Prognostic factors and outcomes of adult patients with acute myeloid leukemia after first relapse

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The online version of this article has a Supplementary Appendix.

ABSTRACT

Background
Patients with acute myeloid leukemia who are treated with conventional chemotherapy still have a substantial risk of relapse; the prognostic factors and optimal treatments after relapse have not been fully established. We, therefore, retrospectively analyzed data from patients with acute myeloid leukemia who had achieved first complete remission to assess their prognosis after first relapse.

Design and Methods
Clinical data were collected from 70 institutions across the country on adult patients who were diagnosed with acute myeloid leukemia and who had achieved a first complete remission after one or two courses of induction chemotherapy.

Results
Among the 1,535 patients who were treated with chemotherapy alone, 1,015 relapsed. Half of them subsequently achieved a second complete remission. The overall survival was 30% at 3 years after relapse. Multivariate analysis showed that achievement of second complete remission, salvage allogeneic hematopoietic cell transplantation, and a relapse-free interval of 1 year or longer were independent prognostic factors. The outcome after allogeneic transplantation in second complete remission was comparable to that after transplantation in first complete remission. Patients with acute myeloid leukemia and cytogenetic risk factors other than inv(16) or t(8;21) had a significantly worse outcome when they did not undergo salvage transplantation even when they achieved second complete remission.

Conclusions
We found that both the achievement of second complete remission and the application of salvage transplantation were crucial for improving the prognosis of patients with acute myeloid leukemia in first relapse. Our results indicate that the optimal treatment strategy after first relapse may differ according to the cytogenetic risk.

Key words: acute myeloid leukemia, allogeneic hematopoietic cell transplantation, first relapse, second remission, cytogenetic risk.

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Introduction

Although up to 80% of patients with acute myeloid leukemia achieve first hematologic complete remission (CR1) with current induction chemotherapy, a substantial number of patients have an individualized risk of relapse.[1] Several risk factors have been defined in CR1 and these are used to stratify the treatment strategy in CR1.[2-4] However, once patients relapse, the probability of achieving a second complete remission (CR2) becomes lower and the duration of the second disease-free interval is generally reported to be shorter, meaning that the prognosis of patients who relapse is still challenging.[5-10]

Several retrospective studies have tried to identify the prognostic factors and optimal treatment strategies after first relapse.[7-12] Breems *et al.* evaluated the prognosis of patients with acute myeloid leukemia in first relapse including those after allogeneic hematopoietic cell transplantation (HCT) and showed that age, relapse-free interval, cytogenetic risks and previous allogeneic HCT were independent prognostic factors.[12] With regard to the treatment strategy, salvage allogeneic HCT has been shown to improve the outcome after relapse.[11] However, clinically important facts, such as the impact of the disease status at salvage allogeneic HCT and what treatment strategy should be used after relapse according to the disease risk have not yet been fully clarified. In addition, these issues have been difficult to analyze in a randomized study setting. We, therefore, performed a retrospective analysis of patients with non-M3 acute myeloid leukemia who relapsed after being treated with conventional chemotherapy in CR1.

Design and Methods

Patients

The study protocol was approved by the Institutional Review Board at the National Cancer Center Hospital. We constructed a new database of adult patients, aged 16 to 70 years, who were diagnosed with acute myeloid leukemia according to the World Health Organization classification between 1999 and 2006, and who had achieved CR1 after one or two courses of induction chemotherapy. Clinical information on over 2,500 patients was collected from 70 institutions across the country. Data from patients with biphenotypic leukemia who were treated with chemotherapy for acute lymphocytic leukemia and those who had extramedullary acute myeloid leukemia without marrow invasion, an extramedullary lesion that did not totally disappear after remission induction chemotherapy or acute promyelocytic leukemia were excluded from the analysis. As patients who relapsed after treatment with conventional chemotherapy alone were analyzed in this study, those who received autologous HCT in CR1 were also excluded.

Statistical analysis

Data were retrospectively reviewed and analyzed as of February 2010. Background differences between two groups were examined with the χ^2 test for categorical variables and the t-test for continuous variables. The primary end-point of the study was overall survival after first relapse. Overall survival from CR1, overall survival and cumulative incidences of relapse and non-relapse mortality from the date of allogeneic HCT were also estimated. The unadjusted probabilities of overall survival were estimated using the Kaplan-Meier product limit method, and 95% confidence intervals were calculated using the Greenwood formula. The log-rank test was used to compare overall survival among different subgroups. The Pepe-Mori test was used to evaluate differences in the cumulative incidence among groups. Overall survival and incidences of relapse and non-relapse mortality were estimated as probabilities at 3 years from the time of the first relapse, allogeneic HCT or CR1. A Cox proportional hazard regression model was used to estimate relative hazard ratios for overall survival, and a risk ratio regression model was used to estimate risk ratios for the achievement of CR2. The following factors were considered as covariates: age, relapse-free interval from CR1, achievement of CR2, application of salvage allogeneic HCT, number of courses of chemotherapy required to achieve CR1, cytogenetic risk according to Southwest Oncology Group,[4] French-American-British cytological classification, white blood cell count, and dysplasia at diagnosis. We considered two-sided *P* values less than 0.05 to be statistically significant. Statistical analyses were performed with the SPSS software package and SAS version 9.1.3 (SAS, Cary, NC, USA).

Results

Patients

Among the 2,029 patients with acute myeloid leukemia who achieved CR1, 494 patients underwent allogeneic HCT in CR1. The remaining 1,535 patients were treated with conventional chemotherapy alone, and 1,015 subsequently relapsed at a median interval of 8.8 months after having attained CR1 (range, 0.3-98.7 months, Figure 1). The median age of those who relapsed was 53 years (range, 16-70 years), and the median follow-up of patients who relapsed was 49 months (range, 5-116 months). As shown in Table 1, there were significant differences in clinical characteristics between patients who underwent allogeneic HCT in CR1 and those who did not, and between patients who relapsed after being treated with chemother-

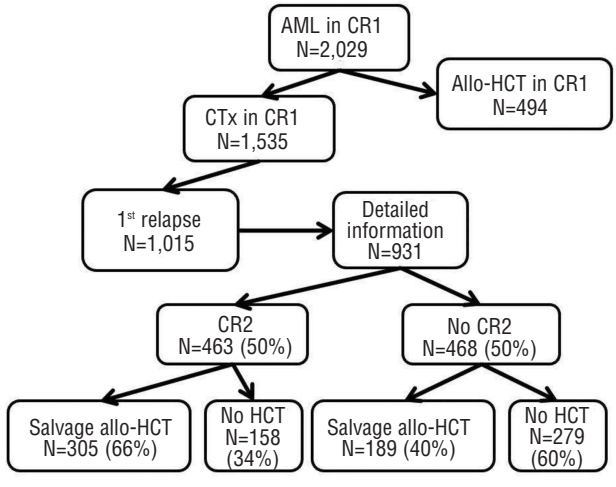

Figure 1. In first complete remission, 494 patients underwent allogeneic hematopoietic cell transplantation (allo-HCT). The remaining 1,535 patients were treated with conventional chemotherapy, and 1,015 of them subsequently relapsed. Of 931 patients for whom detailed information was available, 463 achieved second complete remission, and 305 of them underwent salvage allogeneic transplantation. Among 468 patients who did not achieve second complete remission, 189 underwent salvage allogeneic transplantation.

apy alone and those who did not. As remission induction therapy, 87% of 2,029 patients had received cytarabine- and anthracycline- (daunorubicin or idarubicin) based regimens. The remaining patients were treated with low dose cytarabine-based regimens (5%), BHAC-based regimens (5%), or others (3%). Consolidation therapy was also continued with cytarabine-based regimens with or without maintenance therapy. After first relapse, most patients received cytarabine plus anthracycline-based re-induction chemotherapy at the discretion of their physicians.

Outcome after first relapse

The overall survival of the 1,015 patients who relapsed was 30% at 3 years after first relapse (Figure 2A). Overall

Table 1. Patients' characteristics.

Characteristics	Allo-HCT in CR1	Chemotherapy in CR1			*P* values		
		1st relapse		No relapse[c]			
	n=494 (%)	Allo-HCT[a] n=527 (%)	No allo-HCT[b] n=488 (%)	n=520 (%)	HCT *vs.* CTx in CR1*	Relapse *vs.* no relapse†	HCT in CR1 *vs.* HCT after relapse‡
Age, years median (range)	43 (16-70)	43 (16-70)	60 (16-70)	52 (16-70)	*<0.001*	*0.356*	*0.048*
FAB classification					*<0.001*	*0.007*	*<0.001*
M1, 2, 4, 5	339 (69)	472 (90)	401 (82)	472 (91)			
M0, 6, 7	81 (16)	33 (6)	48 (10)	23 (4)			
Others	74 (15)	22 (4)	39 (8)	25 (5)			
Cytogenetic risk (SWOG)					*<0.001*	*<0.001*	*<0.001*
Favorable	29 (6)	138 (26)	69 (14)	153 (29)			
Intermediate	272 (55)	238 (45)	259 (53)	280 (54)			
Unfavorable	115 (23)	88 (17)	98 (20)	60 (12)			
Unknown	78 (16)	63 (12)	62 (13)	27 (5)			
Remission induction					*<0.001*	*<0.001*	*<0.001*
1 course	340 (69)	432 (82)	376 (77)	468 (90)			
2 courses	154 (31)	95 (18)	112 (23)	52 (10)			
White blood cell count ($\times 10^9$/L)					*0.123*	*0.005*	*<0.001*
≤20	303 (61)	254 (48)	300 (61)	339 (65)			
>20	163 (33)	224 (43)	171 (35)	175 (34)			
Data not available	28 (6)	49 (9)	17 (3)	6 (1)			
Dysplasia					*<0.001*	*0.016*	*<0.001*
No	338 (68)	458 (87)	363 (74)	446 (86)			
Yes	156 (32)	69 (13)	125 (26)	74 (14)			

*CR1: first complete remission; allo-HCT: allogeneic hematopoietic cell transplantation; CTx: chemotherapy. FAB, French-American-British; others of FAB includes refractory anemia with excess blasts in transformation. and others which were not categorized in the FAB classification. *P value of "Allo-HCT in CR1" versus "Chemotherapy in CR1[a+b+c]". †P-value of "1st relapse[a+b]" versus "No relapse[c]". ‡P-value of "Allo-HCT in CR1" versus "Allo-HCT after relapse[a]".*

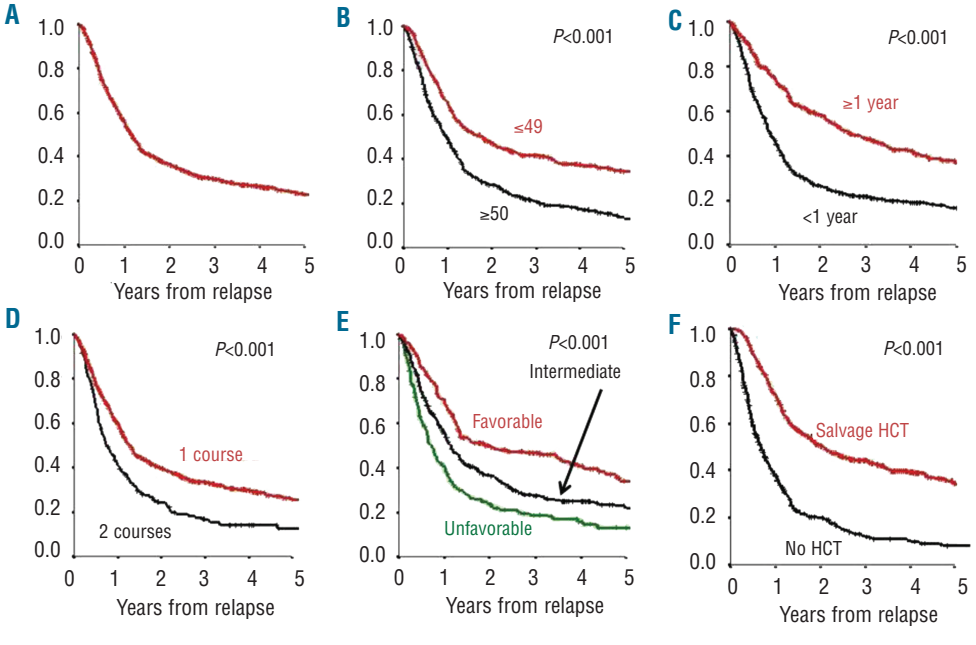

Figure 2. Overall survival after first relapse (A) for the total population, and according to (B) age, (C) relapse-free interval from first complete remission, (D) the number of courses of remission induction chemotherapy to achieve first complete remission, (E) cytogenetic risk according to the SWOG criteria, and (F) application of salvage allogeneic hematopoietic cell transplantation.

survival after relapse was significantly affected by age, relapse-free interval from CR1, the number of courses of chemotherapy required to achieve CR1 and cytogenetic classification (Figure 2B-E).

Salvage allogeneic hematopoietic cell transplantation after first relapse

Among 931 patients for whom detailed information after relapse was available, 463 achieved CR2 (50%, Figure 1) with different probabilities according to the cytogenetic risk [inv(16), 84%; t(8;21), 58%; intermediate, 48%; unfavorable, 31%]. After CR2 had been achieved, 305 patients (66%) underwent salvage allogeneic HCT, of whom 242 (80%) received the transplant while remaining in CR2. On the other hand, 189 (40%) of the 468 patients who did not achieve CR2 underwent salvage allogeneic HCT in non-remission status. Overall, half of the patients underwent salvage allogeneic HCT after their first relapse and had a better overall survival than that of patients who survived at least 2 months after relapse and did not undergo allogeneic HCT (44% *versus* 14% at 3 years from the first relapse, $P<0.001$, Figure 2F).

Comparison of disease status at allogeneic hematopoietic cell transplantation

We compared the outcome after salvage allogeneic HCT to that after allogeneic HCT in CR1. As shown in Table 1, 527 patients who underwent allogeneic HCT after relapse were less frequently associated with unfavorable factors compared to 494 patients who underwent allogeneic HCT in CR1. The source of cells for salvage HCT were HLA-matched related donors (31%), one-antigen mismatched related donors (6%), bone marrow from unrelated donors (40%), or cord blood from unrelated donors (24%). The conditioning regimens were myeloablative (65%, median age: 37 years) or reduced-intensity (35%, median age: 55 years) regimens (*Online Supplementary Table S1*). The source of stem cells was more frequently an unrelated donor, especially in the form of unrelated cord blood, in allogeneic HCT after relapse and there was a slight increase in the use of a reduced-intensity conditioning regimen for these transplants. Overall survival was significantly better after allogeneic HCT in CR1 than after relapse (67% *versus* 51% at 3 years from CR1, $P<0.001$, Figure 3A). This result did not change when patients who relapsed within 2 months of CR1 were excluded from among those who underwent allogeneic HCT after relapse. The statistical difference between the outcomes of the two groups also remained whether the donor was a matched relative or an unrelated donor.

When overall survival was compared in relation to disease status at allogeneic HCT after relapse, patients who underwent their transplant in CR2 had a significantly better overall survival than those who achieved CR2 but subsequently relapsed by the time of the transplant and those who never achieved CR2 (59%, 29%, and 21% at 3 years from HCT, $P<0.001$, Figure 3B). This result led us to compare the outcomes of allogeneic HCT in CR1 and CR2. There was no significant difference in terms of overall survival, non-relapse mortality or relapse after allogeneic HCT between the two groups (overall survival, 64% *versus* 59%, $P=0.090$; non-relapse mortality, 18% *versus* 20%, $P=0.316$; relapse, 22% *versus* 27%, $P=0.061$, Figure 3C, E, and F). The overall survival was also compared

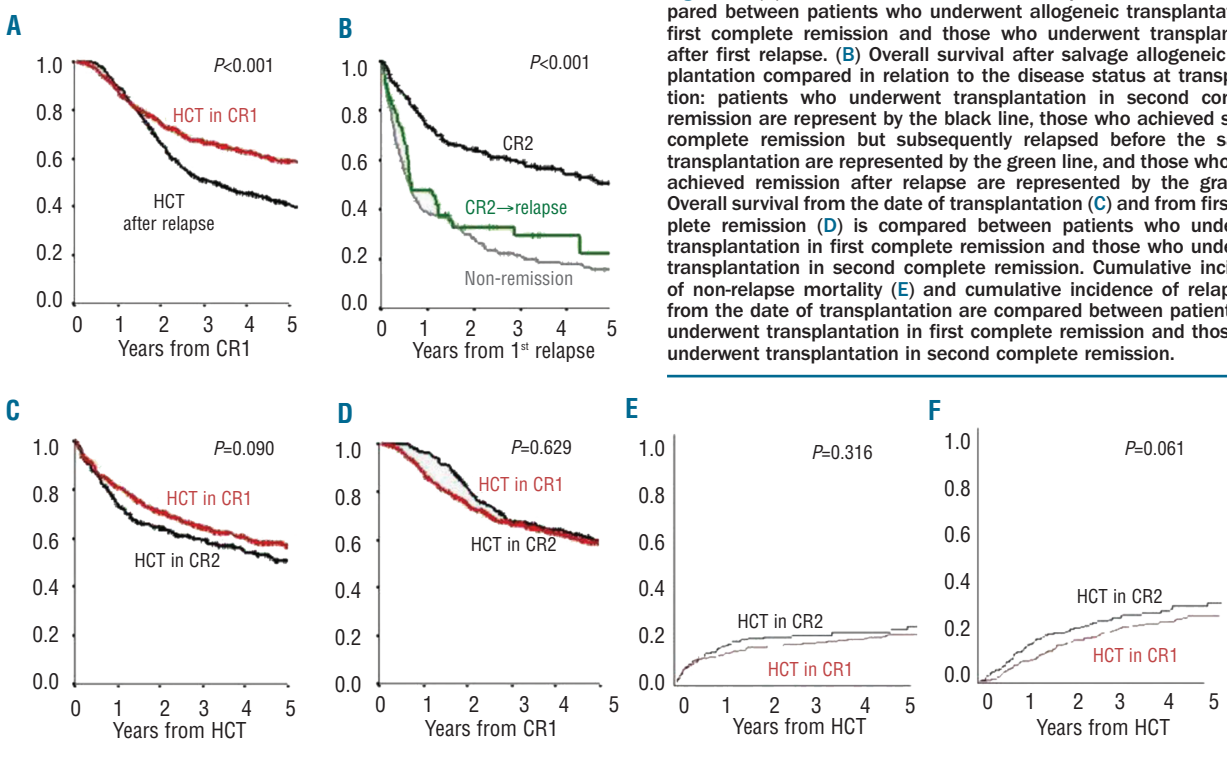

Figure 3. (A) Overall survival from first complete remission is compared between patients who underwent allogeneic transplantation in first complete remission and those who underwent transplantation after first relapse. (B) Overall survival after salvage allogeneic transplantation compared in relation to the disease status at transplantation: patients who underwent transplantation in second complete remission are represent by the black line, those who achieved second complete remission but subsequently relapsed before the salvage transplantation are represented by the green line, and those who never achieved remission after relapse are represented by the gray line. Overall survival from the date of transplantation (C) and from first complete remission (D) is compared between patients who underwent transplantation in first complete remission and those who underwent transplantation in second complete remission. Cumulative incidence of non-relapse mortality (E) and cumulative incidence of relapse (F) from the date of transplantation are compared between patients who underwent transplantation in first complete remission and those who underwent transplantation in second complete remission.

from CR1, and the survival curves were almost identical (67% *versus* 68%, *P*=0.629, Figure 3D).

Treatment strategy after first relapse

We also investigated the outcomes of patients who did or did not undergo subsequent allogeneic HCT after the achievement of CR2 and the effectiveness of allogeneic HCT when CR2 was not achieved or sustained (Figure 4). We divided the 1,015 patients who relapsed into four subgroups according to their cytogenetic risk: a subgroup with inv(16) (n=61), another with t(8;21) (n=139), a subgroup with intermediate risk (n=469) and a subgroup with unfavorable risk (n=177) according to Southwest Oncology Group criteria (cytogenetic risk unknown, n=125; data not available on treatment after first relapse, n=44). Among patients with inv(16), overall survival after

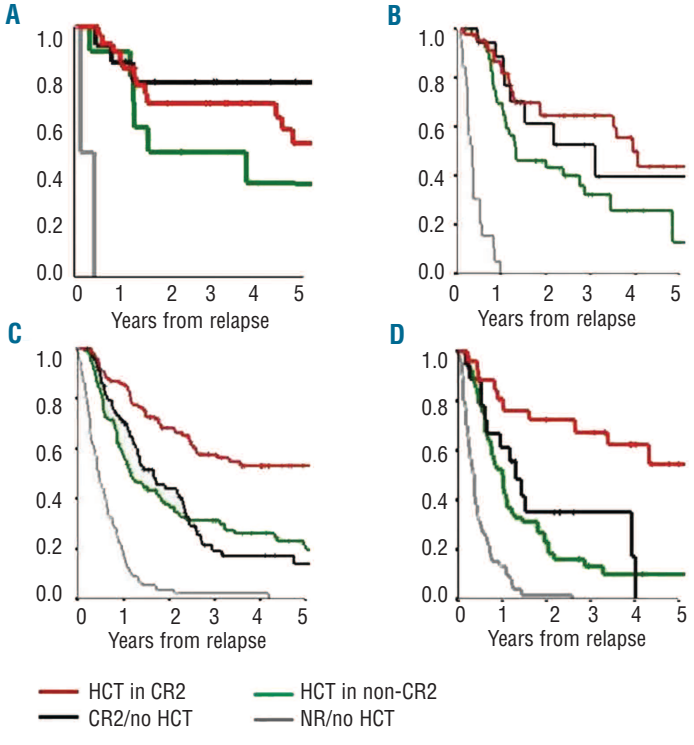

Figure 4. Overall survival after first relapse is shown according to treatment after relapse: allogeneic hematopoietic cell transplantation in second complete remission (HCT in CR2, indicated by red line), no allogeneic transplantation after achievement of second complete remission (CR2/no HCT, black line), allogeneic transplantation in a disease status other than second complete remission (HCT in non-CR2, green line), and no achievement of second complete remission without salvage allogeneic transplantation (NR/no HCT, gray line). *P* values among each of the cytogenetics groups are in the following order: (i) HCT in CR2 *vs.* CR2/no HCT, (ii) HCT in CR2 *vs.* HCT in non-CR2, (iii) HCT in CR2 *vs.* NR/no HCT, (iv) CR2/no HCT *vs.* HCT in non-CR2, (v) CR2/no HCT *vs.* NR/no HCT, (vi) HCT in non-CR2 *vs.* NR/no HCT. (A) inv(16): 3-year overall survival from relapse: HCT in CR2, n=31, 70%; CR2/no HCT, n=14, 78%; HCT in non-CR2, n=13, 50%; NR/no HCT, n=3, 0%; *P* values, (i) 0.415, (ii) 0.280, (iii)<0.001, (iv) 0.130, (v)<0.001, (vi) 0.003. (B) t(8;21): HCT in CR2, n=46, 64%; CR2/no HCT, n=18, 53%; HCT in non-CR2, n=50, 32%; NR/no HCT, n=25, 0%; *P* values, (i) 0.600, (ii) 0.012, (iii) <0.001, (iv) 0.163, (v) <0.001, (vi) <0.001. (C) intermediate-risk acute myeloid leukemia: HCT in CR2, n=109, 58%; CR2/no HCT, n=82, 19%; HCT in non-CR2, 31%, n=129; NR/no HCT, n=149, 2%; *P* values, (i) <0.001, (ii) <0.001, (iii) <0.001, (iv) 0.814, (v)<0.001, (vi)<0.001 (D) unfavorable-risk acute myeloid leukemia: HCT in CR2, n=27, 67%; CR2/no HCT, n=18, 35%; HCT in non-CR2, n=61, 13%; NR/no HCT, n=71, 0%; *P* values, (i) 0.005, (ii) <0.001, (iii)<0.001, (iv) 0.288, (v) <0.001, (vi) <0.001.

Table 2. Multivariate analysis.

Variables	Overall survival			Achievement of CR2		
	Hazard ratio	(95%CI)	*P*	Risk ratio	(95%CI)	*P*
Achievement of CR2 (*versus* Yes)						
No	3.23	(2.65-3.94)	<0.001	-	-	-
Salvage allo-HCT (*versus* Yes)						
No	2.61	(2.10-3.25)	<0.001	-	-	-
Interval from CR1 to relapse (*versus* ≥1 year)						
<1 year	1.80	(1.45-2.23)	<0.001	1.56	(1.37-1.78)	<0.001
Age (*versus* ≤49 years)						
≥50 years	1.15	(0.92-1.44)	0.21	1.04	(0.92-1.19)	0.530
Cytogenetic risk (SWOG, *versus* Favorable)						
Intermediate	1.11	(0.86-1.42)	0.421	1.14	(0.99-1.31)	0.074
Unfavorable	1.34	(1.00-1.78)	0.049	1.64	(1.24-2.17)	<0.001
Unknown	0.93	(0.66-1.32)	0.693	1.05	(0.86-1.27)	0.644
FAB (*vs.* M1, 2, 4, 5)						
M0, 6, 7	1.07	(0.80-1.43)	0.633	1.49	(1.02-2.17)	0.040
Remission induction (*versus* 1 course)						
2 courses	1.23	(1.01-1.52)	0.044	1.27	(1.02-1.59)	0.031
Dysplasia (*versus* No)						
Yes	1.24	(0.97-1.57)	0.084	1.43	(1.09-1.88)	0.011
WBC at diagnosis (*versus* ≤20×10⁹/L)						
>20×10⁹/L	1.08	(0.90-1.29)	0.414	0.88	(0.79-0.98)	0.025

CR2: second complete remission; allo-HCT: allogeneic hematopoietic cell transplantation; CR1: first complete remission; FAB: French-American-British classification.

relapse did not differ significantly between those who underwent allogeneic HCT in CR2 and those who did not undergo allogeneic HCT after achieving CR2 (70% *versus* 78% at 3 years after relapse, P=0.415, Figure 4A). For patients with t(8;21), overall survival probabilities were generally inferior to those of patients with inv(16) (allogeneic HCT in CR2, 64%; no allogeneic HCT after CR2, 53%; allogeneic HCT in non-CR2, 32%; no achievement of CR2 without salvage allogeneic HCT, 0%, Figure 4B). Also in this group of patients, there was no significant difference in overall survival between patients who underwent allogeneic HCT in CR2 and those who did not undergo allogeneic HCT after CR2 (P=0.600). Allogeneic HCT in a disease status other than CR2 provided significantly better survival than no achievement of CR2 without salvage allogeneic HCT (P<0.001).

Among patients with intermediate-risk acute myeloid leukemia, overall survival in those who did not undergo allogeneic HCT after they had achieved CR2 was significantly worse than that in patients who did undergo allogeneic HCT in CR2 (58% *versus* 19% at 3 years from relapse, P<0.001, Figure 4C). We performed subset analyses according to relapse-free interval (≥ 1 year *versus* < 1 year) and the number of courses of remission induction therapy (1 course or 2 courses) among intermediate-risk patients. The performance of allogeneic HCT in CR2 was associated with significantly better overall survival than no allogeneic HCT after the achievement of CR2 or allogeneic HCT in a disease status other than CR2 in all subgroups other than those who required two courses of remission induction chemotherapy (*Online Supplementary Figure S1*). Allogeneic HCT in non-CR2 provided a comparable or better overall survival than no allogeneic HCT after CR2, and a significantly better overall survival than no remission/no allogeneic HCT.

Among patients with unfavorable-risk acute myeloid leukemia, only selected patients who underwent allogeneic HCT in CR2 had an improved overall survival (allogeneic HCT in CR2, 67%; no allogeneic HCT after CR2, 35%; allogeneic HCT in non-CR2, 13%; no achievement of CR2 without salvage allogeneic HCT, 0%, Figure 4D).

Prognostic factors after first relapse

A multivariate analysis showed that the achievement of CR2, salvage allogeneic HCT, a longer relapse-free interval from CR1, a more favorable cytogenetic risk and a single course of induction therapy to achieve CR1 were significantly associated with improved overall survival after relapse (Table 2). Since CR2 was shown to be an important step toward an improved prognosis after the first relapse, we also performed a multivariate analysis to identify factors that may be associated with the likelihood of the achievement of CR2. Except for age, these already-known prognostic factors were found to independently predict the achievement of CR2 with a relatively higher risk ratio in relapse-free interval.

Discussion

In this study, we investigated the prognosis of 1,015 patients with acute myeloid leukemia who relapsed after being treated with conventional chemotherapy during CR1. The independent prognostic factors we identified were achievement of CR2, performance of salvage allogeneic HCT, a relapse-free interval of 1 year or longer, a more favorable cytogenetic risk and achievement of CR1 after a single course of remission induction chemotherapy. Although the outcome of patients who underwent allogeneic HCT after a first relapse were inferior to that of patients transplanted in CR1, we found that a comparable outcome was achieved when allogeneic HCT was successfully performed in CR2. We also found that the outcome according to the treatment strategy after the first relapse varied depending on the patients' cytogenetic risk.

The global overall survival of the 1,015 relapsed patients was 30% at 3 years after the first relapse. The overall survival differed significantly according to factors that have been reported to be prognostic at diagnosis or after relapse. Breems *et al.* presented a prognostic score to predict the outcome of patients with acute myeloid leukemia after first relapse, including patients who relapsed after allogeneic HCT in CR1.[12] They indicated that a longer relapse-free interval, a favorable cytogenetic risk, and younger age were favorable prognostic factors and that the performance of allogeneic HCT before first relapse unfavorably influenced the outcome after relapse. Armistead *et al.* showed that allogeneic HCT was effective in patients with refractory or recurrent acute myeloid leukemia who were stratified into diverse subgroups according to age, relapse-free interval and cytogenetics.[11] In our study, achievement of CR2, performance of salvage allogeneic HCT, a longer relapse-free interval, more favorable cytogenetic characteristics and achievement of CR1 after a single course of remission induction chemotherapy were independent prognostic factors in patients who relapsed after conventional chemotherapy. Our database only consisted of information from patients who successfully achieved CR1 and subsequently relapsed after treatment with chemotherapy alone, which may be one of the reasons why we found slightly different prognostic factors from these found in prior studies. Salvage chemotherapy obtained a CR2 in half of the patients, which was consistent with the previously reported probability.[5]

We found that, overall, allogeneic HCT after first relapse provides an inferior overall survival compared to allogeneic HCT in CR1. This result did not change when we excluded patients who relapsed early after they had achieved CR1. The outcome after salvage allogeneic HCT was significantly affected by the disease status at the time of transplantation. Patients who underwent salvage allogeneic HCT in a disease state other than CR2 had a significantly worse overall survival than those who received the transplant in CR2. Patients who never achieved CR2 may include not only those who received chemotherapy but also those who never received chemotherapy after relapse. Nevertheless, our results may indicate that immediate salvage allogeneic HCT after relapse without an effort to induce CR2 by giving remission induction chemotherapy does not improve the prognosis.

Achievement of CR2 was shown to be a crucial step for an improved outcome after relapse. Additionally, one of the intriguing facts we found was that patients who underwent allogeneic HCT in CR2 had an overall survival that was comparable to that in patients who underwent allogeneic HCT in CR1. For patients who do not have a definite indication for allogeneic HCT in CR1, the likelihood of successfully receiving an allogeneic transplant in CR2 if they relapsed would be invaluable information. However, among the available prognostic factors that are

generally used to predict the ultimate prognosis of acute myeloid leukemia at diagnosis, all of the factors except for age were shown to be independent factors that predicted the achievement of CR2. As a result, it was difficult to clearly define candidates for allogeneic HCT, not in CR1, but rather in CR2 using already-known prognostic factors. These results may suggest the need for further information on how parameters such as WT-1 or other molecular markers behave in acute myeloid leukemia after relapse.

We also investigated the advantage of additional allogeneic HCT after the achievement of CR2 as well as the effectiveness of allogeneic HCT if CR2 was not achieved or sustained. The outcomes were analyzed based on stratification according to cytogenetic risk. We found that the outcome of patients with core-binding factor acute myeloid leukemia who did not undergo additional allogeneic HCT after they had achieved CR2 was comparable to that of patients who did undergo allogeneic HCT in CR2. Over 80% of the patients with inv(16) achieved CR2 with a comparable overall survival regardless of additional allogeneic HCT. Considering the likelihood of the achievement of CR2 and the favorable outcome thereafter, we think that patients with inv(16) may not be indicated for prompt allogeneic HCT in CR2 under close monitoring. Acute myeloid leukemia with t(8;21) has been reported to have a worse prognosis than that with inv(16), as also confirmed in this study.[13-15] Although we did not find a significant improvement in outcome with additional allogeneic HCT after the achievement of CR2 among patients with t(8;21), some patients may have an improved outcome if they are consolidated with allogeneic HCT even after they achieve CR2. Since we do not have detailed information on the chemotherapy after the first relapse or minimal residual disease monitoring, the true indications for allogeneic HCT after the achievement of CR2 in patients with core binding factor acute myeloid leukemia need to be investigated more closely. A molecular profile such as c-Kit mutation may provide more potent prognostic factors.[16-18]

For patients with intermediate-risk acute myeloid leukemia, there was a significant difference in overall survival between those who underwent allogeneic HCT in CR2 and those who did not after they had achieved CR2. Although the molecular profile at diagnosis has been reported to have an effect on the prognosis of patients with intermediate-risk acute myeloid leukemia,[19-21] how these parameters predict the outcome of relapsed acute myeloid leukemia remains to be clarified. Based on our current understanding, consolidation with allogeneic HCT after the achievement of CR2 should be suggested for patients with intermediate-risk acute myeloid leukemia.

Among patients with unfavorable-risk acute myeloid leukemia, only one third achieved CR2. Although allogeneic HCT in CR2 provided an improved outcome after relapse, only 15% of all the patients with unfavorable-risk acute myeloid leukemia who relapsed had a successful HCT in CR2. Since survival is less likely after the first relapse, patients with unfavorable-risk acute myeloid leukemia should be promptly prepared for allogeneic HCT in CR1, as has been demonstrated in many prior studies.[2,4,22-25]

Our results may be susceptible to the disadvantages of any retrospective study, such as the heterogeneity in the treatment strategies chosen at the discretion of physicians. The performance of allogeneic HCT after relapse may include several inherent selection biases such as unfavorable features in those who did not have a chance to undergo transplantation because of disease progression or comorbidity. Our database also lacked detailed information on chemotherapy treatment after achievement of CR1 or after relapse. However, the results we obtained from this large database containing clinical information on patients who were treated with chemotherapy alone or salvage allogeneic HCT after relapse should provide valuable information on this issue which is difficult to evaluate in a prospective, randomized manner.

In summary, using a large amount of retrospectively collected data, we showed that both the achievement of CR2 and the application of salvage allogeneic HCT after relapse are crucial factors in improving the outcome after first relapse. Our results also suggest that the optimal treatment strategy after relapse may differ based on the risk of the disease. Further studies on molecular profiles are needed to stratify the prognosis and treatment strategies for acute myeloid leukemia after first relapse.

Authorship and Disclosures

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