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Comparison of Allogeneic Hematopoietic Cell Transplantation and Chemotherapy in Elderly Patients with Non-M3 Acute Myelogenous Leukemia in First Complete Remission

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The benefits of allogeneic hematopoietic cell transplantation (allo-HCT) for patients with acute myelogenous leukemia (AML) in first complete remission (CR1) have mostly been evaluated in younger patients. Although favorable outcomes of allo-HCT over chemotherapy have been reported with the use of reduced-intensity conditioning (RIC) regimens in elderly patients with AML in CR1, information is still limited, especially on the effects of cytogenetic risks and donor sources. We collected data from AML patients aged 50 to 70 years who achieved CR1, and compared the outcome in 152 patients who underwent allo-HCT in CR1 (HCT group) to that in 884 patients who were treated with chemotherapy (CTx group). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62%). Both overall survival (OS) and relapse-free survival (RFS) were significantly improved in the HCT group (OS: 62% versus 51%, $P = .012$), not only in the whole population, but also in the intermediate-risk group. Among patients who had a suitable related donor, the outcomes in the HCT group were significantly better than those in the CTx group. The introduction of appropriate treatment strategies that include allo-HCT may improve the outcome in elderly patients with AML in CR1.

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KEY WORDS: Acute myelogenous leukemia, Elderly patients, Allogeneic hematopoietic cell transplantation, First complete remission

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INTRODUCTION

The biologic characteristics of acute myelogenous leukemia (AML) change as the patient becomes older, because such patients are more often associated with unfavorable profiles such as antecedent hematologic disorder (AHD), expression of P-glycoprotein in blasts, and unfavorable-risk cytogenetic abnormalities [1-4]. In addition, elderly patients are more likely to have a worse performance status and an increased risk of comorbidities, which makes it difficult for them to undergo aggressive therapies [5,6]. Consequently, the reported probability of achieving a first complete remission (CR1) is lower than that in younger patients. In most previous studies, the duration of remission has been reported to be 6 to 8 months, with a 3-year survival rate of <20% [7-10].

Although allogeneic hematopoietic cell transplantation (allo-HCT) is an effective strategy for decreasing the risk of relapse in younger patients, an increase in the risk of treatment-related toxicity is inevitable. Although >50% of the reported AML patients are 50

years of age or older, most previous studies have investigated treatment strategies that include allo-HCT in related younger donor/patient pairs by allocating treatment options based on donor availability. Over the past decade, several studies showed that allo-HCT with reduced-intensity conditioning (RIC) is acceptably safe and effective in elderly patients [11-18]. Allo-HCT with RIC has also been reported to be superior to conventional chemotherapy in elderly AML patients in CR1, particularly when they have a matched related donor [19,20]. However, most of these studies included small numbers of patients, and there is still limited information available on the effects of risk factors of AML, differences in donor sources, and conditioning regimens. To address these critical questions, we performed a nationwide retrospective survey.

PATIENTS AND METHODS

Data Source

The study protocol was approved by the institutional review board at the National Cancer Center Hospital. The targeted population was adult patients who were diagnosed with AML between 1999 and 2006, aged 50 to 70 years, and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. The diagnosis of AML was determined by the WHO classification and included myelodysplastic syndrome with 20% or more bone marrow (BM) blasts. CR was evaluated according to standard criteria for hematologic CR, which was defined as a normocellular BM aspirate containing 5% or less blasts with normal maturation. The presence of minimal residual disease was not molecularly examined in this study. Among them, patients with acute biphenotypic leukemia who were treated with chemotherapy for acute lymphoblastic leukemia, those who had extramedullary AML without BM invasion or extramedullary lesion that did not totally disappear after remission induction chemotherapy, those with acute promyelocytic leukemia, and those who received autologous HCT in CR1 were excluded from the analysis. Information about the disease risks at diagnosis, clinical course, HLA typing and donor availability during CR1, conditioning regimen, and donor source of allo-HCT were collected. Related donors included an HLA-matched or 1-antigen (Ag)-mismatched related donor. A haploidentical related donor who had 2 or more Ag mismatches was considered as an alternative donor. Unrelated donors included volunteer BM donors with 0 or 1-Ag mismatches and unrelated cord blood with three or less-Ag mismatches. As HLA typing for unrelated BM donors was predominantly performed by matches at serum levels in this era, detailed information on allele-level matches was not completely available.

Statistical Analysis

Data were retrospectively reviewed and analyzed as of December 2009. Background differences between the 2 groups was examined with the chi-square test for categoric variables, and with *t*-test for metric variables. The primary endpoints of the study were relapse-free survival (RFS) and overall survival (OS) from when CR1 was achieved. The unadjusted probabilities of RFS and OS were estimated using the Kaplan-Meier product limit method according to the treatment group, and 95% confidence intervals (CIs) were calculated using the Greenwood formula. To compare RFS and OS between the treatment groups, the log-rank test was used. We performed landmark analyses by excluding patients who died or relapsed within 60 days from CR1 for those who were treated with chemotherapy alone. Cumulative incidences were estimated for relapse and nonrelapse mortality (NRM) to take into account competing risks. The Pepe and Mori's test was used to evaluate the differences between groups. RFS, OS, incidences of relapse, and NRM were estimated as probabilities at 3 years from CR1. Associations between treatment groups and outcome were evaluated using Cox proportional hazard regression models. In addition to whether allo-HCT in CR1 was performed or not, the following factors were considered as covariates: cytogenetic classification according to the Southwest Oncology Group (SWOG), FAB classification, the number of courses of chemotherapy required to achieve CR1, initial white blood cell (WBC) count, and dysplasia at diagnosis. We considered 2-sided *P*-values of $<.05$ 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

Clinical data for around 1300 patients were collected from 67 institutions. After excluding 45 patients who received autologous HCT in CR1 or other ineligible patients as described in Patients and Methods, 1036 were eligible for this study (Table 1). The median follow-up of the surviving patients was 44 months. As a remission induction therapy, 89% of elderly patients had received cytarabine- and anthracycline (daunorubicin or idarubicin)-based regimens. Low-dose cyatarabine-based regimens were performed in 8% of the elderly patients. Consolidation therapy was continued with cytarabine-based regimens with or without maintenaice therapy at the discretion of physicians.

Donor Availability and Consideration of allo-HCT in CR1

Information on HLA typing during CR1 and the availability of related donors was obtained in 953

Table 1. Patient Characteristics

Characteristics	All Patients n = 1036	Allo-HCT in CR1 n = 152 (%)	No HCT in CR1 n = 884 (%)	*P*
Median age				
years, (range)	60 (50-70)	55 (50-70)	61 (50-70)	<.001
Median time from diagnosis to CR1				
days, (range)	40 (26-283)	48 (26-242)	39 (13-283)	<.001
Disease				
M0, 6, 7	102	24 (16)	78 (9)	<.001
AHD	37	19 (13)	18 (2)	<.001
Cytogenetic risks (SWOG)				<.001
Favorable	164	5 (3)	159 (18)	
Intermediate	589	93 (61)	496 (56)	
Unfavorable	166	27 (18)	139 (16)	
Unknown	99	25 (16)	74 (8)	
Remission induction				0.13
2 courses	199	36 (24)	163 (18)	
WBC (/μL)				<.001
Higher than 20,000	335	28 (18)	307 (35)	
Dysplasia				<.001
Yes	268	74 (49)	194 (22)	

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR1, first complete remission; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

elderly patients. Among these patients, HLA typing was performed in 331 patients in CR1 (35%) and these patients were younger than those who did not have their HLA typed during CR1 (median, 56 years versus 62 years) (Table 2 and Figure 1). Patients who had their HLA typed were associated with more unfavorable features, such as unfavorable FAB types, AHD, a requirement of 2 courses of remission induction therapy, dysplasia at diagnosis, and a lower frequency of favorable-risk AML by the SWOG classification. Related donors (HLA-matched and 1-Ag-mismatched related donors) were found in 134 patients (40%). No significant difference was found in the distribution of age and risk factors between patients who found a related donor and those who did not after HLA typing (Table 2). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT during CR1. Among the 197 patients who did not find a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1 (Figure 1).

Patients Who Received allo-HCT in CR1

Of the total 1036 patients, 152 underwent allo-HCT in CR1 (15%). Patients who received allo-HCT in CR1 were younger and associated with more unfavorable characteristics than those who did not (Table 1). As shown in Table 3, 49% of the patients

Table 2. Donor Search and Transplantation

		HLA Check in CR1, n = 331				Statistical Differences		
Characteristics	No HLA Check in CR1 N = 622 (%)	Related Donor Available/HCT+*[a] n = 76 (%)	Related Donor Available/HCT−[b] n = 58 (%)	Related Donor not Available/HCT+[c] n =76 (%)	Related Donor not Available/HCT−[d] n =121 (%)	*P**	*P*†	*P*‡
Age, median, years	62	55	55	55	57	<.001	.396	.906
Disease								
M0, 6, 7	47 (8)	17 (22)	5 (9)	7 (9)	13 (11)	0.008	.170	.160
AHD	11 (2)	4 (5)	2 (3)	15 (20)	2 (2)	<.001	186	.450
Cytogenetic risks (SWOG)						<.001	.561	.045
Favorable	118 (19)	4 (5)	12 (21)	1 (1)	19 (16)			
Intermediate	354 (57)	43 (57)	28 (48)	50 (66)	69 (57)			
Unfavorable	92 (15)	13 (17)	9 (16)	14 (18)	17 (14)			
Unknown	48 (8)	16 (21)	9 (16)	11 (14)	14 (12)			
Remission induction						.009	.541	.871
2 courses	103 (17)	19 (25)	14 (24)	17 (22)	29 (24)			
WBC (/μL)						.021	.178	.004
Higher than 20,000	223 (36)	11 (14)	19 (33)	17 (22)	39 (32)			
Dysplasia						<.001	.991	.117
Yes	127 (20)	31 (41)	16 (28)	43 (57)	26 (21)			

CR indicates complete remission; HCT, allogeneic hematopoietic cell transplantation; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

*P-value of comparing "No HLA check in CR1" versus "HLA check in CR1."

†P-value of comparing "Related donor available[a+b]" versus "Related donor not available[c+d]".

‡P-value of comparing "HCT+[a]" versus "HCT-[b]" among those who had a related donor.

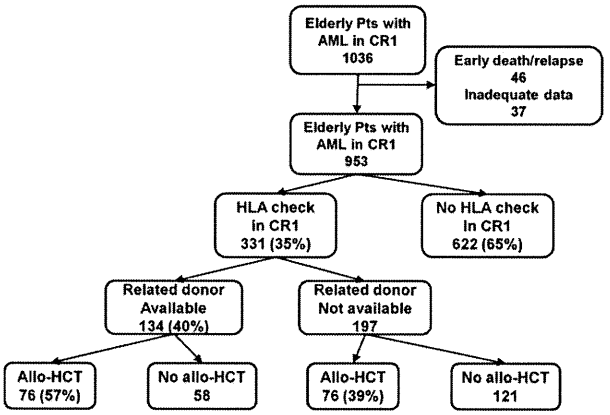

Figure 1. Patient flow. Among 953 patients for whom information was available, HLA typing was performed in 331 patients in CR1 (35%). Related donors were found in 134 patients (40%). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT in CR1. Among the 197 patients without a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1.

received allo-HCT in CR1 from an HLA-matched or 1-Ag-mismatched related donor. The median interval from CR1 to allo-HCT was 139 days. An RIC regimen was given to 93 patients (61%) with a higher median age of 58 years compared to those who received a myeloablative (MA) regimen, 52 years. Extensive chronic graft-versus-host disease (cGVHD) developed in 61 patients (45%) among 135 who lived and had a follow-up period of longer than 100 days.

Comparison of the Outcomes of allo-HCT versus Chemotherapy in CR1

The outcome in patients who received allo-HCT in CR1 (HCT group) was compared to that in patients who did not receive allo-HCT in CR1 (CTx group). Landmark analyses were performed in all subgroups by excluding 46 patients from the CTx group who relapsed or died within 60 days after achieving CR1. In the CTx group, 183 patients ultimately received salvage allo-HCT after relapse (33% of relapsed patients). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62% at 3 years from CR1, $P < .001$) (Figure 2). The cumulative incidence of NRM in the HCT group was higher than that in the CTx group (21% versus 3%, $P < .001$). The 3-year RFS in the HCT group was significantly higher than that in the CTx group (56% versus 29%, $P < .001$). Although the difference between the HCT and CTx groups decreased, the 3-year OS in the HCT group was also significantly higher than that in the CTx group (62% versus 51%, $P = .012$). Multivariate analyses for survival showed that performance of allo-HCT, a single course of induction therapy to achieve CR1, lack of dysplasia, WBC below 20,000/μL at diagnosis, and a more favorable cytogenetic risk were significantly associated with better RFS and OS (Table 4). We also used the Cox proportional hazards model with time-dependent variables after taking into account the time from CR1 to allogeneic HCT. By adjusting the influence of waiting time to allogeneic HCT in this analysis, we found that allogeneic HCT in CR1 was also independently associated with better OS.

In a subset analysis according to the cytogenetic risk, patients with intermediate-risk AML showed the similar trends in relapse, NRM, RFS, and OS to the entire patient population (OS: 67% versus 54%, $P = .024$) (Figure 3A). Among patients with unfavorable-risk AML, 27 received allo-HCT in CR1 and 125 did not. In this group of patients, relapse incidence in the HCT group was also substantial (Figure 3B) (41% at 3 years; 95% CI, 21%-61%), which led to OS that did not differ significantly compared to that in the CTx group (OS: 47% versus 35%, $P = .206$).

We also evaluated the outcome in relation to donor availability (Figure 4). Among 134 patients

Table 3. Characteristics of Transplantation in CR1

Characteristics	Allo HCT in CR1 n = 152 (%)	Median Age, Years (Range)	Median Interval from CR1 to HCT, Days (Range)
Total		55 (50-70)	139 (14-981)
Donor			
Matched related	64 (42)	55 (50-70)	121 (14-574)
1-Ag-mismatched related	10 (7)	57 (50-60)	99 (15-436)
Haplo-identical	3 (2)	51 (50-54)	144 (21-147)
Unrelated bone marrow	52 (34)	55 (50-64)	177 (40-981)
Cord blood	23 (15)	55 (50-67)	127 (14-650)
Conditioning			
Myeloablative			
TBI regimen	16 (11)	52 (50-58)	167 (52-436)
Non-TBI regimen	40 (26)	52 (50-59)	141 (14-361)
Reduced-intensity			
Flu/Bu-based	48 (32)	58 (50-70)	147 (15-574)
Flu/Mel-based	29 (19)	58 (50-66)	126 (14-981)
Others	16 (11)	58 (50-69)	99 (23-304)

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR, complete remission; Ag, antigen; TBI, total body irradiation; Flu, fludarabine; Bu, busulfan; Mel, melphalan.

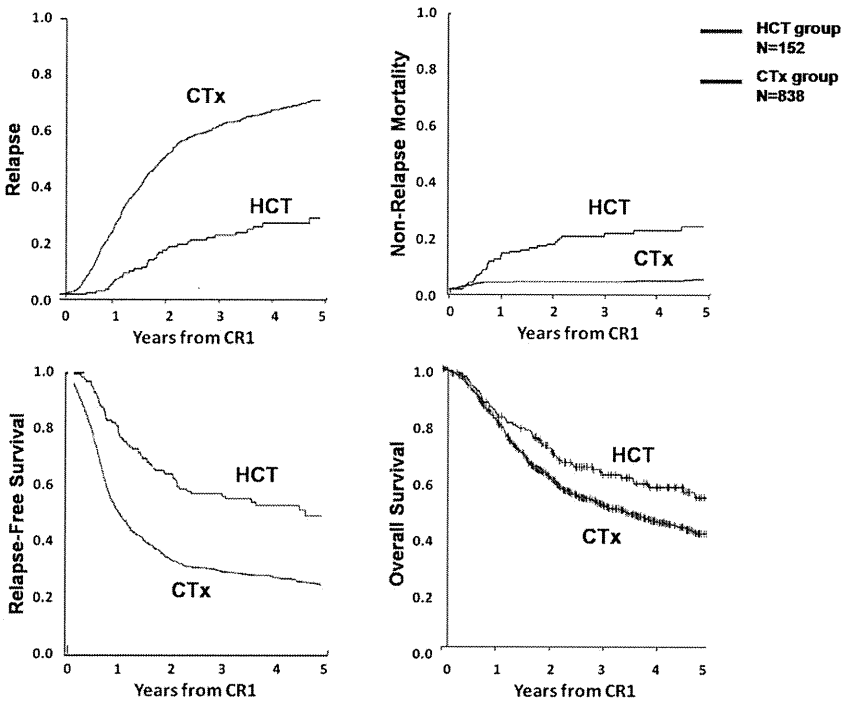

Figure 2. Outcomes according to treatment in CR1 (total elderly patients). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown. Forty-six patients who died or relapsed within 60 days from CR1 were excluded as described in the Statistical Analysis. OS was significantly improved in the HCT group ($P = .012$).

who had a related donor, 76 underwent allo-HCT in CR1. The incidence of NRM among the patients who received allo-HCT from a related donor was 14%, which was significantly lower compared to that observed in the whole HCT group. On the other hand, patients who found a related donor but did not undergo allo-HCT in CR1 had a substantial incidence of relapse (80%; 95% CI, 70%-90%). These results led to significant differences in RFS and OS between the HCT and CTx groups (RFS: 64% versus 11%, $P < .001$, OS: 66% versus 43%, $P = .001$) (Figure 4A). These results did not change when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the CTx group (66% versus 54%, $P = .011$) (Appendix 1-A) or when landmark was extended to 5 months from CR1 for the patients in the CTx group who had a related donor (66% versus 54%, $P = .068$) (Appendix 1-B). We also performed the same comparison limited to intermediate-risk AML patients who had a related donor, and found significant differences between the HCT and CTx groups (RFS: 78% versus

Table 4. Multivariate Analysis

	RFS		OS	
Variables	HR (95% CI)	P	HR (95% CI)	P
Allo HCT in CR1 (versus Yes)				
No	2.58 (1.97-3.37)	<.001	1.81 (1.35-2.42)	<.001
Cytogenetic Risk (versus Favorable)				
Intermediate	1.14 (0.90-1.44)	.283	1.10 (0.84-1.45)	.487
Unfavorable	1.70 (1.28-2.24)	<.001	1.89 (1.37-2.59)	<.001
Unknown	1.62 (1.18-2.23)	.003	1.34 (0.92-1.95)	.132
FAB (versus M1, 2, 4, 5)				
M0, 6, 7	1.25 (1.00-1.57)	.052	1.38 (1.07-1.77)	.014
Remission Induction (versus 1 course)				
2 courses	1.52 (1.26-1.84)	<.001	1.61 (1.31-1.99)	<.001
Dysplasia (versus No)				
Yes	1.21 (0.98-1.48)	.075	1.29 (1.02-1.63)	.033
WBC (versus 20,000 or lower)				
Higher than 20,000	1.29 (1.09-1.54)	.004	1.24 (1.01-1.51)	.038

HR indicates hazard ratio; RFS, relapse-free survival; CI, confidence interval; OS, overall survival; allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; WBC, white blood cell count.

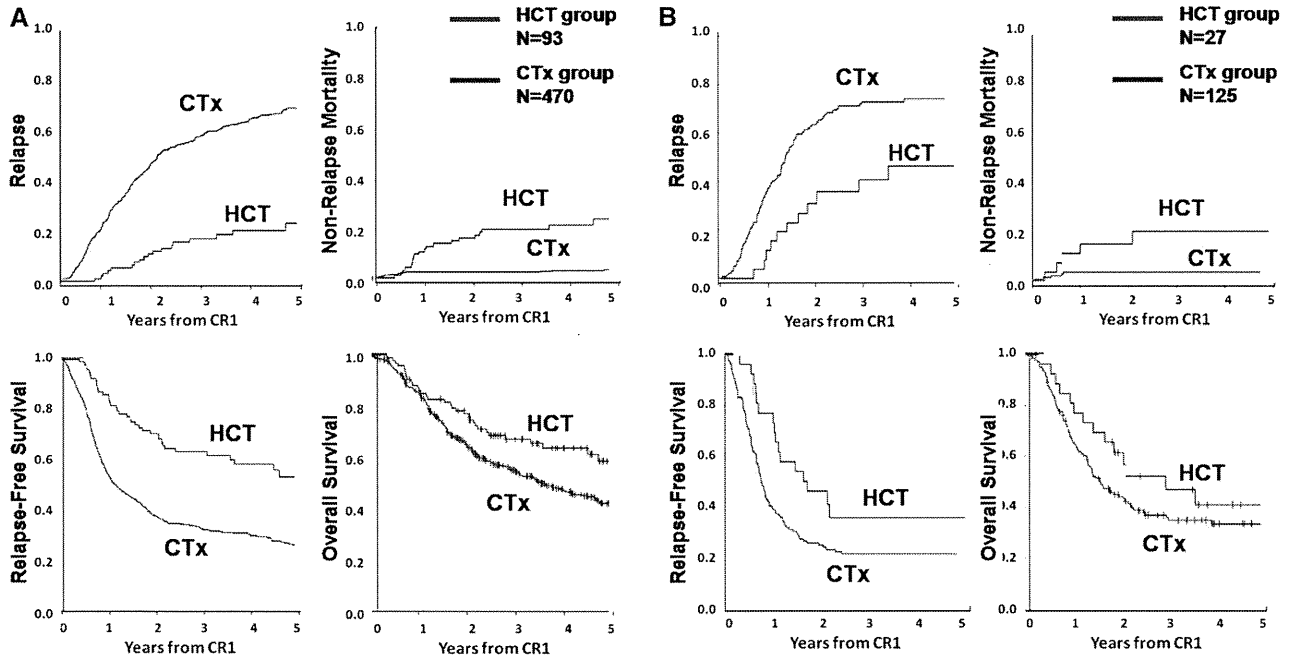

Figure 3. Outcomes according to treatment in CR1 (cytogenetic risks). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) intermediate-risk AML and (B) unfavorable-risk AML. (A) OS was significantly improved in the HCT group among patients with intermediate-risk AML. (B) Relapse incidence was high even after HCT, and OS in the HCT group did not significantly differ from that in the CTx group.

13%, $P < .001$, OS: 78% versus 63%, $P = .048$) (Appendix 1-C).

Among 197 patients who did not have a related donor, 76 underwent allo-HCT from an alternative donor in CR1. Alternative donors included 51 unrelated BM, 22 unrelated CB, and 3 haploidentical related donors. Patients who received allo-HCT in CR1 from an alternative donor had a higher incidence of NRM than those who received allo-HCT from a related donor (28% versus 14% at 3 years, $P = .029$). Additionally, incidence of relapse in allo-HCT from an alternative donor was not reduced compared to that in a related donor transplant setting (22% versus 22%, $P = .743$). Consequently, if we compare the outcomes of the HCT and CTx groups among patients who did not have a related donor, OS did not significantly differ between the two groups (57% versus 47%, $P = .388$) (Figure 4B).

As shown in Table 3, 39% of the patients in the HCT group received an MA regimen. Except for the younger age in those who received an MA regimen, there was no difference in the disease risk between the MA and RIC groups. Additionally, the OS did not significantly differ between the two groups (3-year OS from CR1: 63% versus 61%, $P = .571$) (Appendix 2-A). We also found that OS was not significantly different according to the application of total body irradiation (TBI) (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$) (Appendix 2-B) or among different RIC regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$) (Appendix 2-C).

DISCUSSION

We performed retrospective analyses with a 60-day landmark to compare allo-HCT and CTx in 1036 patients aged 50 to 70 years with non-M3 AML in CR1. The results of this study revealed that, overall, elderly patients with AML who received allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone. Based on cytogenetic subgroup analyses, patients with intermediate-risk AML had a significantly better OS when they received allo-HCT in CR1. On the other hand, patients with unfavorable-risk AML had a higher risk of relapse even after allo-HCT in CR1, which diminished the benefit of allo-HCT. We also observed that patients who had a related donor had a significantly improved outcome when they received allo-HCT in CR1.

Our results that allo-HCT in CR1 provided an improved OS agree with previously reported comparisons of allo-HCT versus chemotherapy in elderly patients with AML in CR1. Mohty et al. [20] performed a retrospective comparison of "donor" versus "no donor" based on their consistent policy of considering allo-HCT with RIC in CR1 when a patient with high-risk AML had an HLA-matched sibling. They reported superior survival rates not only in the "transplant group" compared to the "no transplant group," but also in the "donor group" compared to the "no donor group." Furthermore, Estey et al. [19] reported the first prospective

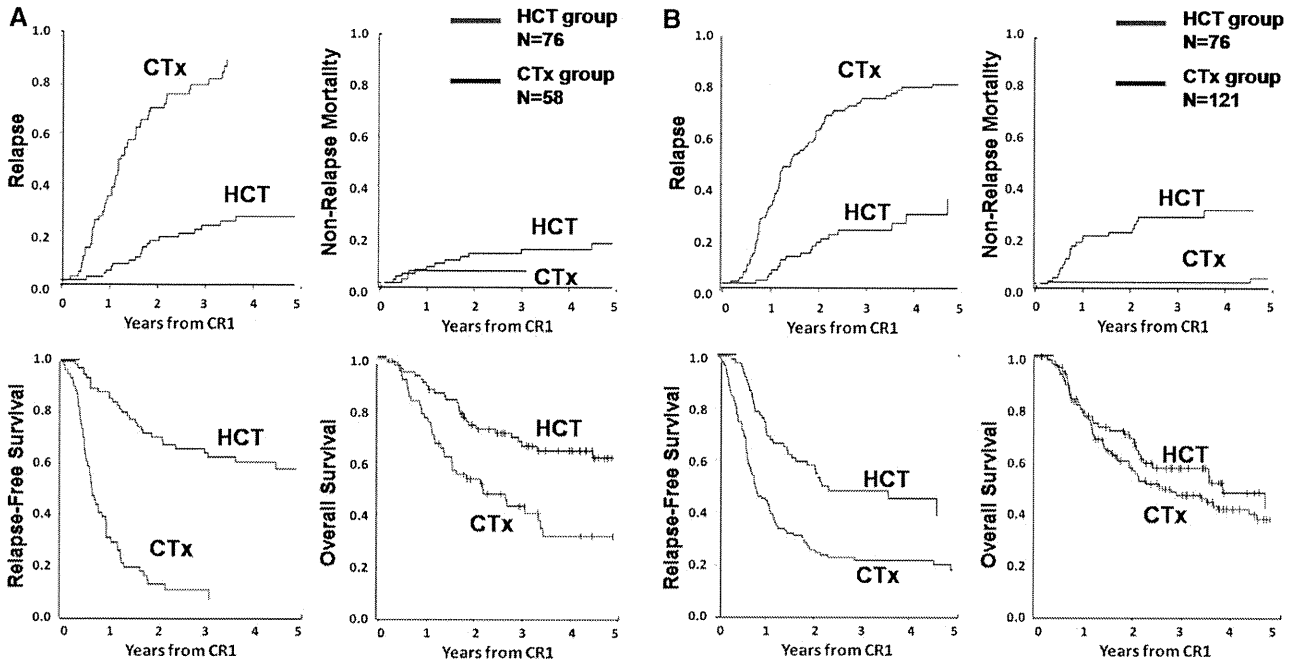

Figure 4. Outcomes according to treatment in CR1 (donor availability). Relapse (upper left), nonrelapse mortality (NRM) (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) patients who had a suitable related donor and (B) patients who did not have a suitable related donor. (A) NRM was reduced in related donor transplant and survival probabilities were significantly improved in the HCT group. (B) OS in alternative donor transplant did not significantly differ from that in the CTx group.

observation of allo-HCT with RIC versus chemotherapy in elderly patients. Although the proportions of patients who were referred for transplantation (54%) and those who actually underwent allo-HCT in CR1 (14%) were relatively small, they presented an encouraging outcome that supported the benefit of allo-HCT.

In elderly patients with intermediate-risk AML, we also found improved OS when they received allo-HCT in CR1. This finding is consistent with the result indicated by a meta-analysis by Koreth et al. [21], although their report mostly included prospective studies that targeted younger patients. No previous studies have reported the effects of cytogenetic risks in the transplant setting for elderly patients. In the intermediate-risk group, we found a 60% relapse incidence at 3 years from CR1 when the patients were treated with chemotherapy alone. We also revealed that the incidence of relapse was reduced by 40% with the use of allo-HCT in CR1 without a significant increase in NRM compared to younger patients, which led to a significant improvement of OS.

Our current study did not show a significant benefit of allo-HCT among patients with unfavorable-risk AML. Although fewer patients were analyzed in this subgroup, which may have led to the unlikelihood of yielding a statistical significance, this result may also be explained by the fact that elderly patients tend to be given less-aggressive chemotherapy before allo-HCT because of concerns about toxicity [7,9]. Because no other realistic option can offer a chance of cure for patients with unfavorable-risk AML, many physicians would consider that allo-HCT is optimal for these patients. However, we clearly need to seek novel strategies to reduce the risk of relapse, for example, by reducing the tumor burden before allo-HCT with more intensified chemotherapy or conditioning regimen, or by prevention of recurrence after allo-HCT by vaccination strategy [22-27]. The role of new drugs such as clofarabine or hypomethylating agents should also be estimated for elderly patients with poor-risk AML who are vulnerable to intensive treatments [28,29].

We observed a markedly reduced incidence of NRM after transplantation from a related donor, which improved the outcome of patients who received allo-HCT in CR1 from a related donor. Among 134 patients who had a suitable related donor, 40% did not undergo allo-HCT during CR1. Unfortunately, the exact reason was not available from our retrospectively collected database. Possible reasons include disease relapse before the anticipated timing for allo-HCT, or failure to receive appropriate therapy because of being too ill. However, an analysis with a landmark extended to 5 months still proved that OS in the HCT group was significantly better compared to that in the CTx group among those who had a related donor.

In contrast to the favorable outcome in the setting of allo-HCT from a related donor, the outcome of allo-HCT from an alternative donor in CR1 was not significantly superior to that of chemotherapy alone. In addition to the significantly higher NRM after alternative

donor transplant, the incidence of relapse was not reduced in the alternative donor transplant compared to that in related donor transplant despite our expectation that a graft-versus-leukemia (GVL) effect would be more potent after allo-HCT from alternative donors. Several reports have indicated that the outcomes of allo-HCT from HLA allele-matched unrelated donors are comparable to those from related donors [14,27]. One possible explanation for this disparity is that patients who received allo-HCT from an alternative donor in our database were significantly more likely to have high-risk AML than those who received allo-HCT from a related donor. Second, HLA typing was predominantly performed serologically in the period of our study. About a third of the patient/donor pairs who are considered to be matched unrelated pairs by a serologic examination have been reported to have an allele-mismatch [30]. In addition, voluntary unrelated donors consisted only of BM donors because peripheral blood harvest is not yet allowed in our country, and unrelated CB accounted for one-third of the alternative donors in our study. Although allo-HCT from an alternative donor was not shown to have a benefit in elderly patients in our study, we may expect a better outcome with a smooth access to an allele-matched unrelated donor.

Whereas prior reports that have compared allo-HCT and chemotherapy in elderly patients targeted only allo-HCT with RIC [19,20], one-third of the HCT group patients in our study received an MA conditioning regimen. However, except for patient age, there were no significant differences in the disease risks between the MA and RIC groups, and OS was similar between the two groups. As has been previously pointed out, there were no significant differences in OS among different RIC regimens [31].

Because our database consists of retrospectively collected clinical data, this cohort of patients may have several inherent selection biases. Although we performed a landmark analysis to eliminate the biases by the patients who did not have a chance to receive allo-HCT in CR1 because of earlier relapse or comorbidity, patients in the HCT group may still have had favorable features that enabled them to successfully reach the point of allo-HCT in CR1. Furthermore, our database did not provide detailed information on consolidation chemotherapy after achievement of CR1 or the reasons why patients did not undergo allo-HCT such as the presence of comorbid conditions. Although the number of the elderly patients who received autologous HCT in CR1 was small, the exclusion of these patients may have made the non-HCT group have even more inherent selection bias, Nevertheless, the results drawn from our database, which includes 850 patients in the CTx group and 150 patients in the HCT group, may allow us to suggest optimal strategies for elderly patients with AML especially stratified by cytogenetic subgroups.

In conclusion, our study indicated that elderly patients with AML who underwent allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone, and also revealed that intermediate-risk AML patients had an improved OS when they underwent allo-HCT in CR1. Because OS was better in elderly patients when they have a matched related donor and successfully undergo allo-HCT in CR1, they should be encouraged to seek the opportunity of allo-HCT in CR1 by performing HLA typing and donor search in the early period after achievement of CR1. Novel strategies to reduce the risk of relapse and better access to allele-matched unrelated donors should further improve the prognosis of elderly patients with AML.

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AUTHORSHIP STATEMENT

Contribution: S.K. designed the study, prepared the data file, performed the analysis, interpreted data, and wrote the manuscript; T.Yamaguchi was primarily responsible for designing the study, data analysis and interpretation of the data; N. Uchida., S.M., K.U., M.W., T. Yamashita., H.K., J. Tomiyama., Y. Nawa., S.Y., J. Takeuchi., K.Y., F.S., N. Uoshima., T. Yano., Y. Nannya, and Y.M. obtained the patients' data and interpreted data; I.M. reviewed the cytogenetic reports and interpreted data; Y.T. interpreted data and helped to write the paper; T.F. was primarily responsible for the entire paper as an accurate and verifiable report.

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APPENDIX: PARTICIPATING CENTERS

National Cancer Center Hospital (Tokyo), Toranomon Hospital (Tokyo), Saiseikai Maebashi Hospital (Gunma), NTT Kanto Medical Center (Tokyo), Fujita Health University (Aichi), Metropolitan Komagome Hospital (Tokyo), Kanagawa Cancer Center (Kanagawa), Metropolitan Bokutoh Hospital (Tokyo), Ehime Prefectural Central Hospital (Ehime), Jikei University (Tokyo), Nihon University (Tokyo), Kurume University (Fukuoka), St. Marianna University Yokohama Seibu Hospital (Kanagawa), Matsushita Memorial Hospital (Osaka), Tokyo Medical Center (Tokyo), University of Tokyo (Tokyo), Sasebo City General Hospital (Nagasaki), Nagasaki University (Nagasaki), Tsukuba University (Ibaraki), Jichi Medical University (Tochigi), Gunma University (Gunma), Teikyo University (Tokyo), Shimane Prefectural Central Hospital (Shimane), Rinku General Medical Center (Osaka), Oakayama Medical Center (Okayama), Miyagi Prefectural Cancer Center (Miyagi), Yokohama City University (Kanagawa), Dokkyo Medical University (Tochigi), Kobe University (Hyogo), Yokohama City University Medical Center (Kanagawa), National Defense Medical College Hospital (Saitama), Sapporo Medical University (Hokkaido), Osaka City University (Osaka), Fukuoka University Hospital (Fukuoka), Saga

Prefectural Hospital Koseikan (Saga), Osaka University (Osaka), Iwate Prefectural Central Hospital (Iwate), Tokushima Red Cross Hospital (Tokushima), Toyama Prefectural Central Hospital (Toyama), Akita University (Akita), Musashino Red Cross Hospital (Tokyo), Kyoto Prefectural University of Medicine (Kyoto), Kawasaki Medical School Hospital (Okayama), University of Yamanashi (Yamanashi), Kyushu Kosei Nenkin Hospital (Fukuoka), Northern Fukushima Medical Center (Fukushima), Okayama University (Okayama), Kagawa University (Kagawa), National Kyushu Cancer Center (Fukuoka), Hirosaki University (Aomori), Hamanomachi Hospital (Fukuoka), Shinshu University (Nagano), Tenri Hospital (Nara), Gifu University (Gifu), Niigata University (Niigata), Hokkaido University (Hokkaido), Tokyo Hitachi Hospital (Tokyo), Kanazawa University (Ishikawa), Yamaguchi University (Yamaguchi), Kumamoto Medical Center (Kumamoto), Mie University (Mie), Koga General Hospital (Miyazaki), St. Luke's International Hospital (Tokyo), Tohoku University (Miyagi), Tokushima University (Tokushima)

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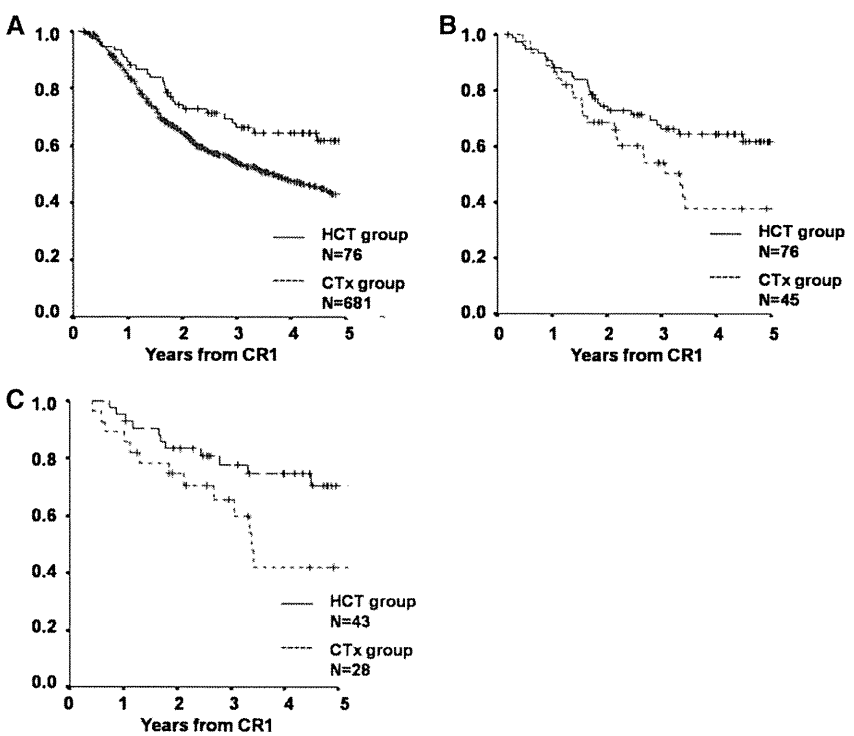
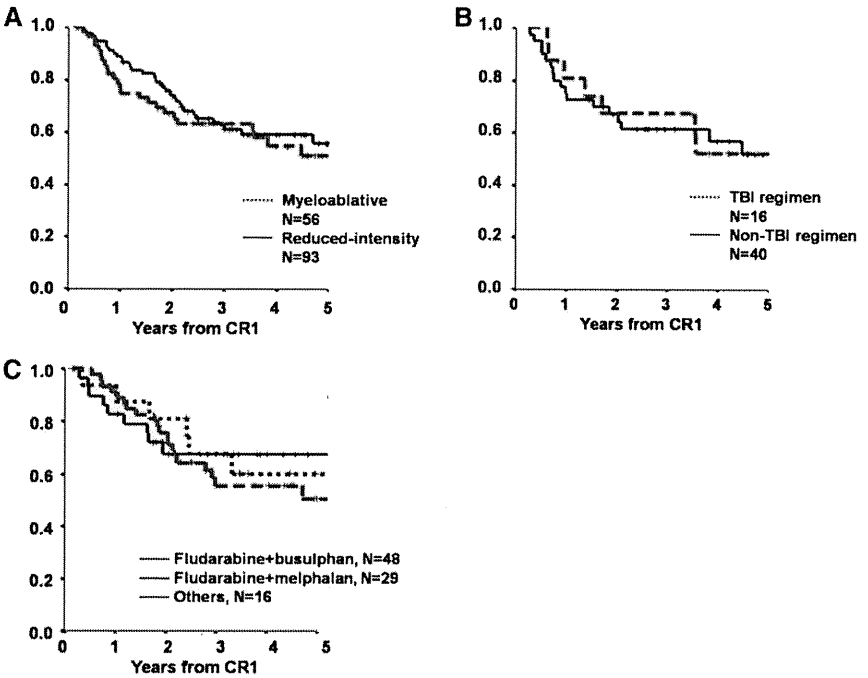


Appendix 1. Overall survival from CR1 are compared between the patients who received allogeneic transplantation in first complete remission and those who did not among the group of patients who had a suitable related donor. (A) Comparison of the two groups when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the chemotherapy group (66% versus 54%, $P = .011$). (B) Comparison of the two groups when landmark was extended to 5 months from CR1 (66% versus 54%, $P = .068$). (C) Comparison of the two groups limited to intermediate-risk AML patients (78% versus 63%, $P = .048$).



Appendix 2. (A) Overall survival (OS) rates from CR1 are compared between myeloablative and reduced-intensity conditioning regimens. There were no significant differences between myeloablative and reduced-intensity conditioning regimens (63% versus 61%, $P = .571$). (B) OS did not differ significantly according to the application of total-body irradiation among patients who received myeloablative regimen (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$). (C) Among patients who received reduced-intensity conditioning regimen, OS from CR1 did not differ significantly among different regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$).

A Markov decision analysis of allogeneic hematopoietic cell transplantation versus chemotherapy in patients with acute myeloid leukemia in first remission

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Various prospective trials have been performed to assess the roles of allogeneic hematopoietic cell transplantation (allo-HCT) and chemotherapy in patients with acute myeloid leukemia (AML) in first complete remission (CR1). However, the results have not always been consistent, and there has been a limited evaluation of quality of life (QOL) in these postremission strategies. We performed a Markov decision analysis that enabled us to compare survival outcomes with a QOL evaluation using a database of 2029 adult AML patients who achieved CR1. The Markov decision model compared 2 strategies: allo-HCT or chemotherapy in CR1. Patients who had intermediate- or unfavorable-risk AML had a longer life expectancy when they received allo-HCT in CR1 than patients treated with chemotherapy alone. Likewise, patients who had a suitable related donor who received allo-HCT in CR1 had a longer life expectancy. The life expectancy was shortened to a greater degree by adjustment for QOL in the allo-HCT group. Nevertheless, QOL-adjusted life expectancies in most of the subgroups remained longer in the allo-HCT group than in the chemotherapy group. Our results showed that older patients with a related donor and younger patients with unfavorable cytogenetics benefited the most from allo-HCT in CR1. (*Blood*. 2011;117(7):2113-2120)

Introduction

Although 60%-80% of patients with acute myeloid leukemia (AML) achieve first hematologic complete remission (CR1) with chemotherapy, a substantial number of patients have an individualized risk of relapse.[1] Allogeneic hematopoietic cell transplantation (allo-HCT) has been established as a powerful treatment method to reduce the risk of relapse in patients with AML. However, this approach still leaves concerns associated with a certain probability of nonrelapse mortality. Although several prospective trials that used genetic allocation have been performed to clarify the roles of postremission strategies, the results have not always been consistent.[2-9] The role of allo-HCT in patients with AML in certain subgroups, including patients with intermediate-risk AML and elderly patients who have remained in CR1, remains unclear. A large meta-analysis that considered many of these prospective studies reported that allo-HCT in CR1 provided survival advantages not only in an unfavorable-risk group but also in an intermediate-risk group.[10] Even with these numerous studies performed in a prospective setting, it is still controversial to simply define allo-HCT as a better decision because of concerns about various late effects such as graft-versus-host disease (GVHD) that might lower the quality of life (QOL) after cure of the disease.

A decision analysis is a statistical technique that is used to help decision making under uncertain conditions with the assumption of a QOL evaluation.[11] When it is combined with a Markov process, it gives a flexible analytical method that makes it possible to track clinical events that occur after a certain decision with different probabilities and desirability over time.[12] This technique can offer valuable information about what clinical decision should be taken by quantitatively integrating the risks and benefits of a certain decision, and, hence, has been widely applied in making decisions in various fields. For example, in the field of hematology, on the basis of the results of a Markov decision analysis, Lee et al[13] reported the indications of allo-HCT for chronic myeloid leukemia in the era before imatinib, and Cutler et al[14] elucidated the recommended timing of allo-HCT for younger patients with myelodysplastic syndrome. Regarding AML, Sung et al[15] reported the results of a decision analysis with a conventional decision tree concerning consolidation strategies for patients in CR1. However, a Markov decision analysis has not yet been reported for postremission strategies in AML in CR1. To address this point, we performed a Markov decision analysis with the use of clinical information collected from 2029 patients.

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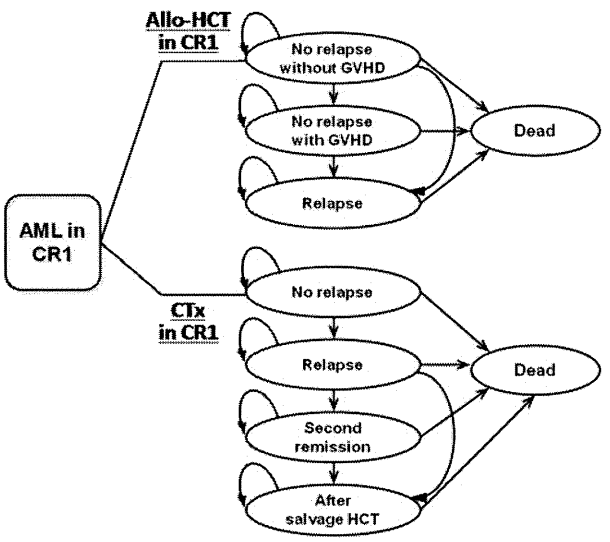

Figure 1. Markov decision model. Markov model that compares allo-HCT in CR1 and chemotherapy in CR1 is shown. Possible health states for each of the 2 groups are indicated in circles. Arrows indicate possible transitions between states. CR1 indicates first complete remission; allo-HCT, allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

Methods

Data source

The study protocol was approved by the Institutional Review Board at National Cancer Center Hospital. We constructed a new database that included the clinical data of adult patients (age 16-70 years) whose conditions were diagnosed as AML by the World Health Organization classification between 1999 and 2006 and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. Clinical information on > 2600 patients was collected from 70 institutions across the country. Patients with biphenotypic leukemia who were treated with chemotherapy for acute lymphocytic leukemia; patients who had extramedullar AML without marrow invasion, an extramedullary lesion that did not totally disappear after remission induction chemotherapy, or acute promyelocytic leukemia; and patients who received autologous HCT in CR1 were excluded from the analysis. Consequently, a total of 2029 patients were considered for this analysis.

Decision strategy

The primary decision examined in this study was whether to perform allo-HCT in patients with AML who remained in CR1. Statistical analyses were performed as of January 2010 with the use of the software package TreeAge Pro 2009 (TreeAge Software Inc) and the SPSS software package (SPSS Inc).

Markov model. We constructed a Markov decision model to compare 2 strategies: performing allo-HCT in CR1 (HCT group) and continuing chemotherapy without allo-HCT in CR1 (CTx group; Figure 1). The possible health states that were considered to occur after each decision/strategy included, for the HCT group, (1) no relapse without GVHD, (2) no relapse with GVHD, (3) relapse, and (4) dead, and for the CTx group, (1) no relapse, (2) relapse, (3) second remission, (4) after salvage allo-HCT, and (5) dead. The "GVHD" state included chronic extensive GVHD. The "dead" state included death from any cause. A schematic of the tree file is shown in supplemental Figure 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article.

State transition probabilities. Transition probabilities between the states were calculated from the information in the database collected for this analysis as described in "Data source." The probabilities of state transition were allowed to vary over time. As a result, patients were distributed in various health states with different proportions along with cycle advances, that is, as time advanced from CR1, as shown in Figure 2. To take into account patients who were unable to receive allo-HCT in CR1 even though they had made a decision to receive allo-HCT, patients who died or relapsed within 3 months from CR1 were excluded from the database when we calculated the probabilities. The cycle length between state transitions has previously been set at the time considered to represent the clinical features and decision-making process for the target disease. In a Markov decision analysis that targeted myelodysplastic syndrome,[14] the cycle length was set at 6 months. In this analysis that targets patients with AML, we chose a shorter cycle length (3 months), and the analysis was performed for 40 cycles (10 years). The results are presented as life expectancy (LE), which is the average duration of life when patients are followed up for 10 years.

QOL utilities. We also assessed QOL-adjusted life expectancy (QALE) for the HCT and CTx groups. The time spent in each health state was adjusted for the estimated QOL that patients experienced while they remained in that state, which was represented by a utility value. In this study, utility values were derived from a questionnaire (supplemental Figure 2) that used a visual analog scale and was presented to 35 physicians who were familiar with the treatment of AML. Among them, 25 were physicians who were mainly involved in transplantation, and 10 were physicians mostly involved in chemotherapy with knowledge of transplantation. The utility values were expressed as numerical values between 0 (a

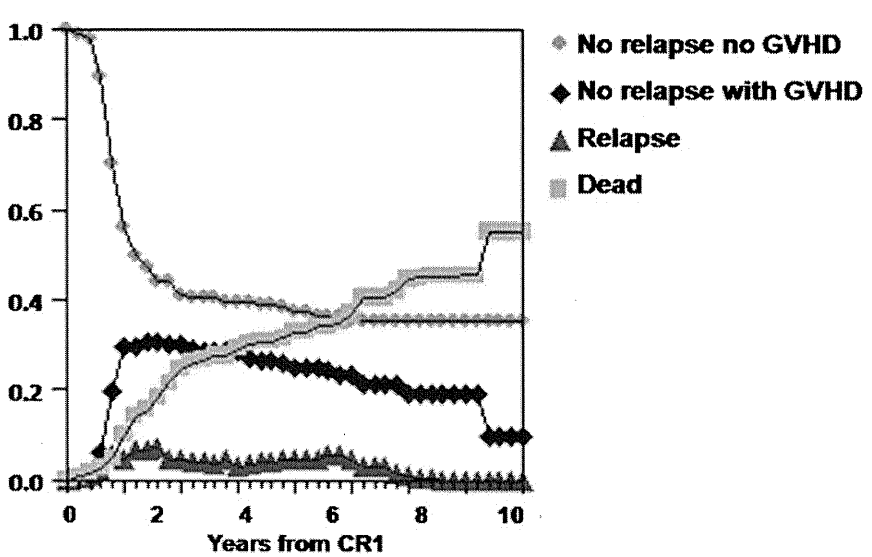

Figure 2. Distribution of patients in each health state. Distribution of patients with intermediate-risk AML in each health state is shown. Transition probabilities between the states were calculated for each subgroup with the use of the database. The probabilities of state transition were allowed to vary along with the cycle (1 cycle = 3 months) advances, depending on the states that the cohorts move from and to. As a result, the patients were distributed in each health state in changing proportions at different times from CR1. GVHD indicates graft-versus-host disease; and CR1, first complete remission.

Table 1. Quality-of-life utilities

	Median	Range
Allo-HCT in CR1		
No relapse without GVHD	0.90	0.60-1.00
No relapse with GVHD	0.60	0.40-0.80
Relapse	0.30	0.20-0.70
Chemotherapy in CR1		
No relapse	0.90	0.80-1.00
Relapse	0.50	0.20-0.80
Second remission	0.80	0.40-0.95
After salvage allo-HCT	0.66	0.10-1.00

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR1, first complete remission; and GVHD, graft-versus-host disease.

health state equivalent to dead) and 1 (perfect health) (Table 1) and were used to adjust for QOL by being multiplied by the expected length of life for each state in each cycle. For long-term survivors who developed chronic extensive GVHD, the utility value was changed on the basis of the previously reported probability of the discontinuation of immunosuppressive treatment.[16,17]

Comparison of HCT with CTx in CR1 and sensitivity analyses. Both LE and QALE were analyzed for the HCT group and the CTx group. LE and QALE, which represent the average expected duration of life in 10-year follow-up from CR1, were obtained from the area under the survival curves depicted by TreeAge Pro software. An annual discount rate of 3% was used for all analyses. Subgroup analyses were performed on the basis of patient age, the Southwest Oncology Group (SWOG) cytogenetic classification,[2] and donor availability. We performed sensitivity analyses to test the robustness of our conclusions. Variable measures that were tested in the sensitivity analysis included the range of patients who were excluded from the database on the assumption that they were unable to receive the decided treatment, the plausible range of QOL utilities, 95% confidence intervals of the state transition probabilities, and the age range of subgroups.

Results

Patients

A total of 2029 patients were eligible for this analysis (Table 2). The median age was 50 years, and the median follow-up of the surviving patients was 49.8 months (range, 0.2-116.3 months). The proportions of patients with favorable, intermediate, unfavorable, and unknown cytogenetic risk according to the SWOG criteria were 19%, 52%, 18%, and 11%, respectively. Therapies performed at CR1 were allo-HCT in 494 patients (24%) and chemotherapy in 1535 patients (76%). The HCT group included all the 494 patients who received allo-HCT in CR1. The median interval from CR1 to allo-HCT was 4.7 months (range, 0-37 months). Among patients who were treated with chemotherapy in CR1, 118 patients who died or relapsed within 3 months were excluded when calculating state transition probabilities on the assumption that they might have decided to receive allo-HCT while they remained in CR1. As a consequence, 1417 patients, including 478 who received allo-HCT after their first relapse, were included in the CTx group (Figure 3). The patients in the HCT group were younger and were more often associated with unfavorable features compared with those in the CTx group. Table 3 and Figure 3 show donor availability and actual application of allo-HCT in CR1. Among 1076 patients for whom human leukocyte antigen (HLA) was typed in CR1, 431 had HLA-matched or 1-antigen (Ag)–mismatched related donors (40%). Donor group included the 431 patients who had a suitable related donor. Among them, 243 actually received allo-HCT in CR1 (related donor, 240; unrelated donor, 3). The no-donor group included the 645 patients who did not find a related donor and 953 for whom HLA was not typed in CR1. Among them, 251 received allo-HCT in CR1 from an alternative donor (unrelated bone marrow, 177; unrelated cord blood, 62; haploidentical related donor, 12). In both the donor and no-donor groups, subgroup analyses were separately performed by comparing patients who received allo-HCT in CR1 (HCT group) and patients who did not (CTx group). Overall survival curves obtained by a Kaplan-Meier estimation of all of the patients registered in our original database stratified according to the SWOG classification and the treatment chosen in CR1 are shown in supplemental Figure 3. Survival curves depicted by TreeAge Pro are shown in supplemental Figure 4.

Markov decision analysis

The discounted LE and QALE for the HCT and CTx groups were analyzed for patients of all ages, younger patients (16-49 years) and older patients (50-70 years; Table 4). In each age group, LE and QALE were analyzed in different cytogenetic subgroups and donor-availability subgroups.

Analysis of all patients. An analysis that included patients of all ages showed that LE in the HCT group was 3 months longer than that in the CTx group (69.7 vs 66.7 months; Table 4). After we adjusted for QOL, QALE in the HCT group was only 0.5 months longer than that in the CTx group (55.9 vs 55.4 months). The LE was generally shortened to a greater degree in the HCT group after adjustment for QOL. This trend was consistent throughout all of the subgroups.

We performed subset analyses according to cytogenetic risk stratified according to the SWOG criteria. Patients with favorable-risk AML in the CTx group had a longer LE than patients in the HCT group. In contrast, patients with intermediate, unfavorable, and unknown-risk AML in the HCT group had a longer LE than patients in the CTx group (intermediate, 73.6 vs 66.4 months; unfavorable, 61.6 vs 53.4 months). Although QALE was shortened to a greater degree in the HCT group, we found that QALE

Table 2. Patient characteristics

Characteristics	Allo-HCT in CR1	CTx in CR1	All patients	P*
No. of patients	494	1535	2029	
Median age, y	42	53	50 (16-70)	< .001
Cytogenetic risks (SWOG)				< .001
Favorable, n (%)	29 (6)	360 (23)	389 (19)	
Intermediate, n (%)	272 (55)	777 (51)	1049 (52)	
Unfavorable, n (%)	115 (23)	246 (16)	361 (18)	
Unknown, n (%)	78 (16)	152 (10)	230 (11)	
FAB				< .001
M1, 2, 4, 5, n (%)	339 (81)	1345 (93)	1684 (90)	
M0, 6, 7, n (%)	81 (19)	104 (7)	185 (10)	
WBC count				.123
≤ 20 000 μ/L, n (%)	303 (65)	887 (61)	1190 (62)	
> 20 000 μ/L, n (%)	163 (35)	570 (39)	733 (38)	
Remission induction courses				< .001
1 course, n (%)	340 (69)	1276 (83)	1616 (80)	
2 courses, n (%)	154 (31)	259 (17)	413 (20)	
Dysplasia				< .001
No, n (%)	337 (68)	1264 (83)	1601 (79)	
Yes, n (%)	156 (32)	268 (17)	424 (21)	

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CTx, chemotherapy; SWOG, Southwest Oncology Group; FAB, French-American-British; and WBC, white blood cell.

*Comparing "Allo-HCT in CR1" with "CTx in CR1."

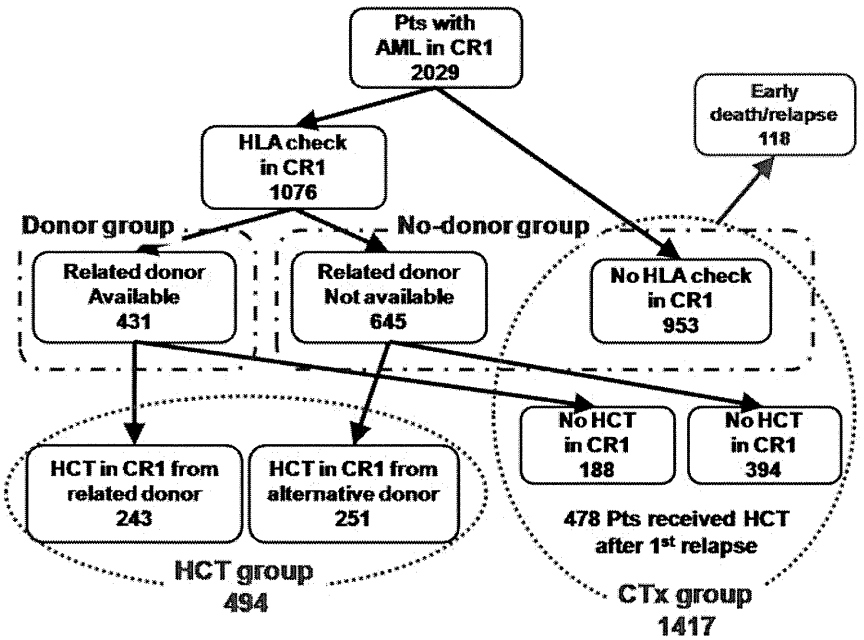

Figure 3. Patient flow. The flow of HLA check, donor availability, and actual application of allo-HCT in CR1 are shown. Among the total of 2029 patients with AML in CR1, 494 received allo-HCT in CR1 and were included in the HCT group. Among the remaining 1535 patients, 118 patients who died or relapsed within 3 months were excluded to take into account patients who were unable to receive allo-HCT in CR1 even though they had made a decision to receive HCT in CR1. Consequently, 1417 patients were included in the CTx group. Among them, 478 received allo-HCT after first relapse. The donor group included the 431 patients who had a suitable related donor. The no-donor group included the 645 patients who did not find a related donor and 953 for whom HLA was not typed in CR1. CR1 indicates first complete remission; and HCT, hematopoietic cell transplantation.

remained longer in the HCT group for all cytogenetic risks except for the favorable-risk group (favorable, 56.0 vs 64.3 months; intermediate, 59.4 vs 55.6 months; unfavorable, 47.6 vs 44.4 months). In the analysis of AML other than favorable risk, patients in the HCT group had a longer LE and a longer QALE than patients in the CTx group (LE, 69.5 vs 62.5 months; QALE, 55.8 vs 52.0 months).

We also performed subset analyses on the basis of the availability of a related donor. Patients who were known to have an HLA-matched or 1-Ag– mismatched related donor (donor group) in the HCT group had a longer LE and a longer QALE than patients in the CTx group (LE, 72.2 vs 63.0 months; QALE, 57.6 vs 49.9 months). However, in patients who did not have a suitable related donor (no-donor group), there were no differences in LE or QALE between the HCT and CTx groups (LE, 67.7 vs 67.0 months; QALE, 54.6 vs 54.4 months). Analyses of the donor and no-donor groups were also conducted with the database whereby the favorable-risk patients were excluded. There was almost no change in LE and QALE in the HCT group (less than a month) compared with the results obtained with the whole database. However, LE and QALE in the CTx group were shortened by several months by excluding the patients with favorable-risk AML from analysis. Consequently, in the donor group, the differences of LE and QALE between the HCT and CTx group increased (LE, 72.0 vs 60.5 months; QALE, 57.2 vs 47.6 months). Meanwhile in the no-donor group, LE and QALE in the HCT group became longer than those in the CTx group (LE, 67.3 vs 64.2 months; QALE, 54.5 vs 52.2 months). Survival curves that compare the HCT and CTx groups in these subgroups depicted by TreeAge Pro software are shown in Figure 4.

Analysis of younger patients. For younger patients, LE and QALE were analyzed with the data from patients aged 16-49 years

Table 3. Donor availability and transplantation in CR1

Characteristics	No HLA check in CR1	HLA check in CR1 (n = 1076)			
		Related donor available/HCT+	Related donor available/HCT–	Related donor not available/HCT+	Related donor not available/HCT–
Total no. of patients	953	243	188	251	394
Cytogenetic risks (SWOG)					
Favorable, n (%)	233 (24)	12 (5)	47 (25)	17 (7)	80 (20)
Intermediate, n (%)	496 (52)	140 (58)	84 (45)	132 (53)	197 (50)
Unfavorable, n (%)	139 (15)	52 (21)	38 (20)	63 (25)	69 (18)
Unknown, n (%)	85 (9)	39 (16)	19 (10)	39 (16)	48 (12)
No. of younger patients, n (%)	257	167	127	175	267
Cytogenetic risks					
Favorable, n (%)	106 (41)	8 (5)	35 (28)	16 (9)	60 (22)
Intermediate, n (%)	101 (39)	97 (58)	55 (43)	82 (47)	125 (47)
Unfavorable, n (%)	30 (12)	39 (23)	27 (21)	49 (28)	50 (19)
Unknown, n (%)	20 (8)	23 (14)	10 (8)	28 (16)	32 (12)
No. of older patients, n (%)	696	76	61	76	127
Cytogenetic risks					
Favorable, n (%)	127 (18)	4 (5)	12 (20)	1 (1)	20 (16)
Intermediate, n (%)	395 (57)	43 (57)	29 (48)	50 (66)	72 (57)
Unfavorable, n (%)	109 (16)	13 (17)	11 (18)	14 (18)	19 (15)
Unknown, n (%)	65 (9)	16 (21)	9 (15)	11 (14)	16 (13)

CR1 indicates first complete remission; HLA, human leukocyte antigen; HCT, allogeneic hematopoietic cell transplantation; and SWOG, Southwest Oncology Group.

Table 4. Discounted life expectancy

	All patients				Younger patients (median age, 35 y)				Older patients (median age, 60 y)			
	LE		QALE		LE		QALE		LE		QALE	
Decision at CR1	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx
Total	69.7	66.7	55.9	55.4	71.4	73.2	57.7	60.2	65.8	60.0	52.1	50.6
Cytogenetic risks (SWOG)												
Favorable	69.6	77.0	56.0	64.3	67.0	82.3	53.8	67.6				
Intermediate	73.6	66.4	59.4	55.6	76.2	75.1	62.0	62.4	68.5	60.7	54.5	51.4
Unfavorable	61.6	53.4	47.6	44.4	62.8	55.3	48.7	44.8	61.6	53.3	46.0	45.0
Unknown	65.6	59.3	54.1	46.8	67.4	68.3	56.3	53.6	63.1	48.8	50.6	38.9
Other than favorable	69.5	62.5	55.8	52.0								
Donor availability												
Related donor	72.2	63.0	57.6	49.9	73.0	67.6	58.3	54.2	73.4	53.2	57.7	40.4
No related donor	67.7	67.0	54.6	54.4	71.0	70.7	57.7	57.2	57.4	57.7	45.4	46.8
Donor availability (other than favorable-risk)												
Related donor	72.0	60.5	57.2	47.6								
No related donor	67.3	64.2	54.5	52.2								

Life expectancies are shown in months.
LE indicates life expectancy; QALE, quality of life–adjusted life expectancy; allo-HCT, allogeneic hematopoietic cell transplantation; and CTx, chemotherapy.

(median 35 years). In the HCT group, LE in younger patients was 6 months longer than that in older patients (71.4 vs 65.8 months). In the CTx group, LE in younger patients was longer than that in older patients by more than a year (73.2 vs 60.0 months).

Younger patients with favorable-risk AML had both a longer LE and a longer QALE in the CTx group than in the HCT group. Allo-HCT in CR1 among younger patients was associated with a longer LE in both the unfavorable-risk group (62.8 vs 55.3 months) and donor group (73.0 vs 67.6 months). After we adjusted for QOL, these patients in the HCT group had a longer QALE than those in the CTx group (unfavorable, 48.7 vs 44.8 months; donor group, 58.3 vs 54.2 months). Younger patients with intermediate-risk AML in the HCT group had a slightly longer LE than those in the CTx group (76.2 vs 75.1 months). However, QALE did not improve when they received allo-HCT in CR1 (62.0 vs 62.4 months).

Analysis of older patients. The outcomes for older patients were analyzed with the data from patients aged 50-70 years (median, 60 years). Older patients who received allo-HCT in CR1 had a longer LE than patients who received chemotherapy in all subgroups, except for the no-donor group (intermediate, 68.5 vs 60.7 months; unfavorable, 61.6 vs 53.3 months; donor group, 73.4 vs 53.2 months). The data available for favorable-risk patients who received allo-HCT in CR1 were insufficient to perform an

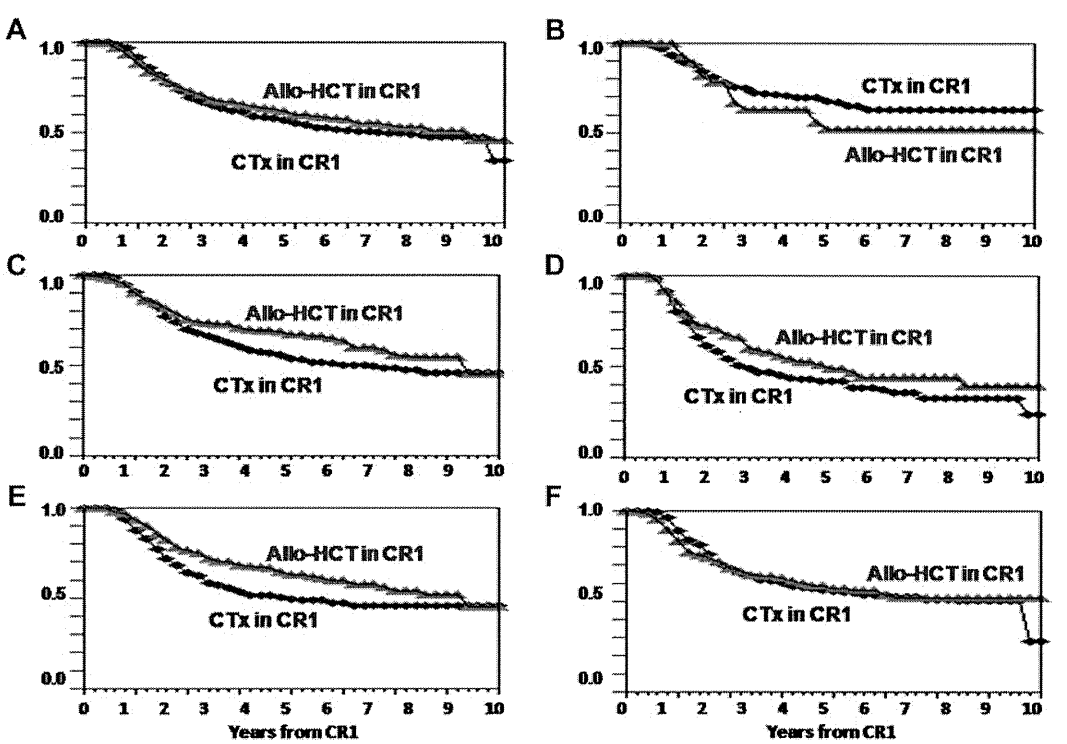

Figure 4. Survival curves of allo-HCT versus CTx by TreeAge. The overall survival curves of the HCT and CTx groups depicted by TreeAge Pro 2009 in (A) total patients, (B) SWOG favorable-risk group, (C) intermediate-risk group, (D) unfavorable-risk group, (E) donor group, and (F) no-donor group. allo-HCT indicates allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and CR1, first complete remission.

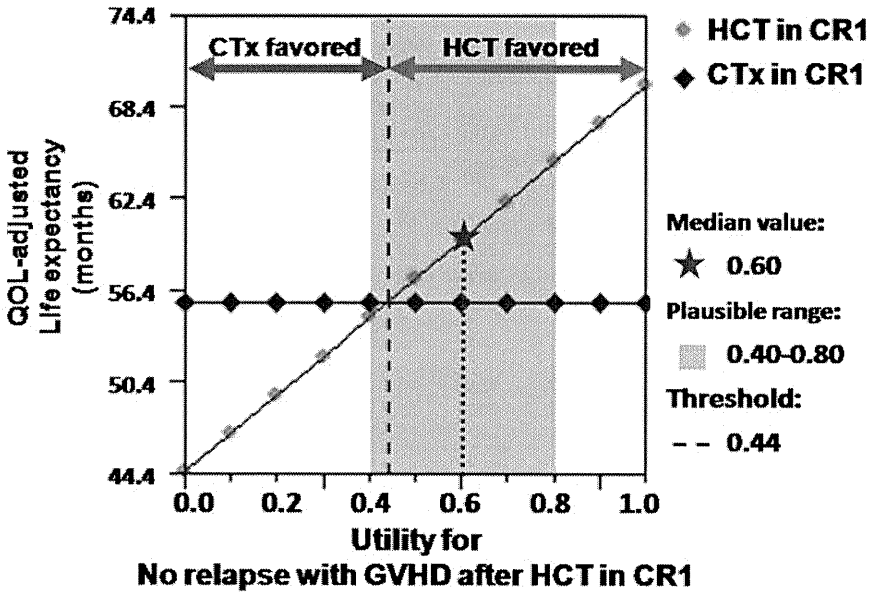

Figure 5. One-way sensitivity analysis. One-way sensitivity analysis for the utility of the state "No relapse with GVHD" after allogeneic transplantation in CR1 among patients with intermediate-risk AML is shown. The green dot represents the QOL-adjusted life expectancy when allo-HCT was performed in CR1. The blue dot represents the QOL-adjusted life expectancy when treated with chemotherapy in CR1. The median value of the utility for this state provided by physicians was 0.60, shown as a red star. At the median value, QOL-adjusted life expectancy in the HCT group is shown to outweigh that in the CTx group. The threshold value at which the favored decision is altered was 0.44, shown as a black dotted line. The plausible range of the utility provided by physicians was 0.40-0.80, shown as a red transparent square. Because the threshold value, 0.44, was included within the plausible range, this sensitivity analysis indicates that this result favoring HCT may be altered, depending on how the QOL of chronic GVHD is evaluated. Such results that favored a decision may change within the plausible range are interpreted as "sensitive." If the plausible range was provided in 0.50-0.80, this result would turn to "not sensitive," indicating that the favored decision does not change. QOL indicates quality of life; CR1, first complete remission; HCT, allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

analysis. Because of the large decrease in LE in the CTx group among older patients, differences in LE between the HCT and CTx groups became more prominent in older patients than in younger patients. Although the difference in the duration of life between the HCT and CTx groups decreased after we adjusted for QOL, we found that older patients in the HCT group had a longer QALE in the intermediate- and unfavorable-risk groups. The difference in QALE between the HCT and CTx groups was most prominent among older patients who had a suitable related donor (donor group, 57.7 vs 40.4 months).

Sensitivity analysis and external validation. Sensitivity analyses were performed for the assumption of "patients who were unable to receive allo-HCT in CR1 despite the decision to perform allo-HCT," the plausible range of QOL utilities (Figures 5-6; supplemental Figure 5), 95% confidence intervals of the state transition probabilities, and the age range. We found that the optimal decisions could be altered in both directions, allo-HCT favored versus CTx favored, by changing the population that was excluded from the database, changing the utility values within the plausible range of physicians' opinions, changing the state transition probabilities within the range of the confidence interval, and changing the cutoff point for the age at which the age subgroups were divided. We also compared the overall survival curves depicted by TreeAge Pro software with the use of our database with those obtained by a Kaplan-Meier estimation as reported in prospective studies from other countries.[2,6] The curves had similar shapes (supplemental Figure 4).

Discussion

We performed a decision analysis that applied a Markov process to evaluate 2 postremission strategies: allo-HCT and CTx in AML in

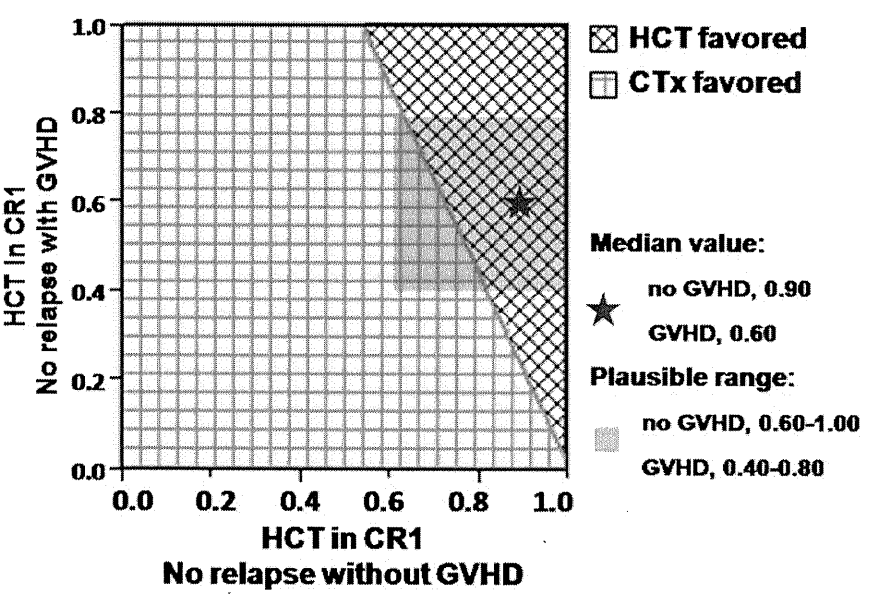

Figure 6. Two-way sensitivity analysis. Two-way sensitivity analysis for the utilities of the states "No relapse without GVHD" and "No relapse with GVHD." The blue area represents the range in which HCT is favored. The green area represents the range in which CTx is favored. Although the median value (0.90 for "without GVHD" and 0.60 for "with GVHD," shown as a red star) indicates that HCT in CR1 is favored, the plausible range (0.60-1.00 for "without GVHD" and 0.40-0.80 for "with GVHD," shown as a red transparent square) overlaps the threshold line. This result is interpreted as "sensitive," which means the outcome is changeable within the plausible range of QOL evaluation provided by physicians. CR1 indicates first complete remission; HCT, allogeneic hematopoietic stem cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

CR1. Our results showed that the LE of patients with intermediate- and unfavorable-risk AML were longer when they received allo-HCT in CR1. We also found that patients who were known to have a suitable related donor had a longer LE in the HCT group. After adjustment for QOL, QALE in most of these subgroups remained longer in patients who received allo-HCT in CR1 than in patients who received chemotherapy.

In subset analyses according to the cytogenetic risk, we showed that favorable-risk patients had a longer LE and a longer QALE in the CTx group, which is consistent with previous reports. However, the results in favorable-risk patients may not be reliable because only a few patients with favorable-risk AML received allo-HCT in CR1 and patients in the HCT group may have had specific reasons (eg, 2 courses of remission induction chemotherapy or antecedent hematologic dysplasia).

In intermediate-risk and unfavorable-risk patients, LE was longer in the HCT group. This result was consistent with that of a large meta-analysis.[10] If we integrate the assumption about the QOL obtained after the 2 strategies using utility values provided by physicians, the LE was shortened to a greater degree in the HCT group. This observation may indicate that there are more concerns about the deterioration of the QOL after allo-HCT than after chemotherapy alone. However, we still found that the QALE was longer in the HCT group, except for younger intermediate-risk patients.

In subset analyses that were based on donor availability, we found that patients who had an HLA-matched or 1-Ag–mismatched related donor had a longer LE and a longer QALE when allo-HCT was performed during CR1. A purposeful delay of allo-HCT has not been fully studied in patients with AML when they have a suitable related donor.[6] This result may recommend that we consider allo-HCT in CR1 rather than wait until after relapse when a suitable related donor is available. LE in older patients who received allo-HCT from a suitable related donor was even comparable to that in younger patients (73.0 vs 73.4 months), which led to a more conspicuous superiority of allo-HCT compared with CTx when older patients had a suitable related donor. In addition, the QALE of older patients with a related donor was 17 months longer in the HCT group than in the CTx group. This result suggests that allo-HCT in CR1 from a suitable related donor for older patients may provide an improved outcome even after we take into account transplantation-related toxicities, which are generally a greater concern among older patients.[18] However, among patients who did not have a suitable related donor, we did not find any advantages of allo-HCT from an alternative donor in CR1 compared with the CTx group. In recent years, the outcomes of allo-HCT from a matched related donor and that from a matched unrelated donor have been reported to be comparable.[19] Because this database included the clinical information of patients treated between 1999 and 2006, most of the unrelated bone marrow (BM) donor sources were selected on the basis of HLA serum matches and not on allele matches. In addition, our database included 1-Ag–mismatched unrelated BM and unrelated cord blood as alternative donors. Regarding the indications for allo-HCT from an alternative donor, further studies may be needed to evaluate whether there is a population that benefits from allo-HCT from well-matched unrelated BM.

The ability to consider QOL is one of the advantages of performing a decision analysis. We adjusted for QOL by applying QOL utility values provided by physicians. Utility values for various health states were obtained over a wide range. This observation may indicate that, even for the same patient, different therapeutic strategies may be chosen at the discretion of the physician. Another reason why the range of utility was broad may be the diverse symptoms and QOL within the same health state, such as the severity of "extensive chronic GVHD."[20,21] Consequently, in our study, sensitivity analyses showed that a better decision with a higher QALE was frequently altered to the other decision within the plausible range of utility values provided by physicians. There were no significant difference between the values provided by transplantation physicians and chemotherapy physicians. However, interestingly, median values of QOL utility in our study were lower than those used in prior analyses performed in North America. For example, although the utility for "no relapse with GVHD" was set at 0.6 (range, 0.4-0.8) in our study, this value was set at around 0.9 in other studies.[13-15,22] This trend was more prominent in the HCT group, which might indicate differences in approaches to estimating the same complications that may be due to ethnicity or differences in the contents of questionnaires.

It might be ideal to evaluate QALE based on QOL utility values obtained from patients who actually live with various disease states.[23,24] However, most prior studies on decision analysis in this field have used utility values provided by physicians.[13-15] Sung et al[15] stated that their utility values provided by physicians were consistent with those provided by patients in the European Organization for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell' Adulto trial.[24] Patients may even give diverse QOL values for a certain health state according to differences in age, background, and philosophy. We believe that a QOL validation by patients is an important issue and is worth being pursued in another study.

Our data surely reflect the nature of a retrospectively collected database, including a diverse heterogeneity in treatment strategies chosen after the achievement of CR1. However, it may be difficult to obtain a database that was collected purely prospectively, especially in patients who were treated with chemotherapy alone. Therefore, we considered that this database, which consists of the clinical information for 2029 patients, was sufficient for us to perform this analysis. Another concern is that, because we collected clinical data on Japanese patients, the application of these results to other ethnic populations needs to be carefully evaluated. However, we have shown that the survival curves obtained from this analysis are similar to those reported in prospective studies from other countries. In decision analysis, the *P* value is not used to show the "significantly" better decision. Sensitivity analysis is a way to investigate the robustness of our conclusions when various parameters are changed within a possible range. It might be difficult to draw a definite conclusion in this study because, as a result of the sensitivity analysis, a favorable decision could be switched to the other decision. Nevertheless, we have been able to show that a decision analysis with a Markov model can be effectively used to evaluate the QOL-adjusted survival outcomes of allo-HCT versus chemotherapy in CR1.

In summary, by using a Markov decision analysis that was based on an original database collected for this study, we have shown that patients with intermediate- and unfavorable-risk AML and patients who had a suitable related donor had a longer LE and a longer QALE when they received allo-HCT in CR1. A subgroup analysis showed that older patients with a suitable related donor benefited the most from allo-HCT in CR1. Although it is clear that both methods of treatment still require improvement, we believe