/day for related transplantation and i.v. tacrolimus 0.03 mg/kg/day for unrelated transplantation) as a continuous infusion from day –1. Subsequently, when patients were able to tolerate oral administration, they received calcineurin inhibitors orally (cyclosporine 6 mg/kg/day and tacrolimus 0.12 mg/kg/day) until day 60 (for sibling transplantation) or day 90 (for unrelated transplantation). The dosages of the calcineurin inhibitors were then gradually tapered with the intent to discontinue them by 3–6 months after SCT. All patients in this group received antifungal prophylaxis with itraconazole from day –14 to day +60. *Pneumocystis jiroveci* pneumonia prophylaxis with cotrimoxazole (Bactrim, Roche, Basel, Switzerland) was given throughout conditioning, discontinued 48 h before stem cell infusion, and then readministered from day +21 to day +90.

All study subjects were treated in specific rooms with laminar airflow isolation and received G-CSF at a dose of 5 μ g/kg/day subcutaneously from the day on which the absolute neutrophil count was $<0.5 \times 10^9$ cells/l until it reached $>1.0 \times 10^9$ cells/l. The patients were given irradiated and leukocyte-filtered blood components before transfusion.

Definitions and Statistical Analysis

Time to hematopoietic recovery was defined as an absolute neutrophil count of $>0.5 \times 10^9$ cells/l for 3 consecutive days and a platelet count of $>20 \times 10^9$ cells/l with no requirement for platelet transfusion during the previous 5 consecutive days. Engraftment was assessed by analyzing a routine marrow aspirate on day +21. GVHD was diagnosed and graded using published criteria [12]. Patients who were alive in CR at the last follow-up were censored after adjusting for relapse as a competing risk event. NRM and relapse were

calculated by using cumulative incidence estimates and after considering the competing risk structure [13]. NRM was defined as death occurring in relapse-free patients. When calculating relapse incidence, relapse was considered an adverse event and patients who were alive without relapse at the last follow-up were censored after adjusting for death without evidence of relapse as a competing risk event. Acute and chronic GVHD were considered as time-dependent covariates and their incidences were also calculated by using cumulative incidence estimates. Survival curves for relapse and NRM were plotted using the cumulative incidence estimates and compared by the Gray test. All analyses were based on a retrospective review, and the cut-off date for the statistical analysis was 31 December 2013. SPSS v16.0 software (SPSS, Chicago, Ill., USA) was used throughout the study. Cumulative incidence analyses were carried out with R software (freely distributed on the Web, <http://www.r-project.org/>).

Results

Pretransplantation Characteristics of Patients

Between March 2007 and June 2012, we performed SCT in a total of 59 consecutive AML patients with t(8;21); 29 patients received autografts and 30 patients received allografts (table 1). There were 43 men and 16 women with a median age of 36 years (range 16–64 years). Lack of the Y chromosome (–Y) in males and lack of the X chromosome (–X) were the most frequent additional cytogenetic abnormalities. The median time to CR and SCT from the time of diagnosis was 29 and 183 days, respectively. The pretransplantation characteristics were well balanced between the autograft group and the allograft group except for age and time to SCT. Allograft recipients were older

Table 2. Clinical and biologic characteristics of patients at transplantation

Variables	ASCT (n = 29)	RIC-SCT (n = 30)	p
Graft type, n (%)			
Peripheral blood	24 (80.0)	17 (56.7)	<0.001
Bone marrow	1 (3.3)	13 (43.3)	
Bone marrow + peripheral blood	4 (13.3)	0	
Number of cells infused, median (range)			
CD34 × 10 ⁶ /kg	2.45 (1.0–5.7)	4.7 (1.5–23.8)	<0.001
CD3 × 10 ⁷ /kg	–	22.5 (2.2–61.6)	
Median follow-up duration after transplantation, months (range)	37.5 (18.8–56.2)	37.4 (22.6–52.3)	0.935
Median hematopoietic recovery ^a , days (range)			
Neutrophils	12.0 (10–26)	12.0 (10–16)	0.324
Platelets	15.5 (4–49)	4.0 (0–22)	0.185
Median transfusion requirement, units (range)			
Packed red cells	4 (0–15)	4 (0–6)	0.901
Platelet concentrates	7 (0–62)	4 (0–12)	0.005
HLA incompatibility, n (%)	n.a.		
Matched sibling		17 (56.7)	
HFD		6 (20.0)	
Matched unrelated		2 (13.3)	
≤2-allele mismatched unrelated		5 (16.7)	
Sex incompatibility, n (%)			
Matched	n.a.	13 (43.3)	
Male to female		5 (16.7)	
Female to male		12 (40.0)	
Blood type incompatibility, n (%)			
Matched	n.a.	15 (50.0)	
Minor		11 (36.7)	
Major or bidirectional		4 (13.3)	
Acute GVHD, event/evaluable number, incidence (%)	n.a.	18/30 (60.0)	
Grade I/II		13/30 (43.3)	
Grade III/IV		5/30 (16.7)	
Chronic GVHD, event/evaluable number, incidence (%)	n.a.	22/28 (78.6)	
Limited		4/22 (18.2)	
Extensive		18/22 (81.8)	

Bold values indicate statistical significance. n.a. = Not applicable.

^a ANC of $>0.5 \times 10^9$ cells/l for 3 consecutive days and a platelet count of 20×10^9 cells/l with no platelet transfusion needed for 3 consecutive days.

and underwent transplantation earlier than autograft recipients ($p = 0.023$ and $p < 0.001$, respectively) because according to our institution's protocol and transplant policy, patients >50 years were considered preferentially for RIC-SCT and autograft recipients were supposed to receive transplantation after completing an additional cycle of consolidation chemotherapy.

Transplant Outcome

Table 2 summarizes the main characteristics of patients at transplantation. Donors were siblings for 23 patients (including 6 HFDs) and were unrelated for 7

patients. Peripheral blood stem cells were the main source of hematopoietic stem cells in both transplantation modalities. There were no differences in hematopoietic recovery between the ASCT group and the RIC-SCT group. The requirement for platelet concentrates was lower in the RIC-SCT group ($p = 0.005$). As for GVHD, 18/30 patients who received allografts developed acute GVHD with a 5-year cumulative incidence at day 100 of 60% (95% CI 39.8–75.3); the majority of patients developed grade I/II GVHD ($n = 13$). Of the 28 patients who survived ≥ 100 days, 22 developed chronic GVHD, i.e. limited GVHD ($n = 4$) or

Fig. 1. Survival of patients. **a** OS. **b** DFS. OS (**c**) and DFS (**d**) according to the transplant modality.

extensive GVHD ($n = 18$), which resulted in a 5-year cumulative incidence of 73.3% (95% CI 52.6–86.1). At the time of analysis, 17 patients had died, which resulted in an OS of 71.2% after a median follow-up of 60.9 months (range 50.0–71.9; fig. 1a). Disease-free survival (DFS) was 69.5% (fig. 1b). The 5-year cumulative incidence of relapse (CIR) and of NRM (CIN) was 16.9% (95% CI 8.6–27.6) and 13.6% (95% CI 6.3–23.6), respectively.

Of the 30 RIC-SCT recipients, 21 patients were alive and all of them remained in continuous CR, resulting in an OS and DFS of $70.0 \pm 8.3\%$, which was not different from those in the ASCT group (OS: $72.4 \pm 8.3\%$, $p = 0.813$ and DFS: $69.0 \pm 8.6\%$, $p = 0.919$; fig. 1c, d). The causes of death were leukemia relapse, infection and GVHD (1 acute and 2 chronic cases) in 3 patients each. Of the 29

patients who received autografts, 8 died with relapse cited as the principal cause of death in 6.

The 5-year CIR was 10.3% (95% CI 2.5–24.6) and 24.1% (95% CI 10.4–40.9) in the RIC-SCT group and the ASCT group, respectively, and no statistically significant difference was noted between the 2 groups ($p = 0.161$). The 5-year CIN was 20.7% (95% CI 8.2–37.1) and 6.9% (95% CI 1.2–20.0) in the RIC-SCT group and the ASCT group, respectively, again with no statistically significant difference between the 2 groups ($p = 0.153$).

Factors Affecting Transplant Outcome

Advanced age (≥ 50 years) and $-X$ were adverse prognostic factors for both OS and DFS (table 3). If we analyze survival after considering each transplantation mo-

Table 3. Factors affecting survival of all patients receiving SCT

Variables	n = 59	OS		DFS	
		% ± SE	p	% ± SE	p
Sex					
Male	43	74.4±6.7	0.407	72.1±6.8	0.469
Female	16	62.5±12.1		62.5±12.1	
Age					
<50 years	49	77.6±6.0	0.009	75.5±6.1	0.013
≥50 years	10	40.0±15.5		40.0±15.5	
White blood cell count, ×10 ⁹ /l					
Normal	33	69.7±8.0	0.729	69.7±8.0	0.930
Above normal	26	73.1±8.7		69.2±9.1	
<8.6	28	75.0±8.2	0.677	75.0±8.2	0.484
≥8.6	31	67.7±8.4		64.5±8.6	
LDH, IU/l					
<765	21	81.8±11.6	0.384	81.0±8.6	0.179
≥765	38	68.8±6.7		63.2±7.8	
Cytogenetics					
–Y in men	28	67.9±8.8	0.207	64.3±9.1	0.136
No –Y in men	15	86.7±8.8		86.7±8.8	
–X	10	30.0±14.5	<0.001	30.0±14.5	0.001
No –X	49	79.6±5.8		77.6±6.0	
Time to CR1					
<29 days	17	64.7±11.6	0.495	64.7±11.6	0.530
≥29 days	42	73.8±6.8		71.4±7.0	
Time to SCT					
Shorter ^a	26	73.1±8.7	0.773	69.2±9.1	0.981
Longer ^b	33	69.7±8.0		69.7±8.0	

Bold values indicate statistical significance.

^a <183 days. ^b ≥183 days.

dality separately, both advanced age and –X were significant prognostic factors for survival outcome (table 4). Advanced age was associated with worse OS ($p = 0.007$) and DFS ($p = 0.008$) in the ASCT group (fig. 2a, c), and –X demonstrated a similar outcome (OS: $p = 0.002$ and DFS: $p = 0.003$; fig. 3a, c). However, these factors lost their statistical significance in the RIC-SCT group (age: fig. 2c, d and –X: fig. 3c, d). Multivariate analysis revealed that –X was the significant prognostic factor for both OS ($p = 0.034$) and DFS ($p = 0.29$) in the ASCT group (table 5).

An advanced age was associated with a higher relapse rate in the ASCT group and the RIC-SCT group, and although the differences between groups were not statistically significant, the difference in relapse rate was diminished in the RIC-SCT group (table 6). Advanced patient age was also associated with a higher rate of NRM in both groups. However, again there was no statistically signifi-

cant difference according to age in each group. There was no statistically significant difference in CIN according to X chromosome status in either group; however, a significantly higher CIR was noted in the patients with –X in the ASCT group ($p = 0.038$).

Discussion

There are several merits to this study including a homogenous population [de novo AML with t(8;21), SCT in CR1], uniform transplantation strategy such as single preparative regimen and a long follow-up duration adequate enough to confirm the survival outcome (median follow-up duration >5 years).

Our strategy to intensify postremission treatment by SCT either with autografts or RIC allografts seems to have been a reasonable option, based on the fact that

Table 4. Univariate analysis of factors affecting survival

Variables	OS						DFS					
	ASCT (n = 29)			RIC-SCT (n = 30)			ASCT (n = 29)			RIC-SCT (n = 30)		
	n	% ± SE	p	n	% ± SE	p	n	% ± SE	p	n	% ± SE	p
Sex												
Male	21	76.2±9.3	0.570	22	72.7±9.5	0.525	21	71.4±9.9	0.692	22	72.7±9.5	0.525
Female	8	62.5±17.1		8	62.5±17.1		8	62.5±17.1		8	62.5±17.1	
Age												
<50 years	25	80.0±8.0	0.007	24	75.0±8.8	0.254	25	76.0±8.5	0.008	24	75.0±8.8	0.254
≥50 years	4	25.0±21.7		6	50.0±20.4		4	25.0±21.7		6	50.0±20.4	
White blood cell count, ×10 ⁹ /l												
Normal	17	64.7±11.6	0.259	16	75.0±10.8	0.536	17	64.7±11.6	0.478	16	75.0±10.8	0.536
Above normal	12	83.3±10.8		14	64.3±12.8		12	75.0±12.5		14	64.3±12.8	
<8.6	13	69.2±12.8	0.628	15	80.0±10.3	0.280	13	69.2±12.8	0.845	15	80.0±10.3	0.244
≥8.6	16	75.0±10.8		15	60.0±12.6		16	68.8±11.6		15	60.0±12.6	
LDH, IU/l												
<765	11	81.8±11.6	0.454	10	80.0±12.6	0.375	11	81.8±11.6	0.318	10	80.0±12.6	0.375
≥765	18	66.7±11.1		20	65.0±10.7		18	61.1±11.5		20	65.0±10.79	
Cytogenetics												
–Y in men	14	71.4±12.1	0.517	14	64.3±12.8	0.253	14	64.3±12.8	0.362	14	64.3±12.8	0.253
No –Y in men	7	85.7±13.2		8	87.5±11.7		7	85.7±13.2		8	87.5±11.7	
–X	5	20.0±17.9	0.002	5	40.0±21.9	0.060	5	20.0±17.9	0.003	5	40.0±21.9	0.060
No –X	24	83.3±7.6		25	76.0±8.5		24	79.2±8.3		25	76.0±8.5	
Time to CR1												
<29 days	17	64.7±11.6	0.269	0	^a		17	64.7±11.6	0.491	0	^a	
≥29 days	12	83.3±10.8		30			12	75.0±12.5		30		
Time to SCT												
Shorter ^b	14	78.6±11.0	0.443	12	66.7±13.6	0.703	14	71.4±12.1	0.727	12	66.7±13.6	0.770
Longer ^c	15	66.7±12.2		18	72.2±10.6		15	66.7±12.2		18	72.2±10.6	
Donor type		n.a.						n.a.				
Sibling				23	73.9±9.2	0.374				23	73.9±9.2	0.374
Unrelated				7	57.1±18.7					7	57.1±18.7	
HLA incompatibility		n.a.						n.a.				
Matched				19	68.4±10.7	0.915				19	68.4±10.7	0.915
Mismatched				11	72.7±13.4					11	72.7±13.4	
Sex incompatibility		n.a.						n.a.				
Matched				13	76.9±11.7	0.535				13	76.9±11.7	0.535
Mismatched				17	64.7±11.6					17	64.7±11.6	
ABO blood group incompatibility		n.a.						n.a.				
Matched				15	73.3±11.4	0.745				15	73.3±11.4	0.682
Mismatched				15	66.7±12.2					15	66.7±12.2	
Acute GVHD		n.a.						n.a.				
Positive				18	66.7±11.1	0.620				18	66.7±11.1	0.620
Negative				12	75.0±12.5					12	75.0±12.5	
Chronic GVHD		n.a.						n.a.				
Positive				22	77.3±8.9	0.570				22	77.3±8.9	0.477
Negative				6	6.7±19.2					6	66.7±19.2	

Bold values indicate statistical significance. n.a. = Not applicable.

^a No comparison analysis is performed because all patients with RIC-SCT had a longer time to CR (≥29 days).

^b <206 days for ASCT and <147 days for allo-SCT.

^c ≥206 days for ASCT and ≥147 days for allo-SCT.

OS and DFS in these patients was approximately 70% and NRM was considerably low (14%) with a long-term follow-up duration (>5 years). This result appears to be favorable or at least equivalent to those in several previous studies where patients with t(8;21) were

treated with HDARA-C-based consolidation chemotherapy [3, 5, 6, 14–16]; however, there are no direct comparisons. The previous studies included heterogeneous patient populations and postremission treatment modalities, which makes it difficult to discern the

Fig. 2. Survival according to the age of the patients. **a** OS of ASCT recipients. **b** OS of RIC-SCT recipients. **c** DFS of ASCT recipients. **d** DFS of RIC-SCT recipients.

role of postremission treatment in AML patients with t(8;21).

Data regarding RIC-SCT for patients with AML and t(8;21) are still very limited, although there have been several studies evaluating the role of MC-SCT or ASCT in these patients. Schlenk et al. [17] studied the role of HLA-MSD SCT in treating AML patients in CR1, and they concluded that there was no improvement in OS after SCT, because the reduction in relapse was offset by a high NRM. This might have resulted from the fact that the majority of the patients (88.1%) received MC, and the NRM was considerably high, exceeding 30%. RIC-SCT has been known to reduce NRM while preserving the antileukemic efficacy and is therefore expected to improve the transplant outcome. In our study, RIC-SCT demonstrated considerable efficacy, approximating 70%, in improving OS and DFS, and the CIR was only 10% after a median

follow-up duration of >60 months, which is clearly a lower relapse rate than that in several previous studies [15, 18]. However, RIC-SCT was still found to be associated with a considerable NRM of approximately 20%, so efforts should be made to further reduce procedure-related toxicity.

We used modified transplant-associated microangiopathy as a standard conditioning regimen for ASCT, because it resulted in favorable outcomes and acceptable toxicities, with a DFS of >70% and an NRM of 2% for adult patients with AML in CR1 [11]. As for the role of ASCT in CR1, there have been no specific studies performed in the subset of core-binding factor AML patients. ASCT is associated with a much lower NRM than allo-SCT, so it remains an obvious option to intensify postremission treatment in these patients. In our study, ASCT was associated with a low NRM of 7% and an OS

Table 5. Multivariate analysis of factors affecting OS and DFS in patients of the ASCT group

Variables	ASCT group			
	OS		DFS	
	hazard ratio (95% CI)	p	hazard ratio (95% CI)	p
Age				
<50 years	1	0.017	1	0.017
≥50 years	5.815 (1.365–24.766)		5.584 (1.356–23.003)	
Cytogenetics				
–X	6.536 (1.619–26.391)	0.008	6.136 (1.603–23.482)	0.008
No –X	1		1	

Bold values indicate statistical significance.

Fig. 3. Survival according to X chromosome status. **a** OS of ASCT recipients. **b** OS of RIC-SCT recipients. **c** DFS of ASCT recipients. **d** DFS of RIC-SCT recipients.

Table 6. Factors affecting CIR and CIN according to the transplantation modality

Variables	CIR				CIN			
	ASCT	p	RIC-SCT	p	ASCT	p	RIC-SCT	p
Age								
<50 years	20.0 (7.1–37.6)	0.133	8.7 (1.4–24.7)	0.577	4.0 (0.3–17.4)	0.120	17.4 (5.2–35.4)	0.423
≥50 years	50.0 (1.3–89.6)		16.7 (0.4–55.6)		25.0 (0.3–71.4)		33.3 (3.0–71.0)	
Cytogenetics								
–X	60.0 (4.9–91.7)	0.038	20.0 (0.4–62.1)	0.416	20.0 (0.4–62.1)	0.225	40.0 (2.5–79.6)	0.290
No –X	16.7 (5.0–34.1)		8.3 (1.4–23.8)		4.2 (0.3–18.0)		16.7 (5.0–34.1)	

Bold values indicate statistical significance.

and DFS of approximately 70%; however, the advantage of a low NRM was offset by a high rate of relapse (24.1%). Although there was a trend for a higher rate of relapse and NRM in the ASCT group and in the RIC-SCT group, respectively, there was no statistically significant difference. We think that after considering all these outcomes together, the survival outcomes of ASCT and RIC-SCT may be equivalent in our study. Based on these outcomes, we believe that ASCT as well as RIC-SCT are equally effective for the intensification of postremission treatment in this favorable population.

The adverse prognostic factor of older age is attributable to the difference both in leukemia-specific factors and patient-specific factors. In our study, advanced age was an adverse prognostic factor for survival in the ASCT group, but it lost its statistical significance in the RIC-SCT group where the survival outcome in the advanced age group approached that in the younger group. This indicates that an inferior outcome in the elderly patients in terms of OS and DFS after ASCT could be overcome by the application of RIC-SCT, based on the finding that the survival difference diminished with loss of statistical significance. Based on this result, we believe that ASCT could not overcome the adverse prognostic effect of age and that RIC-SCT should preferably be offered in this age group. Elderly patients showed a higher CIR and CIN, although this result was not statistically significant; we think that this combination is related to the adverse outcome in elderly patients. –X was another adverse prognostic factor for both OS and DFS in the ASCT group; however, the survival difference in the ASCT group again disappeared when RIC-SCT was performed, which justifies that the patients of this subgroup might benefit from RIC-SCT rather than ASCT, even though the survival of the patients with –X still appeared

to be lower (but statistically insignificant). There are several reports showing that a lack of sex chromosome was the most frequent secondary chromosomal aberration in patients with t(8;21), although as a prognostic factor, its exact role remains uncertain [3, 5, 6]. –X has been reported to have no impact on OS in female patients [6], but this study included heterogeneous postremission treatment regimens to assess the significance of –X and also only included female patients with –X, in contrast to our study which included homogenous postremission treatment and analyzed for significance of –X in patients of both genders. In the multivariate analysis for the ASCT group, advanced age and –X were significant factors for both OS and DFS, so careful attention should be paid to these factors when ASCT is being considered for intensification of postremission treatment. A worse survival outcome in patients with –X after ASCT might have been due to a higher relapse rate rather than a higher NRM, given that statistical differences were noted only in the relapse rate.

RIC-SCT has been known to reduce the relapse rate by virtue of the GVL effect, but it is associated with a higher NRM than in chemotherapy or ASCT. In our study, CIR was lower in the RIC-SCT group, while NRM was higher in the RIC-SCT group, although this did not reach statistical significance. This might be partly related to the fact that AML with t(8;21) is basically a disease with a low probability of relapse, so the role of GVL effect after RIC-SCT might be limited in comparison to that in the disease with a higher probability of relapse. This is probably the reason why RIC-SCT produces an equivalent outcome to ASCT in this disease. Meanwhile, RIC-SCT might have been a better option for a subset of patients with –X or advanced age in our study. These patients showed either a trend of or a definitely higher risk

of relapse after ASCT than those without –X or younger patients, and there was a reduction of a certain degree in relapse after RIC-SCT.

In conclusion, based on the results of our study, the intensification of postremission treatment with autografts or RIC allografts seems to be equally effective in AML patients with t(8;21) in CR1. In our study, the exact role of SCT in t(8;21) AML remained uncertain, but RIC-SCT should preferably be selected for patients with adverse prognostic factors such as advanced age and –X. A

randomized prospective study in a sizeable population will be required to confirm our results, identify the role of RIC-SCT and determine which subset of patients would benefit more from SCT rather than chemotherapy as a postremission treatment.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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