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Re-analysis of the Outcomes of Post-Remission Therapy for Acute Myeloid Leukemia with Core Binding Factor According to Years of Patient Enrolment

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Objective: The purpose of this study was to re-evaluate post-remission therapy outcomes after first remission according to years of patient enrolment in patients with core binding factor acute myeloid leukaemia.

Methods: We conducted a retrospective study on 138 patients aged less than 60 years diagnosed with core binding factor acute myeloid leukaemia between 1994 and 2006, comparing allogeneic stem cell transplantation and high-dose cytarabine chemotherapy as post-remission treatment options after the first remission.

Results: The 5-year probabilities of disease-free survival and overall survival were not different between allogeneic stem cell transplantation and high-dose cytarabine groups. However, 3-year probabilities of disease-free survival (86.7% vs. 67.0%) and overall survival (90.0% vs. 67.3%) showed a trend towards improvement in the allogeneic stem cell transplantation group compared with the high-dose cytarabine group in cohort after 2003 (2003–2006), whereas outcomes were not different in cohort before 2003 (1994–2002). Especially, 3-year probabilities of disease-free survival (95.2% vs. 59.3%, $P = 0.008$) and overall survival (95.2% vs. 59.6%, $P = 0.032$) of allogeneic stem cell transplantation group were significantly better than high-dose cytarabine group in cohort after 2003 of acute myeloid leukaemia patients with t(8;21). The relative risk of overall survival with allogeneic stem cell transplantation, compared with high-dose cytarabine chemotherapy, was significantly improved in the cohort after 2003 (0.33; 95% CI, 0.07–1.48) when compared with that before 2003 (1.92; 95% CI, 0.77–4.82). In multivariate analysis in cohort after 2003, allogeneic stem cell transplantation as post-remission therapy was associated with better disease-free survival.

Conclusions: Allogeneic stem cell transplantation is currently the more effective post-remission therapy than it was prior to 2003 for core binding factor acute myeloid leukaemia achieving first remission. On the contrary to previous findings, allogeneic stem cell transplantation provides significantly improved outcomes than high-dose cytarabine chemotherapy in acute myeloid leukaemia with t(8;21).

Key words: acute myeloid leukemia – core binding factor – stem cell transplantation – cytarabine – post-remission therapy

INTRODUCTION

Cytogenetically, core binding factor (CBF) acute myeloid leukemia (AML) is defined by the presence of t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22). CBF AML is identified in 13−15% adult patients with *de novo* AML (1). In view of the involvement of CBF subunits at the molecular level and positive response to treatment, CBF AML is associated with relatively favourable prognosis, compared to that of patients displaying normal or adverse karyotypes.

AML patients with favourable cytogenetics display a more than 80% chance of attaining complete remission (CR) and improved disease-free survival (DFS), compared with the other cytogenetic groups (2,3). Several chemotherapeutic strategies have been reported, among which high-dose cytarabine (HDAC) is generally the most effective option for successful post-remission therapy (4). The overall survival (OS) rate at 5 years in patients with favourable cytogenetics subjected to intensive HDAC post-remission therapy exceeds 50% (5−7). However, even in CBF AML patients achieving CR, 40−50% relapse has been observed, and the probability of long-term survival has not been still satisfied. Marcucci et al. reported that consolidation therapy with multicourse HDAC in younger patients decreased the relapse rate (RR) (7); however, this did not translate into more favourable survival for CBF AML patients.

Although patients with favourable cytogenetics receiving autologous stem cell transplantation (autoSCT) displayed markedly lower RR after four cycles of chemotherapy than those not given such therapy, a high procedural mortality rate was found in adults subjected to autoSCT, resulting in no differences in OS (5). Furthermore, none of the randomized studies disclosed an advantage of allogeneic SCT (alloSCT) in this group of patients, given the relatively high treatment-related death (TRD) rate (8−12). However, the time of CBF AML patient enrolment in most reports handling post-remission therapy outcomes were earlier than 2003 (8−12), and no relevant studies in patients enrolling after 2003 have appeared to date. Over the last decade, the outcomes of alloSCT in haematologic malignancies have improved as a result of substantially reduced treatment-related mortality following modification of transplant procedures, including graft versus host disease (GVHD) prophylaxis and conditioning regimens (13). Therefore, re-analysis of recent outcomes using alloSCT and HDAC as post-remission therapy for CBF AML patients is required. Here, we report the results of a nationwide retrospective analysis on CBF AML patients aged less than 60 years, comparing alloSCT and HDAC chemotherapy as post-remission treatment options after the first remission.

METHODS

Patients and Data Collection

Data were obtained from questionnaires distributed to each hospital. A questionnaire containing a set of data including demographic, diagnostic, clinical and laboratory data, cytogenetics, presence of extramedullary involvement, French-American-British (FAB) morphological classification, type of post-remission and salvage therapy, transplantation data including conditioning regimen, acute GVHD prophylaxis and stem cell sources, and outcomes was filled out for each patient. Inclusion criteria were as follows: (i) presence of t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22) on standard karyotypic analysis; (ii) age 16−59 years; (iii) achieving first CR after remission-induction chemotherapy; and (iv) availability of clinical data. All consecutive patients who fulfilled the inclusion criteria were included. Among the patients subjected to alloSCT as post-remission therapy (alloSCT group), patients undergoing transplantation without consolidation chemotherapy, and received intermediate-dose cytarabine or HDAC as consolidation chemotherapy were included. Within-patients received HDAC chemotherapy alone as post-remission therapy (HDAC group), patients receiving more than two cycles of HDAC consolidation chemotherapy were included.

Treatment Protocols

Among HDAC group, those treated with a minimum of three cycles of HDAC (3 g/m^2 intravenously every 12 h, days 1, 3 and 5, or 3 g/m^2 intravenously every 12 h for 4 days) were selected, and included regimens containing mitoxantrone, etoposide or idarubicin/daunorubicin. Within the alloSCT group, 29/60 (48.3%) patients received HDAC-containing consolidation chemotherapy before transplantation.

Conditioning regimen, prophylaxis and treatment of GVHD were administered according to the specific protocols of each transplant centre. Out of the 60 alloSCT patients, 38 were prepared using a combination of busulfan (3.2 mg/kg/day intravenously on four consecutive days) and cyclophosphamide (60 mg/kg/day on two consecutive days) with or without etoposide (30 mg/kg/day for one day), whereas 10 received total body irradiation of 12 Gy with 60 mg/kg/day cyclophosphamide on two consecutive days. Another 10 patients received a combination of busulfan (3.2 mg/kg/day intravenously on four consecutive days) and fludarabine (30 mg/m^2 intravenously on six consecutive days). One patient was administered fludarabine with melphalan, and one patient received another regimen. Cyclosporine plus methotrexate (54 patients), FK-506 plus methotrexate (three patients) and methotrexate alone (three patients) were employed as GVHD prophylaxis.

Statistical Analysis

The definition of CR followed the recommended criteria (14). To evaluate the differences between patients subjected to alloSCT and HDAC groups after achieving CR, categorical variables were compared using the χ^2 test, and continuous variables were evaluated with the Mann−Whitney *U* test. Cumulative incidence was used for TRD and RR.

When comparing outcomes of alloSCT and HDAC groups, differences in time to post-remission treatment including SCT is potential sources of bias and require appropriate adjustments. To address this potential bias, semi-landmark analysis was used for analysing DFS and OS of both groups as previously described (15–17). Briefly, in patients of alloSCT group, the day of the stem cells infusion from the first remission was defined as the landmark day; in patients of HDAC group, 5 months from the first remission, which was the median time of the day of the stem cells

Table 1. Characteristics of patients according to post-remission therapy

Characteristics	All patients ($n = 138$)	Allogeneic SCT ($n = 60$)	Chemotherapy ($n = 78$)	P-value
Median Dx day, year (range)	2003 (1994–2006)	2003 (1996–2005)	2003 (1994–2006)	0.351
Median age, years (range)	37 (14–59)	35.5 (15–59)	41 (14–59)	0.122
Sex, male/female (%)	75/63 (54.3/45.7)	41/19 (68.3/31.7)	34/44 (43.6/56.4)	0.004
Median WBC, $\times 10^9$/l (range)	9.8 (0.5–393.0)	10.4 (0.7–338.8)	9.1 (0.5–393.0)	0.234
Median Hb, g/dl (range)	7.9 (2.3–14.7)	7.5 (2.3–13.4)	8.2 (2.4–14.7)	0.376
Median PLT, $\times 10^9$/l (range)	36 (6–593)	33 (6–532)	39 (7–593)	0.650
Median PB blast, % (range)	41 (0–90)	38 (1–89)	42 (0–90)	0.835
Median marrow blast, % (range)	52.7 (8.8–95.2)	52.3 (8.8–93.0)	52.8 (12.5–95.2)	0.699
Median LDH, IL/U (range)	845 (207–23650)	968.5 (267–15690)	702 (207–23650)	0.034
FAB class (%)				
M1	5 (3.6)	3 (5)	2 (2.6)	0.167
M2	103 (74.6)	40 (66.7)	63 (80.8)	
M4	30 (21.7)	17 (28.3)	13 (16.7)	
Core binding factor				
Including t(8;21)	108 (78.3)	43 (71.7)	65 (83.3)	0.100
Including inv(16)	30 (21.7)	17 (28.3)	13 (16.7)	
Del (9)(q22) abnormality (%)				
Yes	10 (7.2)	3 (5.0)	7 (9.0)	0.356
No	122 (88.4)	55 (91.7)	67 (85.9)	
n.a.	6 (4.3)	2 (3.3)	4 (5.1)	
Sex chromosome loss				
Yes	67 (48.6)	33 (55.0)	34 (43.6)	0.212
No	65 (47.1)	25 (41.7)	40 (51.3)	
n.a.	6 (4.3)	2 (3.3)	4 (5.1)	
Complex karyotype				
Yes	24 (17.4)	12 (20.0)	12 (15.4)	0.508
No	108 (78.3)	46 (76.7)	62 (79.5)	
n.a.	6 (4.3)	2 (3.3)	4 (5.1)	
Initial response (%)				
CR	119 (86.2)	52 (86.7)	67 (85.9)	0.897
NR	19 (13.8)	8 (13.3)	11 (14.1)	
Courses to CR (%)				
1 cycle	119 (86.2)	52 (86.7)	67 (85.9)	0.897
2 cycles	18 (13.0)	8 (13.3)	10 (12.8)	
3 cycles	1 (0.7)	0	1 (1.3)	
Median duration of post-remission treatment, months (range)	n.a.	n.a.	8 (5–14)	—
Median time from first CR to transplant, months (range)	n.a.	5 (2–13)	n.a.	—

SCT, stem cell transplantation; WBC, white blood cell; Hb, haemoglobin; PLT, platelet; FAB, French-American-British; LDH, lactate dehydrogenase; CR, complete remission; NR, no remission; Dx, diagnosis; PB, peripheral blood; n.a., not available.

infusion from the first remission was defined as the landmark day. DFS was estimated from the landmark day until the date of AML relapse or death from any cause. OS was measured from the landmark day until death from any cause (4). DFS and OS were calculated according to the Kaplan–Meier method, and patients receiving alloSCT and HDAC alone were compared with the log-rank test. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards model.

RESULTS

Patients and Disease Characteristics

The study patients and disease characteristics are summarized in Table 1. In total, 322 AML patients from 18 institutions in Korea aged 16–59 years with either t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22), who achieved CR after remission-induction chemotherapy between January 1994 and March 2006 were reviewed retrospectively. Among the 322 CBF AML patients, 184 were considered ineligible. Of these, 133 patients were categorized as such based on receiving less than three cycles of consolidation chemotherapy and 20 who received low-dose or intermediate-dose cytarabine consolidation chemotherapy in HDAC group, and 31 who underwent autoSCT. Overall, 138 AML patients undergoing alloSCT and more than two cycles of HDAC consolidation chemotherapy alone in the first CR were analysed. Of the 60 patients who underwent alloSCT, 52 underwent SCT with human leukocyte antigen (HLA)-identical sibling donor and 8 with HLA-identical unrelated donor.

A relatively higher number of female patients were included in HDAC group (male:female = 1:1.29) compared with alloSCT group (male:female = 1:0.46) ($P = 0.004$). Lactate dehydrogenase (LDH) levels were higher in alloSCT group than HDAC group ($P = 0.034$). Thirty-two patients (53.3%) of alloSCT group and 36 patients (46.2%) of HDAC group had initial high WBC count, and it did not show any statistical significance. Other variables, including age, initial platelet counts, haemoglobin, peripheral and bone marrow (BM) blast counts, FAB classification, additional cytogenetic abnormalities, response to remission-induction chemotherapy and number of courses to achieve CR were not significantly different between the two groups.

Outcomes According to Post-Remission Therapy

The median follow-up duration was 46 months (range: 10–151 months). In total, 35 of the 138 patients died, and follow-up loss was reported for nine patients. Among the 138 patients with CR, the probabilities of DFS and OS at 5 years were 69.0 ± 4.0% and 77.9 ± 3.8%, respectively. The 5-year probabilities of DFS and OS did not have any difference between alloSCT and HDAC groups (Fig. 1).

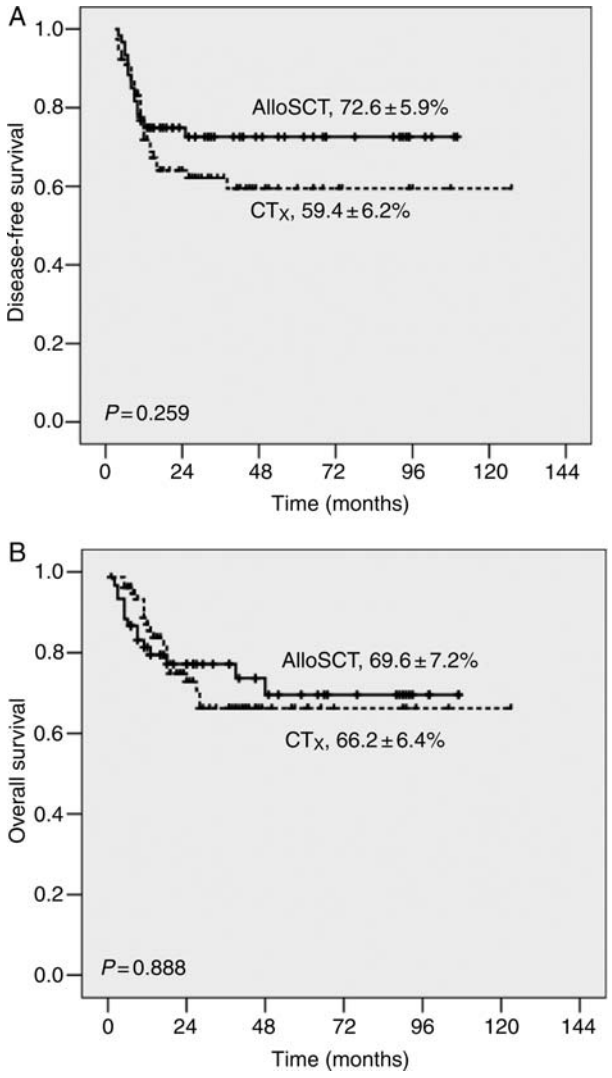

Figure 1. Five-year probabilities of disease-free survival (A) and overall survival (B) according to post-remission therapy.

Comparison of DFS and OS According to Years of Patient Enrolment

As the median year value of patient diagnosis was 2003, outcomes were analysed in patient cohorts enrolled before 2003 (1994–2002) and after 2003 (2003–2006). The median follow-up duration in the cohort before 2003 was 72 months (range, 48–151 months), and 25.5 months after 2003 (range, 10–48 months). The 3-year probabilities of DFS and OS were not significantly different when the alloSCT and HDAC groups before 2003 were compared (Fig. 2). There was trend towards better 3-year probabilities of DFS (86.7 ± 6.2% vs. 67.0 ± 7.7%) and OS (90.0 ± 5.5% vs. 67.3 ± 8.8%) in the alloSCT group after 2003 compared with those of the HDAC group, but this was not statistically significant. We analysed the outcomes of each post-remission therapy according to the treatment before and after 2003. DFS and OS of the HDAC group were comparable, both cohorts before and after 2003. On the other hand, 3-year DFS and

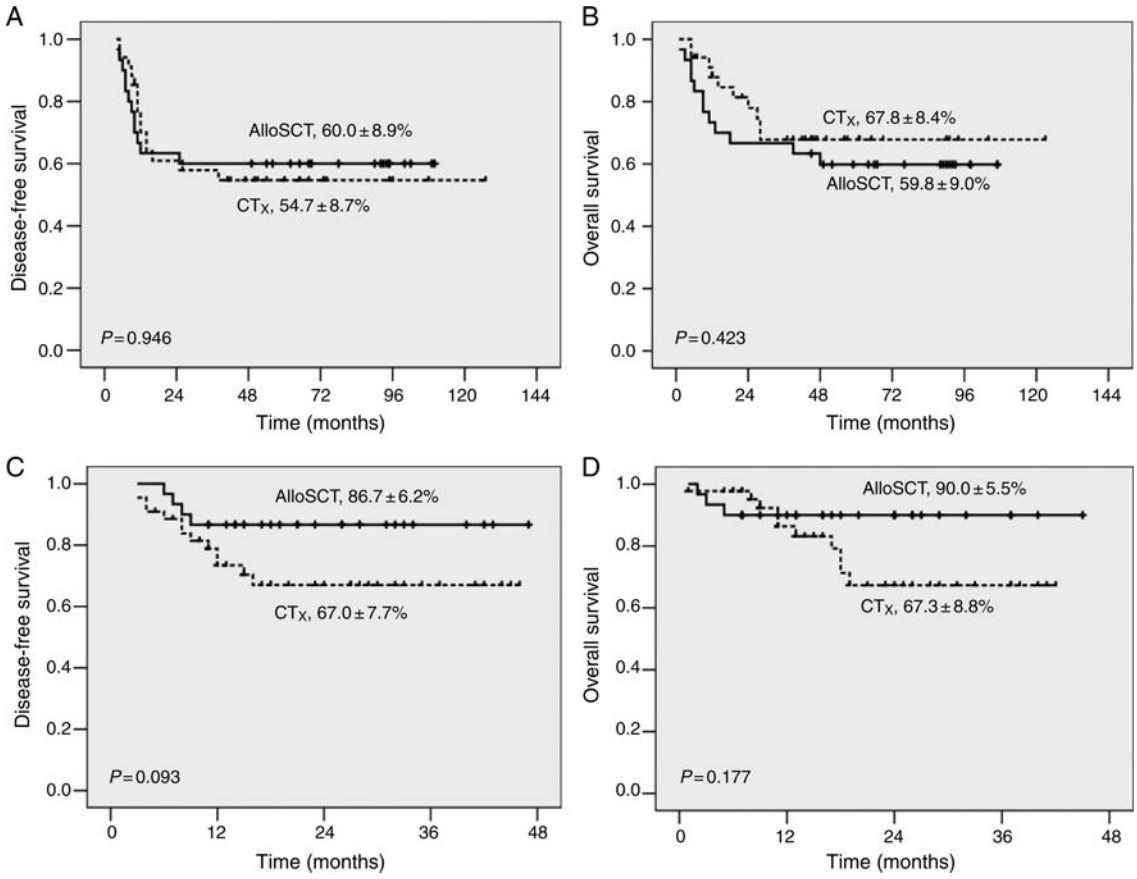

Figure 2. Three-year probabilities of disease-free survival and overall survival according to post-remission therapy in cohorts before and after 2003. Graphs show 3-year probabilities of (A) disease-free survival and (B) overall survival in cohorts before 2003, and 3-year probabilities of (C) disease-free survival and (D) overall survival in cohorts after 2003. AlloSCT, allogeneic stem cell transplantation; CTx, chemotherapy.

OS rates of the alloSCT group in the cohort after 2003 were considerably improved compared with those before 2003 (86.7 ± 6.2% vs. 60.0 ± 8.9%, $P = 0.031$; 90.0 ± 5.5% vs. 59.8 ± 9.0%, $P = 0.055$) (Fig. 3).

We also analysed outcomes of 108 AML patients with t(8;21)(q22;q22) according to post-remission therapy or cohorts before and after 2003. Three-year probabilities of DFS (95.2 ± 4.6% vs. 59.3 ± 8.9%, $P = 0.008$) and OS (95.2 ± 4.6% vs. 59.6 ± 10.3%, $P = 0.032$) of alloSCT group in the cohort after 2003 were higher than HDAC group, while those were not different between two groups in the cohort before 2003 (Fig. 4). Three-year probabilities of DFS (95.2 ± 4.6% vs. 54.5 ± 10.6%, $P = 0.003$) and OS (95.2 ± 4.6% vs. 54.5 ± 10.6%, $P = 0.012$) of the cohort after 2003 in alloSCT group were higher than the cohort before 2003, while those between the cohort before 2003 and after 2003 were not different in HDAC group (Fig. 5). The outcomes of AML patients with inv(16) could not be analysed because small number of patients were included in this group.

The cumulative incidence of TRD between the cohorts before and after 2003 in HADC group was similar, however, it was decreased from 40.2% before 2003 to 10.0% after 2003 in alloSCT group. The cumulative incidence of RR between the two groups before 2003 was not different, but decreased more in the alloSCT group than HDAC group after 2003 (6.7 vs. 29.9%, $P = 0.072$) (Table 2).

Univariate and multivariate analyses for DFS and OS were performed on cohorts divided according to dates before and after 2003. In univariate analysis, no variables influenced DFS or OS in the cohort before 2003, and only alloSCT was associated with favourable DFS ($P = 0.029$) in the cohort after 2003. In multivariate analysis, age at diagnosis significantly influenced DFS and OS in the cohort before 2003, and alloSCT as post-remission therapy significantly improved DFS in the cohort after 2003 (Table 3). In the cohort before 2003, relative risk of DFS and OS were 1.46 (95% CI, 0.63–3.40) and 1.92 (95% CI, 0.77–4.82), respectively, for alloSCT, compared with post-remission HDAC chemotherapy. Interestingly, in cohort after 2003, the relative risks of DFS and OS were significantly decreased (0.25; 95% CI, 0.07–0.94 and 0.33; 95% CI, 0.07–1.48) in the alloSCT group, respectively, compared with the HDAC group.

Analysis of AlloSCT

We defined the characteristics of alloSCT in cohorts before and after 2003 (Table 4). Among these, higher levels of sex

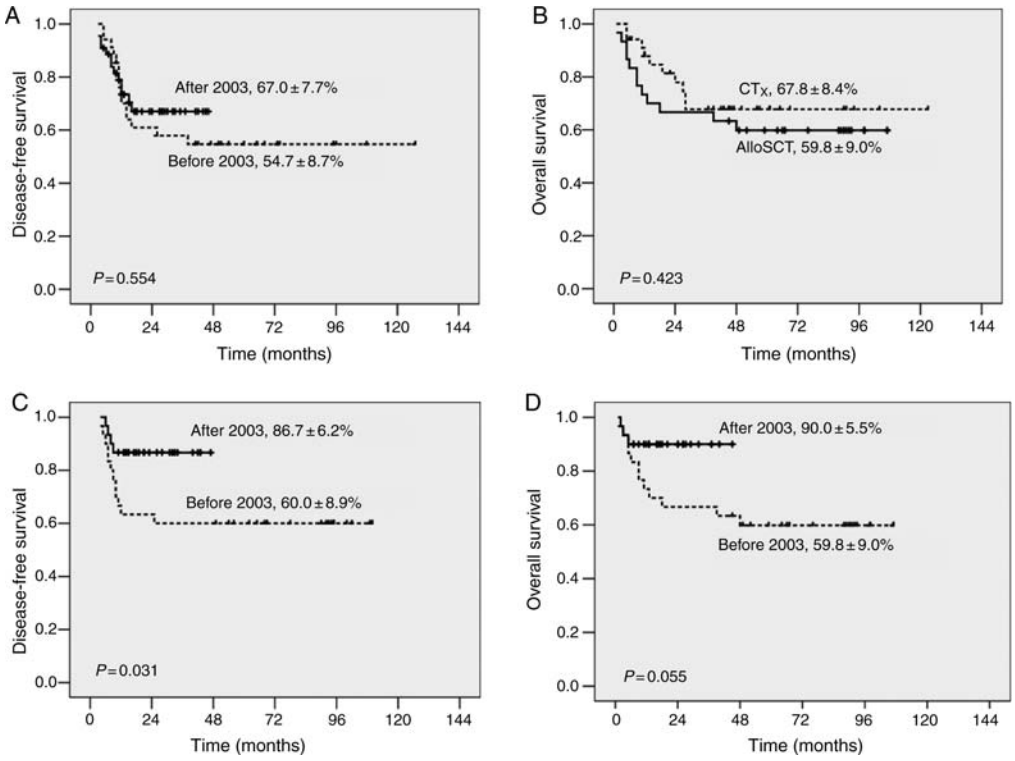

Figure 3. Three-year probabilities of disease-free survival and overall survival according to cohorts before and after 2003 in each post-remission therapy. Graphs show 3-year probabilities of disease-free survival (A) and overall survival (B) of HDAC group, and disease-free survival (C) and overall survival (D) of alloSCT group.

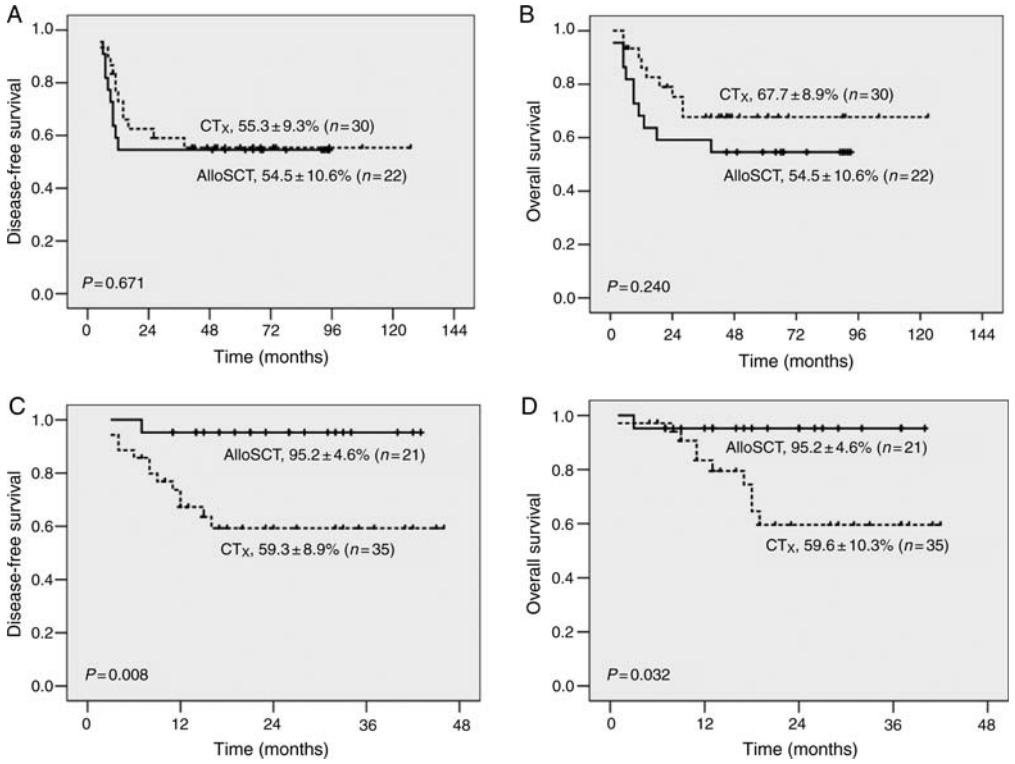

Figure 4. Three-year probabilities of disease-free survival and overall survival according to post-remission therapy in cohorts before and after 2003 of AML patients with t(8;21)(q22;q22). Graphs show 3-year probabilities of (A) disease-free survival and (B) overall survival in cohorts before 2003, and 3-year probabilities of (C) disease-free survival and (D) overall survival in cohorts after 2003. AlloSCT, allogeneic stem cell transplantation; CTx, chemotherapy.

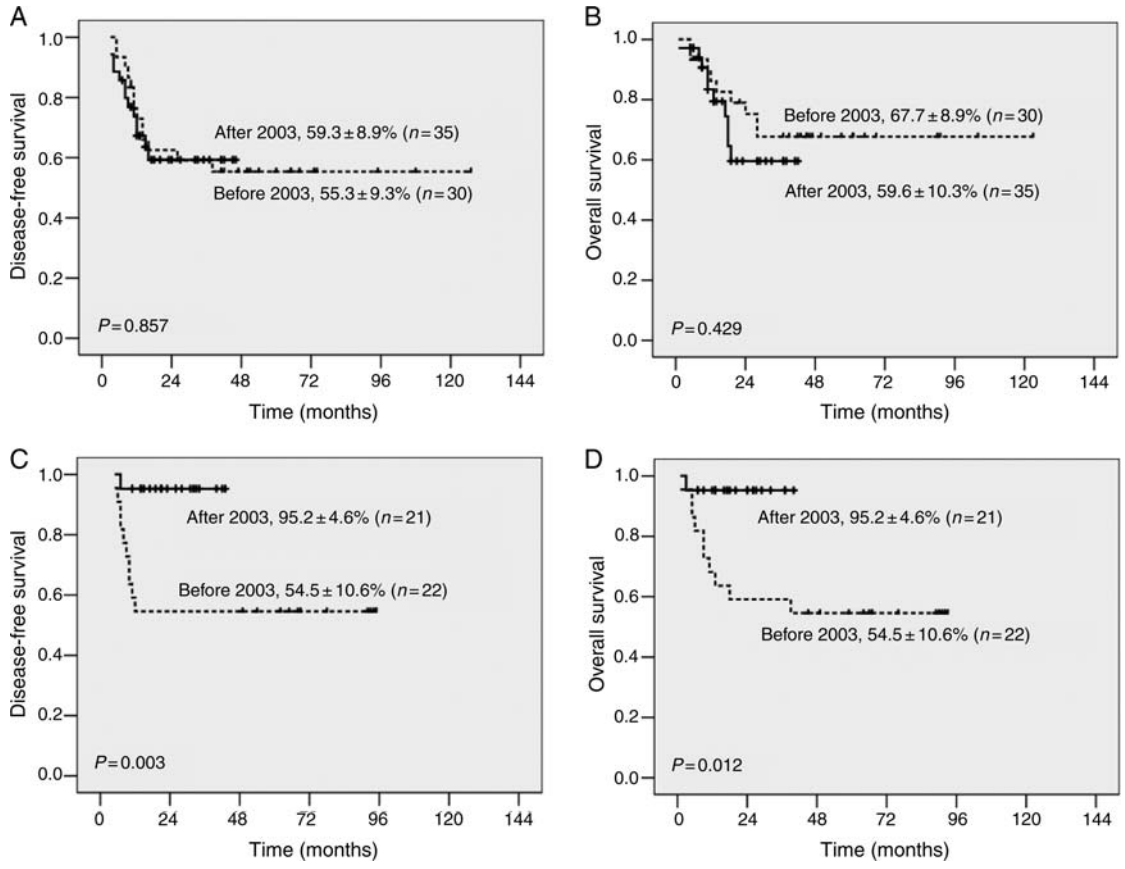

Figure 5. Three-year probabilities of disease-free survival and overall survival of AML patients with t(8;21)(q22;q22) according to cohorts before and after 2003 in each post-remission therapy. Graphs show 3-year probabilities of disease-free survival (A) and overall survival (B) of HDAC group, and disease-free survival (C) and overall survival (D) of alloSCT group.

Table 2. Cumulative incidence of treatment-related death and relapse rate according to enrolment periods

Period	*n*	Treatment-related death			Relapse rate		
		%	95% CI	*P*	%	95% CI	*P*
Before 2003 ($n = 64$)							
Chemotherapy	34	32.2	19.3–53.9	0.658	45.3	31.1–66.0	0.199
AlloSCT	30	40.2	25.9–62.3		23.3	12.2–44.6	
After 2003 ($n = 74$)							
Chemotherapy	44	32.7	19.3–55.4	0.197	29.9	18.5–48.5	0.197
AlloSCT	30	10.0	3.4–29.3		6.7	1.8–25.4	

CI, confidence interval; AlloSCT, allogeneic stem cell transplantation.

chromosome loss were detected in cohort before 2003, compared with those after 2003, in cytogenetic analyses. Matched unrelated donor SCT was more frequently performed in cohort after 2003 compared to cohort before 2003 ($P = 0.044$). Busulfan/cyclophosphamide (BuCy) and total body irradiation/cyclophosphamide (TBICy)-based therapies were used as conditioning regimens in cohort before 2003. On the contrary, other conditioning regimens, such as fludarabine/busulfan (FluBu), were introduced after 2003 ($P = 0.009$). Most patients assigned to cohort before 2003 received BM as the source of cells for SCT, whereas use of peripheral blood (PB) increased in cohort after 2003 ($P = 0.006$).

DISCUSSION

In the current study, DFS and OS were not significantly different between alloSCT and HDAC groups of CBF AML

Table 3. Multivariate analysis of disease-free survival and overall survival in AML with core binding factor according to years of patient enrolment

Parameter	Disease-free survival			Overall survival		
	RR	95% CI	*P*	RR	95% CI	*P*
Before 2003 ($n = 64$)						
Sex						
Male	1	0.24–1.47	0.261	1	0.16–1.35	0.157
Female	0.60			0.46		
Age (years)						
≥35	1	0.16–1.00	0.049	1	0.11–0.81	0.018
<35	0.39			0.29		
WBC ($\times 10^9$/l)						
<10	1	0.23–1.40	0.219	1	0.17–1.17	0.102
≥10	0.57			0.45		
LDH						
Abnormal	1	0.55–7.02	0.297	1	0.67–10.81	0.164
Normal	1.97			2.69		
Initial response						
NR	1	0.34–3.43	0.889	1	0.23–2.51	0.654
CR	1.09			0.76		
Post-remission therapy						
HDAC	1	0.63–3.40	0.375	1	0.63–3.40	0.375
AlloSCT	1.46			1.92		
After 2003 ($n = 74$)						
Sex						
Male	1	0.35–2.83	0.991	1	0.24–2.91	0.785
Female	0.99			0.84		
Age (years)						
≥35	1	0.18–1.94	0.384	1	0.16–2.36	0.483
<35	0.59			0.62		
WBC ($\times 10^9$/l)						
<10	1	0.54–4.41	0.419	1	0.31–4.06	0.853
≥10	1.54			1.13		
LDH						
Abnormal	1	0.13–2.00	0.331	1	0.16–3.30	0.669
Normal	0.51			0.72		
Initial response						
NR	1	0.06–1.17	0.081	1	0.09–2.71	0.412
CR	0.27			0.49		
Post-remission therapy						
HDAC	1	0.07–0.94	0.040	1	0.07–1.48	0.148
AlloSCT	0.25			0.33		

patients achieving first CR as previous data. However, there was a trend towards higher DFS and OS with alloSCT group (86.7 and 90.0%) vs. HDAC group (67.0 and 67.3%) in cohort after 2003, whereas no differences were observed between the two groups in cohorts before 2003. In particular, the relative risk of DFS and OS of alloSCT group in cohort after 2003 reduced significantly to 0.25 and 0.33 compared with HDAC chemotherapy as post-remission therapy, while the relative risk of survival in alloSCT group was higher than HDAC chemotherapy group in cohort before 2003. These results suggest that in contrast to outcomes obtained with cohort before 2003, which showed similar data as previous papers (8–12), alloSCT was useful in AML patients with CBF achieving first CR in cohort after 2003. This translated as a lower incidence of RR in the alloSCT group compared with the HDAC group in cohort after 2003 and reduced TRD and RR of alloSCT in cohort after 2003 compared with in those before 2003. It is possible that HDAC consolidation chemotherapy prior to alloSCT would affect the TRD in cohort between before and after 2003 in alloSCT group. Contrary to our expectation, HDAC chemotherapy was introduced more in cohort after 2003 than before 2003 in alloSCT group [20/30 (66.7%) vs. 9/30 (30.0%), $P = 0.004$].

Interestingly, in the current study, the 3-year survival rates of alloSCT group in cohort after 2003 were significantly higher than those before 2003, whereas no differences in HDAC group were evident before and after 2003. Patients subjected to alloSCT after 2003 were given more PB as a source of SCT cells, and introduced FluBu chemotherapy as the conditioning regimen compared with the cohort before 2003. A randomized multicentre trial of allografting for myeloid malignancies revealed that patients randomized to receive PB displayed significantly better OS when compared with those randomized to receive BM, and this benefit was because of lower non-relapse mortality (18). In early-stage disease, including first CR of AML, the PB SCT source was also associated with lower RR (19). Our study revealed lower RR in alloSCT group in cohorts after 2003, which might be attributed to the use of more PB SCT, compared with those before 2003. The BuCy regimen has been employed most commonly for conditioning in alloSCT. However, high treatment-related mortality caused by the additive cytotoxicity of these two alkylators is still a problem (20,21). Russell and coworkers suggested that the FluBu combination is a well-tolerated and safe low-toxicity myeloablative conditioning treatment (22,23). The outcomes of AML/MDS patients treated with FluBu were significantly better than those given BuCy (24). The possibility that better outcomes of alloSCT group in cohort after 2003 can be attributed to both higher levels of PB SCT and introduction of the FluBu conditioning regimen cannot be ruled out.

CBF AML patients are commonly treated with conventional chemotherapy, and alloSCT is reserved for relapse cases only. However, in the Cancer and Leukemia Group B study, RR was relatively high, reported as 53%, and long-term survival rates of CBF AML patients are still disappointing (5-year OS rate of 50%) (7). Furthermore, survival of

Table 4. Characteristics of patients subjected to allogeneic stem cell transplantation according to years of patient enrolment

Characteristics	Before 2003 ($n = 30$)	After 2003 ($n = 30$)	*P*-value
Sex, male/female (%)	21/9 (70/30)	20/10 (66.7/33.3)	0.781
Median age, years (range)	35.5 (15–48)	35.5 (17–60)	0.258
Core binding factor, t(8;21)/inv(16) (%)	22/8 (73.3/26.7)	21/9 (70.0/30.0)	0.774
Median WBC ($\times 10^9$/l) (range)	17.7 (0.7–338.8)	9.7 (1.2–100.8)	0.110
LDH, IL/U (%)			
Normal/abnormal/n.a.	2/25/3 (6.7/83.3/10.0)	5/24/1 (16.7/80.0/3.3)	0.928
Del (9)(q22) abnormality (%)			
Yes/no/n.a.	2/27/1 (6.7/90.0/3.3)	1/28/1 (3.3/93.3/3.3)	0.553
Sex chromosome loss (%)			
Yes/no/n.a.	20/9/1 (66.7/30.0/3.3)	13/16/1 (43.3/53.3/3.3)	0.063
Complex karyotype (%)			
Yes/no/n.a.	5/24/1 (16.7/80.0/16.7)	7/22/1 (23.3/73.3/3.3)	0.517
Extramedullary involvement (%)			
Yes/no	1/29 (3.3/96.7)	4/26 (13.3/86.7)	0.161
Donor type (%)			
Matched sibling/unrelated	28/2 (93.3/6.7)	24/6 (80.0/20.0)	0.044
Stem cell source (%)			
BM/PB/n.a.	22/4/4 (73.3/13.3/13.3)	12/13/5 (40.0/43.3/16.7)	0.006
GVHD prophylaxis (%)			
CsA + MTX	29 (96.7)	25 (83.3)	0.098
FK-506 + MTX	0	3 (10.0)	
MTX alone	1 (3.3)	0	
Corticosteroid	0	2 (6.7)	
Conditioning regimen (%)			
BuCy based	22 (73.4)	16 (53.3)	0.009
TBICy based	7 (23.4)	3 (10.0)	
FluMel	1 (3.3)	0	
FluBu	0	10 (33.3)	
Other	0	1 (3.3)	

WBC, white blood cell; Hb, haemoglobin; PLT, platelet; FAB, French-American-British; LDH, lactate dehydrogenase; BM, bone marrow; PB, peripheral blood; n.a., not available; GVHD, graft-versus-host disease; CsA, cyclosporine; MTX, methotrexate; BuCy, busulfan plus cyclophosphamide; TBICy, total body irradiation plus cyclophosphamide; FluMel, fludarabine plus melphalan; FluBu, fludarabine plus busulfan.

patients with CBF after the first relapse was poor. In particular, 5-year post-relapse survival of patients with t(8;21) was only 14%, compared to 34% of patients with inv(16). In a meta-analysis of several German AML trials, the CR rate and survival after re-induction therapy were significantly lower in patients with t(8;21) compared to those with inv(16), whose long-term survival was less than 50% (10). In the subset analysis of current study, the DFS and OS of alloSCT group in AML patients with t(8;21) in cohort after 2003 were dramatically increased compared with the HDAC group that showed statistically significant, while survival between both the groups were not different in cohort before 2003. Therefore, at least, alloSCT using recently improved transplantation methods might be beneficial in AML patients with t(8;21) who achieved first CR if they have HLA-matched sibling donor.

The main limitation of this study is not prospective. Since the results were analyzed retrospectively, randomization depending on donor availability could not be performed, and were therefore potentially subject to selection bias. Nevertheless, the data effectively confirm that more recent outcomes of the alloSCT group in CBF AML patients, especially with t(8;21), are better than those of the HDAC group, whereas no differences between the two groups were observed previously, even when patients were not assigned on the bias of donor availability.

To our knowledge, this is the first report showing that recent outcomes of alloSCT as post-remission therapy are

improved compared with HDAC chemotherapy alone following first remission of CBF AML patients, and especially those with t(8;21).

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Conflict of interest statement

None declared.

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APPENDIX

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