Table 1 Patient characteristics ($N=173$)

Characteristic	*Imatinib cohort*	*Pre-imatinib cohort*	P
No. of transplantations	51	122	
Age, n (%)			0.048
–39	27 (53)	71 (58)	
40–54	17 (33)	49 (40)	
55–	7 (14)	2 (2)	
Median (range)	38 (15–64)	38 (15–57)	
Gender (male/female)	29/22	73/49	0.717
HSCT donor, n *(%)*			0.460
Related	24 (47)	73 (60)	
Unrelated	21 (41)	43 (35)	
HLA-mismatched related	6 (12)	6 (5)	
Hematopoietic cell source, n *(%)*			0.246
Bone marrow	35 (69)	94 (77)	
Peripheral blood	16 (31)	28 (23)	
Conditioning regimen, n *(%)*			<0.001
CY+TBI	24 (47)	26 (22)	
CY+CA+TBI	14 (27)	37 (31)	
CY+VP+TBI	2 (4)	21 (17)	
CY+TESPA+TBI	—	7 (6)	
CY+BU+TBI	—	6 (5)	
Flu+BU	3 (6)	—	
Flu+ LPAM ± TBI	2 (4)	—	
Others	6 (12)	25 (20)	
GVHD prophylaxis, n *(%)*			<0.001
Cyclosporine + sMTX	24 (47)	95 (80)	
Cyclosporine ± other	3 (6)	3 (2)	
Tacrolimus + sMTX	22 (43)	17 (14)	
Tacrolimus + other	—	4 (3)	
Median days from diagnosis to HSCT (range)	162 (67–512)	182 (66–834)	0.041

Abbreviations: BU, oral busulfan; CA, cytarabine; CY, cyclophosphamide; Flu, fuludarabine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; LPAM, melphalan; sMTX, short-term methotrexate; TBI, total body irradiation; TESPA, tespamine; VP, etoposide.

regimen of total body irradiation followed by cyclophosphamide and/or cytarabine. Five patients aged >55 in the imatinib cohort were given a reduced intensity regimen consisting of fludarabine and melphalan or busulfan. In the pre-imatinib cohort, a combination of cyclosporine (CsA) and short-term methotrexate (sMTX) was mostly used in the prophylaxis of GVHD. On the other hand, both CsA + sMTX and tacrolimus (FK506) + sMTX combinations were commonly used in the imatinib cohort. In both cohorts, none of the patients received imatinib therapy after HSCT in their first CR. In the imatinib cohort, all patients who showed hematologic relapse after HSCT received salvage treatment comprising of imatinib and/or chemotherapy. As for the pre-imatinib cohort, 13 patients relapsed after the approval of imatinib by the Japanese government (beyond December 2001). However, we have no information on how many patients received imatinib-based therapy after their relapse. The median follow-up period for survivors was 2.6 years (range, 1.0–4.6 years) for the imatinib cohort and 6.9 years (range, 0.1–11.4 years) for the pre-imatinib cohort.

Outcome

OS and DFS. In the pre-imatinib cohort, 80 patients died after HSCT: 46 of disease recurrence and 34 of causes other than leukemia. In the imatinib cohort, 35 patients were alive, 32 of them were free of leukemia and 16 patients died after HSCT: 4 of disease recurrence and 12 of causes other than leukemia. The 3-year OS was 65% (95% confidence interval (CI), 49–78%) for the imatinib cohort and significantly higher than 44% (95% CI, 35–52%) for the pre-imatinib cohort ($P=0.0148$; Figure 1a). The 3-year DFS was 58% (95% CI, 41.8–70.9%) for the imatinib cohort and significantly higher than 37% (95% CI, 28.5–45.6%) for the pre-imatinib cohort ($P=0.039$; Figure 1b).

Table 2 shows the result of risk factor analysis for OS and DFS among all 173 patients. In the multivariate analysis, the only variable found to influence OS and DFS was the pre-transplant imatinib-based therapy (hazard ratio (HR) = 0.44 (95% CI, 0.25–0.77); $P=0.004$ and HR = 0.51 (95% CI, 0.31–0.86); $P=0.011$, respectively). The presence of cGVHD showed a tendency of favorable OS and DFS, but did not reach the statistical significance (HR = 0.66 (95% CI, 0.42–1.06); $P=0.085$ and HR = 0.75 (95% CI, 0.47–1.19); $P=0.217$, respectively).

Other outcomes of transplantation

Relapses. In the pre-imatinib cohort, 48 patients relapsed after HSCT with a median of 240 days (range, 42–2302 days).

In the imatinib cohort, 7 patients (3 of 36 with PCR negative and 4 of 12 with PCR positive at HSCT) relapsed after HSCT with a median of 137 days (range, 68–728 days). The estimated cumulative incidence of relapse at 3 years was 15.0% (95% CI, 6.6–26.7%), and significantly lower than that of the pre-imatinib cohort (50.4% at 3 years (95% CI, 39.6–60.2%); $P=0.002$; Figure 1c). Among patients in the imatinib cohort, patients with PCR negative showed significantly lower relapse rate compared with that of PCR positive (10.0% (95% CI, 2.5–23.6%) versus 41.3% (95% CI, 16.9–64.4%) at 3 years, respectively, $P=0.025$).

Non-relapse mortality. In the pre-imatinib cohort, 34 patients died of non-relapse causes at a median of 159 days (range, 5–2094 days) after HSCT. The estimated cumulative incidence of NRM in the pre-imatinib cohort was 28% (95% CI, 20–36) at 3 years (Figure 2a). In the imatinib cohort, 12 patients died of non-relapse causes at a median of 329 days (range, 41–850 days) after HSCT. The 3-year cumulative incidences of NRM were 21% (95% CI, 11–33%; Figure 2a). There were no significant differences between two cohorts ($P=0.265$).

Cause of death. Recurrence of the primary disease was the leading cause of death in both groups: 55% for the pre-imatinib cohort and 25% for the imatinib cohort. In the pre-imatinib cohort, the causes of NRM were organ failure (11%), infection (9%), GVHD (8%), transplantation-associated thrombotic microangiopathy (TMA) (4%), interstitial pneumonia (3%), graft failure (3%) and other causes (6%). In the imatinib cohort, the causes of NRM included infection (19%), bronchiolitis obliterans with organizing pneumonia (13%), TMA (13%), GVHD (13%), organ failure (6%) and other causes (12%).

Graft-versus-host disease. There was no significant difference in the cumulative incidence of Grades 2–4 aGVHD between two cohorts (31% (95% CI, 19–44%) versus 37% (95% CI, 29–46%), $P=0.391$; Figure 2b). The cumulative incidence of cGVHD at 1 year after HSCT was significantly higher in the imatinib cohort than in the pre-imatinib cohort (49% (95% CI, 31–64%) versus 27% (95% CI, 18–37%), $P=0.0261$; Figure 2c).

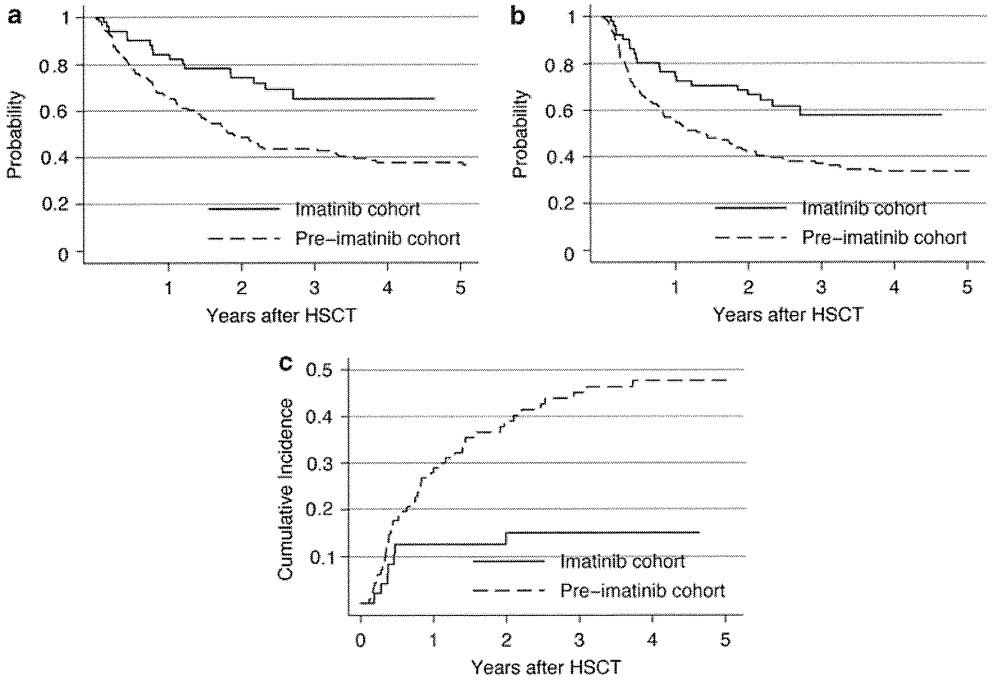

Figure 1 Transplantation outcomes of 51 patients who received imatinib-based therapy and 122 historical patients. (**a**) Overall survival, (**b**) disease-free survival and (**c**) cumulative incidence of relapse.

Table 2 Results of uni- and multivariate analysis of overall survival and disease-free survival among 173 patients with Ph+ALL

Characteristic	*Overall survival*				*Disease-free survival*			
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*		*Multivariate analysis*	
	RR (95% CI)	P	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P
Imatinib-imterim therapy before HSCT	0.45 (0.26–0.77)	0.004	0.44 (0.25–0.77)	0.004	0.51 (0.31–0.83)	0.007	0.51 (0.31–0.86)	0.011
Donor status (RE versus UR)	0.87 (0.57–1.32)	0.521	0.72 (0.40–1.30)	0.275	0.77 (0.51–1.16)	0.211	0.65 (0.37–1.16)	0.147
Age at HSCT (−39 versus 40–55 versus 55−)	1.03 (0.74–1.44)	0.852	1.12 (0.78–1.62)	0.536	0.98 (0.71–1.36)	0.914	1.03 (0.73–1.47)	0.862
HLA-disparity (matched versus mismatched)	0.90 (0.39–2.06)	0.800	0.76 (0.32–1.81)	0.531	1.11 (0.49–2.54)	0.800	1.06 (0.45–2.50)	0.895
Stem-cell source (BM versus PB)	1.15 (0.72–1.82)	0.565	1.23 (0.72–2.10)	0.451	1.30 (0.85–2.00)	0.228	1.34 (0.81–2.20)	0.254
Days from diagnosis to HSCT	1.00 (0.99–1.00)	0.217	1.00 (0.99–1.00)	0.141	1.00 (0.99–1.00)	0.415	1.00 (0.99–1.00)	0.125
cGVHD as time-varying covariate (yes versus no)	0.68 (0.43–1.08)	0.101	0.66 (0.42–1.06)	0.085	0.78 (0.50–1.23)	0.292	0.75 (0.47–1.19)	0.217

Abbreviations: ALL, acute lymphoblastic leukemia; BM, bone marrow; CI, confidence interval; cGVHD, chronic graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hemtopoetic stem cell transplantation; PB, peripheral blood; Ph, Philadelphia chromosome; RE, related; RR, relative risk; UR, unrelated.

However, regarding the cumulative incidence of extensive-type cGVHD, there was no significant difference between two cohorts (22% (95% CI, 10–36%) versus 12% (95% CI, 6–20%), $P=0.119$; Figure 2d).

Association between cGVHD and OS/DFS/relapse. To examine the difference of impacts of cGVHD upon clinical outcome in the pre- and imatinib cohorts, we conducted stratified analysis by cohort, treating cGVHD as a time-varying covariate (Table 3). Multivariate analysis revealed that, in the imatinib cohort, there were no significant associations between cGVHD and OS/DFS/relapse ($P=0.707$, 0.332 and 0.713, respectively). On the other hand, in the pre-imatinib cohort, there was a significant association between cGVHD and OS (HR = 0.59 (95% CI, 0.35–1.00), $P=0.048$), but not between cGVHD and DFS/relapse ($P=0.234$ and 0.338, respectively).

Engraftment. In the pre-imatinib cohort, three patients experienced graft failure. The median periods to reach the neutrophil count of $>0.5\times10^6$/l and platelet count of 50×10^6/l were 15 days (range, 8–49 days) and 25 days (range, 9–120 days), respectively, for evaluable patients. In the imatinib cohort, all 51 patients were engrafted. The median period to reach a neutrophil count of $>0.5\times10^6$/l and platelet count of 50×10^9/l was 15 days (range, 5–41 days) and 25 days (range, 11–504 days), respectively, for evaluable patients. There was no

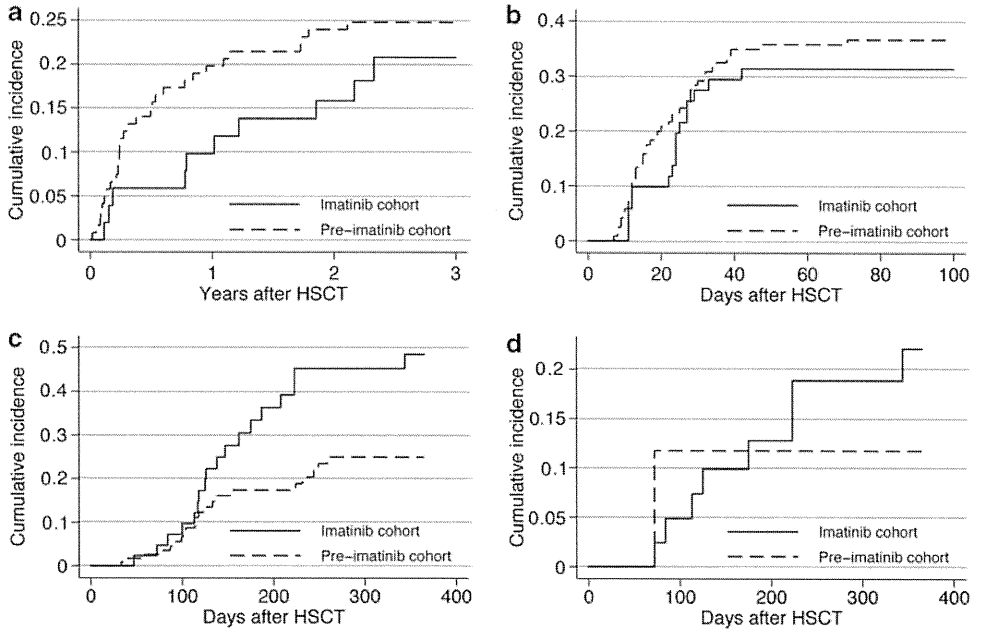

Figure 2 Cumulative incidence of GVHD or NRM. (**a**) Non-relapse mortality, (**b**) Grade 2–4 acute GVHD, (**c**) chronic GVHD and (**d**) extensive-type chronic GVHD.

Table 3 Impact of overall cGVHD on OS, DFS and relapse in multivariate analysis using cGVHD as a time-varying covariate

Cohort	*OS*			*DFS*			*Relapse*		
	Relative risk	*95% CI*	P	*Relative risk*	*95% CI*	P	*Relative risk*	*95% CI*	P
Imatinib cohort	0.80	(0.26–2.51)	0.707	0.59	(0.21–1.71)	0.332	0.74	(0.15–3.67)	0.713
Pre-imatinib cohort	0.59	(0.35–1.00)	0.048	0.73	(0.43–1.23)	0.234	0.75	(0.39–1.44)	0.388

Abbreviations: CI, confidence interval; cGVHD, chronic graft-versus-host disease; DFS, disease-free survival; HLA, human leukocyte antigen; OS, overall survival; PBSC, peripheral blood stem cell.
Data were adjusted for age categories, donors from unrelated subjects, HLA-matching status, PBSC graft and days to transplantation. Cox proportional hazard models were applied to OS and DFS, and a competing risk regression model was applied to relapse.

significant difference in neutrophil and platelet recovery between two cohorts ($P = 0.201$ and 0.783, respectively).

Discussion

This study showed that patients with Ph + ALL who achieved CR by imatinib-based therapy and subsequently received allo-HSCT in their first CR showed significantly superior survival outcome to those in the pre-imatinib era. To our knowledge, our current report is the first to describe the superiority of imatinib-based therapy for this disease by analyzing a substantial number of patients with sufficient follow-up period. The treatment of Ph + ALL has changed dramatically since the introduction of imatinib and >90% of patients have achieved CR,[7,14,15] and allows SCT to be performed in a substantial proportion of patients in major or complete molecular remission.[8,16–18] Actually, in the imatinib cohort, 97 of 100 patients (97%) achieved CR and 60 (60%) could receive allo-HSCT in their first CR. Several studies reported improved OS rates compared with that in the pre-imatinib era by incorporation of imatinib-based therapy.[14,15,19,20] However, there had been few reports focusing on the clinical impact of pre-transplant imatinib administration on the outcome of HSCT. Lee *et al.*[8] reported superior outcome of HSCT by imatinib-based therapy compared with the historical control data, in which 29 patients with prior imatinib treatment showed better outcomes in terms of relapse, DFS and OS than the historical control patients. However, their comparative analysis included patients who received HSCT for refractory disease or beyond their first CR (4 of 29 patients in the imatinib group and 16 of 33 patients in the historical group). Several studies showed that remission status at the time of HSCT was one of the most important prognostic factors for outcome.[21,22] Therefore, we contend that it would be better to assess a greater number of patients and exclude patients with advanced stage at HSCT to accurately compare the clinical impact of imatinib-based therapy on the outcome of HSCT. To our knowledge, this study has the largest number of Ph + ALL patients receiving allo-HSCT in their first CR with the longest follow-up duration yet reported.

It is noteworthy from our findings that a lower rate of relapse was found in the imatinib cohort. Our results thus suggest that an imatinib-based therapy provides a survival benefit for newly diagnosed Ph + ALL patients by lowering the rate of subsequent relapse after HSCT. Despite the lack of comparative data of MRD in the pre-imatinib cohort, 75% of patients in the imatinib cohort achieved RQ–PCR negativity for *BCR/ABL* at the time of HSCT. Moreover, the relapse rate was significantly lower among

patients with PCR negative. From these, we believe that a powerful anti-leukemia activity of the imatinib-based therapy mostly contributed to the prevention of subsequent relapse after HSCT in the present analysis. Thinking of the reduced relapse rate after HSCT, impact of cGVHD should also be considered. Several studies in the pre-imatinib era reported beneficial impact of cGVHD on relapse incidence and survival.[23–25] In this study, the incidence of cGVHD was significantly higher in the imatinib cohort compared with that in the pre-imatinib cohort. In the imatinib cohort, more patients received PB as a stem cell source, which might have contributed to the high frequency of cGVHD. Besides, longer leukemia-free survival period in the imatinib cohort might have contributed to the increased frequency of cGVHD, which is a late complication often observed in the recipients of allo-HSCT who had survived without disease for at least 3 months after transplantation. One could argue that this observation could be related to a stronger graft versus leukemia effect and contribute to the lower relapse rate. However, the presence of cGVHD had no significant impact on the OS/DFS/relapse rate in our imatinib cohort by multivariate analysis.

To assist the proper interpretation of our current results, the strengths and limitations need to be considered. As discussed earlier, one of the strengths of this study is the large sample size for the imatinib cohort, which gives us a better estimation of the end points and also adds statistical power to the analyses. In addition, adjustments for potential confounders in the comparisons with the pre-imatinib cohort from a nationwide registry allow unbiased estimates to be made, at least in Japan. Given the evidence for a substantial impact of imatinib in Ph + ALL patients,[7,14–16] it is unrealistic to conduct a prospective study comparing treatments with or without imatinib. Hence, a retrospective cohort design could be suboptimal to address the key questions.

One of the possible limitations of our current analysis could be the presence of residual confounding factors both of known and unknown. Among the known factors, a difference in the conditioning regimens could be noted. The City of Hope National Medical Center reported a favorable result from the use of a fractionated TBI–etoposide regimen in the treatment of Ph + ALL.[26] However, in the comparative analysis, the clinical advantage of this approach seemed to be established mostly among patients transplanted in their second CR.[27] Moreover, this approach was commonly applied in our pre-imatinib cohort rather than in the imatinib cohort (22 and 4%, respectively). Differences in GVHD prophylaxes should also be considered. Tacrolimus was more frequently used in the imatinib cohort than in the pre-imatinib cohort, which reflects the change in practice within the field of allo-HCT in Japan as tacrolimus was widely used for unrelated allo-HSCT since 2000. Nevertheless, the lack of any differences in the incidence of aGVHD between two cohorts indicates that this factor had minimal impact in our analysis.

It may be argued that the improved outcome of the imatinib cohort have been influenced by the pre-transplant chemotherapy in the JALSG Ph + ALL 202 study. Although detailed information on the pre-transplant chemotherapy in the pre-imatinib cohort was not available, it was clear that the majority of patients were most likely treated by the JALSG ALL93 or JALSG ALL97 protocols as pre-transplant chemotherapy,[2] as these were widely used regimens in Japan at the time. The chemotherapeutic regimen in the JALSG Ph + ALL202 study was similar to those used in these protocols. Thus, the effectiveness on Ph + ALL would have been similar between the two cohorts. At least in JALSG, there had been neither remarkable progress in the chemotherapy of Ph + ALL until the clinical introduction of imatinib, nor in other groups including the MD Anderson Cancer Center.[28] Thus, in the present analysis, the influence of pre-transplant chemotherapy appears to be quite limited.

The difference of transplant year between the two cohorts (1995–2001 and 2002–2005, respectively) could have affected the outcome of HSCT, and the improvement of transplantation procedure might have contributed to the favorable outcome in the imatinib cohort. However, Nishiwaki *et al.*[29] analyzed the clinical outcome of 641 Japanese patients with Ph-negative ALL who had received allo-HSCT in their first CR in 1993–1997, 1998–2002 and 2003–2007, and reported that there was no statistical difference in OS and NRM between three periods. In this study, the incidence of NRM was lower in the imatinib cohort, but did not reach the statistical significance. Therefore, the influence of transplantation year is thought to be limited in this study.

Considering potential benefit by imatinib, the lack of information about post-transplant imatinib use in the pre-imatinib cohort might have led us to underestimate the difference between two cohorts.

In conclusion, we have found that there is a significant improvement in the OS and DFS of Ph + ALL patients who received allo-HSCT following imatinib-based therapy. Although further validation using larger cohorts from different populations is essential to confirm our findings, imatinib-based therapy is likely to be a useful strategy for not only giving patients with Ph + ALL more chance to receive allo-HSCT, but also for improving their outcome after allo-HSCT.

Conflict of interest

Dr Naoe has received research funding and honoraria from Novartis Japan. Dr Ohnishi has received research funding from Novartis Japan. Dr Miyazaki has received honoraria from Novartis Japan. The remaining authors declare no conflict of interest.

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ORIGINAL ARTICLE

A decision analysis of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission who have an HLA-matched sibling donor

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Clinical studies using genetic randomization cannot accurately answer whether adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) who have a human leukocyte antigen (HLA)-matched sibling should undergo allogeneic hematopoietic stem cell transplantation (HSCT) or chemotherapy in first remission, as, in these studies, patients without a sibling donor undergo alternative donor transplantation or chemotherapy alone after a relapse. Therefore, we performed a decision analysis to identify the optimal strategy in this setting. Transition probabilities and utilities were estimated from prospective studies of the Japan Adult Leukemia Study Group, the database of the Japan Society for Hematopoietic Cell Transplantation and the literature. The primary outcome measure was the 10-year survival probability with or without quality of life (QOL) adjustments. Subgroup analyses were performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior in the whole population (48.3 vs 32.6%) and in all subgroups. With QOL adjustments, a similar tendency was conserved (44.9 vs 31.7% in the whole population). To improve the probability of long-term survival, allogeneic HSCT in first remission is recommended for patients who have an HLA-matched sibling.
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Introduction

With modern intensive chemotherapy, 74–93% of adult patients with acute lymphoblastic leukemia (ALL) achieve complete remission. However, the overall survival rate is only 27–48% because of the high rate of relapse.[1] Therefore, the establishment of optimal postremission therapy is important. The efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) for adult patients with ALL in first remission has been demonstrated through clinical studies using genetic randomization, in which patients with a human leukocyte antigen (HLA)-matched sibling donor were allocated to the allogeneic HSCT arm, and those without a donor were placed in the chemotherapy or autologous transplantation arm. First, the LALA-87 trial showed that overall survival in patients with a donor was better than that in patients without a donor in a subgroup analysis of patients with high-risk characteristics.[2] A meta-analysis of seven similar studies confirmed that the donor group was superior to the non-donor group in patients with high-risk ALL in first remission.[3] However, such genetic randomization studies cannot accurately answer the question of whether patients with an HLA-matched sibling should undergo allogeneic HSCT or chemotherapy in first remission. In these studies, patients without a sibling donor had to choose transplantation from an alternative donor or chemotherapy alone once they had a relapse. The outcome of these treatments has been reported to be inferior to that of HSCT from an HLA-matched sibling donor in patients with relapsed ALL; therefore, the expected survival after the decision to continue chemotherapy in first remission in patients without a sibling donor is assumed to be originally poorer than that in patients with a sibling donor. However, it is practically difficult to perform a clinical trial in which patients with an HLA-matched sibling in first remission are randomly assigned to receive allogeneic HSCT or chemotherapy alone. Another important problem has been poor compliance with the assigned treatment in some studies. In addition, previous genetic

randomization studies did not consider the quality of life (QOL), especially that associated with graft-versus-host disease (GVHD). Therefore, we performed a decision analysis incorporating QOL adjustments using a decision tree based on the results of Japan Adult Leukemia Study Group (JALSG) prospective studies (ALL93[4] and ALL97[5]), the database of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)[6] and literature. Patients with Philadelphia chromosome (Ph)-positive ALL were not included in our analysis because the outcome of treatment in these patients has improved dramatically since tyrosine kinase inhibitors became available.[7]

Recently, the Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) trial demonstrated the efficacy of allogeneic HSCT in ALL patients and in standard-risk patients, but not in high-risk patients,[8] which was inconsistent with previous studies. This difference might partly depend on the definition of high-risk patients. In the MRC/ECOG study, an age of higher than 35 years was considered to be a high-risk factor. Therefore, we performed separate subgroup analyses according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years.

Methods

Model structure

We constructed a decision tree (Figure 1) to identify the optimal treatment strategy for adult patients with Ph-negative ALL in first remission who have an HLA-matched sibling.[9,10] The square at the left represents a decision node. We can decide to either proceed to allogeneic HSCT or continue chemotherapy in first remission. We did not include a decision to perform autologous HSCT, as autologous HSCT has not been shown to be superior to chemotherapy alone in a meta-analysis.[3] Circles, called chance nodes, follow each decision, and each chance node has two or three possible outcomes with a specific probability called the transition probability (TP). Every branch finally ends with triangles, called terminal nodes, and each terminal node has an assigned payoff value, called utility, according to different health states. Calculations were performed backward, from right to left in the decision tree. The sum of the products of TPs and utilities of the branches becomes the expected value for each chance node, and eventually the sum of the expected values in all of the chance nodes following the decision nodes becomes the expected value of each decision. The following analyses were performed using TreeAge Pro 2009 software (Williamstown, MA, USA). This study was approved by the Committee for Nationwide Survey Data Management of JSHCT, and the Institutional Review Board of Jichi Medical University.

Data sources

Outcomes after continuing chemotherapy in first remission were estimated from JASLG studies (ALL93 and ALL97). Patients with Ph-negative ALL, aged 15–54 years, were included, and those who never achieved remission with chemotherapy were excluded. Data from 122 patients in ALL93 and 119 patients from ALL97 were analyzed separately, and then combined by weighting the number of patients. Outcomes after allogeneic HSCT in various disease statuses were estimated from the database of the JSHCT. Patients with Ph-negative ALL, aged 16–54 years, who underwent a first myeloablative allogeneic HSCT from a serologically HLA-A, -B, -DR loci-matched sibling between 1993 and 2007 were included. Of them, 408, 61, 14 and 94 patients were in first remission, second remission, third or later remission and non-remission, respectively, at allogeneic HSCT.

The characteristics of the patients included in this study are summarized in Table 1. There was no significant difference in their baseline characteristics. To determine the following TPs,

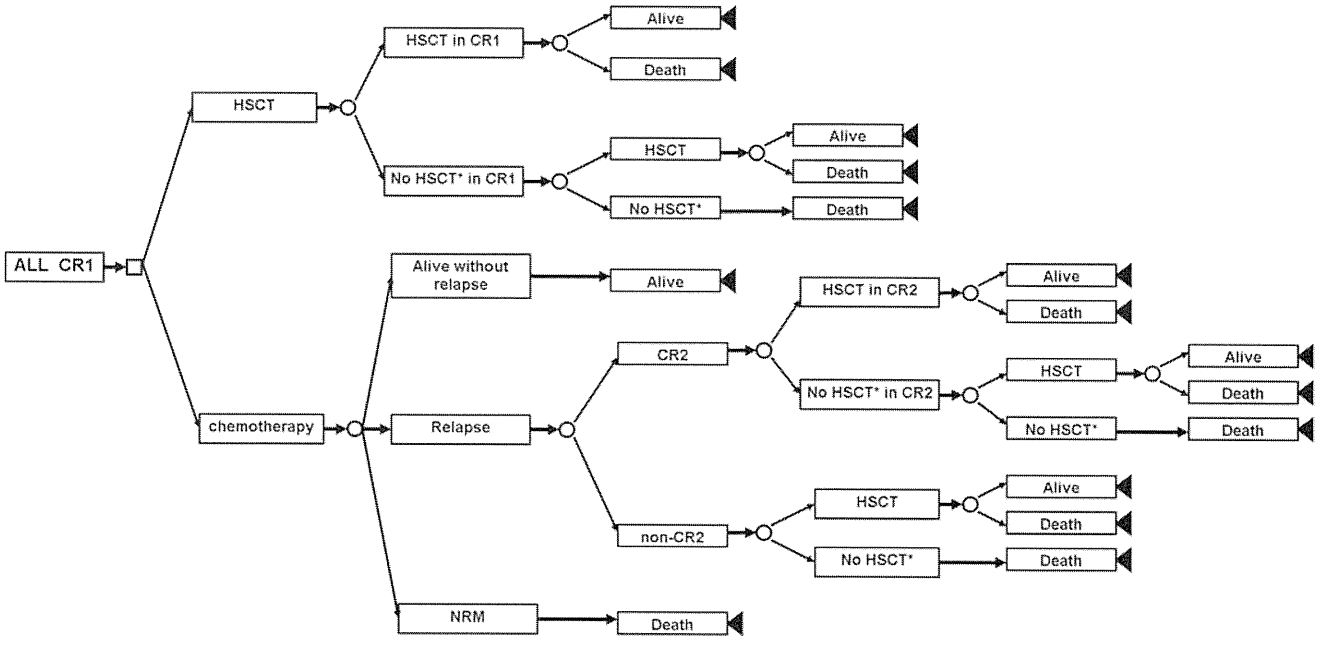

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic GVHD. *HSCT was not performed because of early relapse, death and so on. ALL, acute lymphoblastic leukemia; CR, complete remission; NRM, non-relapse mortality.

Table 1 Patient characteristics in the three data sources

	Chemotherapy in CR1		*HSCT in CR1*	P[a]
	JALSG ALL93	*JALSG ALL97*	*JSHCT*	
No. of patients	122	119	408	
Median age (range)	26 (15–54)	26 (15–54)	29 (16–54)	0.72
No. of males/females	72/50	54/65	230/178	0.06
Median WBC count at diagnosis (range) ($\times 10^9$/l)	9.5 (0.6–468.0)	10.2 (0.3–398.0)	10.4 (0.4–801.0)	0.91
Karyotype standard:high[b], ratio	20:1	30:1	15.4:1	0.55

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; JALSG, Japan Adult Leukemia Study Group; JSHCT, Japan Society for Hematopoietic Cell Transplantation; WBC, white blood cell.
[a]Statistical analyses were performed using the Kruskal–Wallis test for continuous variables and the χ^2-test for categorical variables.
[b]t(4;11) and t(1;19) were classified as high-risk karyotypes, and other karyotypes were classified as standard risk.

overall survival and leukemia-free survival (LFS) with a 95% confidence interval (CI) were calculated using the Kaplan–Meier method, whereas the cumulative incidences of non-relapse mortality and relapse with 95% CI were calculated using Gray's method,[11] considering each other as a competing risk. Probabilities that we could not estimate from these data were estimated from the literature.

Transition probabilities (TPs) and utilities

TPs of the whole population were determined as summarized in Table 2. Each TP has a baseline value and a plausible range. Baseline decision analyses were performed on the basis of baseline values.

Patients may have been precluded from undergoing allogeneic HSCT because of early relapse or comorbidities even if they decided to undergo allogeneic HSCT, and therefore the TP of actually undergoing allogeneic HSCT in first remission after the decision branch to undergo allogeneic HSCT was determined as follows: first, the median duration between the achievement of first remission and HSCT without relapse was calculated as 152 days on the basis of JSHCT data. Next, LFS rates at 152 days after achieving first remission were calculated using the data of all patients who achieved remission in the JALSG studies, and the combined LFS was 0.80 (95% CI: 0.76–0.85). We considered this to be the TP for actually receiving HSCT in first remission, and assigned a baseline value of 0.80 and 95% CI to the plausible range. Similarly, patients may be precluded from undergoing allogeneic HSCT even though they have achieved second remission after they had a relapse of leukemia following a decision to continue chemotherapy. This TP of undergoing allogeneic HSCT in second remission could not be calculated from our data. We assigned a plausible range of 0.5–0.80; the former value was the only available rate in a large study[12] and the latter was the TP calculated above. The median of this range was taken as the baseline value. Probabilities regarding the actual rate of receiving HSCT in other disease statuses could not be obtained, even in the literature. Therefore, a baseline value of 0.5 was assigned with a wide plausible range of 0.3–0.7, although these values may not be closely related to the final expected value, as the probability of survival after receiving HSCT in these situations was extremely low. The TPs of 'Alive at 10 years' following HSCT in various disease statuses were determined on the basis of the JSHCT database. We assigned 95% CI to the plausible ranges.

The TPs of 'Alive without relapse at 10 years' and non-relapse mortality following chemotherapy in first remission were determined on the basis of JALSG studies, and the TP of relapse following chemotherapy was determined by subtracting the sum of these TPs from 1. The TP of achieving second remission after relapse in patients who decided not to undergo allogeneic HSCT in first remission was estimated to have a baseline value of 0.4, with a plausible range of 0.3–0.5 based on the literature.[12–14]

The primary outcome measure was the 10-year survival probability as described in the Discussion. The survival curve nearly reaches a plateau after 5 years and therefore 'Alive at 10 years' reflects 'Cure of leukemia', which is the primary goal of allogeneic HSCT. First, we considered only two kinds of health states, 'Alive at 10 years' and 'Dead', and assigned utility values of 100 to the former and 0 to the latter without considering QOL. Next, we performed a decision analysis while adjusting for QOL. 'Alive after chemotherapy without relapse at 10 years', 'Alive with active GVHD at 10 years' and 'Alive without active GVHD at 10 years' were considered as different health states. The proportion of patients with active GVHD among those who

Table 2 Transition probabilities of the whole population

	Baseline value (plausible range)
HSCT in CR1	0.80 (0.76–0.85)
Alive at 10 years following HSCT in CR1	0.57 (0.52–0.63)
HSCT after failure of HSCT in CR1	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR1[a]	0.27 (0.16–0.38)
Alive at 10 years without relapse following CTx	0.21 (0.15–0.28)
NRM at 10 years following CTx	0.07 (0.04–0.10)
Achievement of CR2 after relapse following CTx	0.4 (0.3–0.5)
HSCT in CR2	0.66 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.27–0.53)
HSCT after failure of HSCT in CR2	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR2[b]	0.18 (0.16–0.2)
HSCT in non-CR after relapse following CTx	0.5 (0.3–0.7)
Alive at 10 years following HSCT in non-CR after relapse	0.16 (0.1–0.27)
Rate of active GVHD at 10 years[c]	0.18 (0.1–0.25)

Abbreviations: CR, complete remission; CTx, chemotherapy; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
[a]This rate was estimated from the survival rate following HSCT in CR2 and HSCT in non-CR.
[b]This rate was estimated from the survival rate following HSCT in CR3 or more and HSCT in non-CR.
[c]The same baseline value and plausible range were used as the rate of active GVHD at 10 years following HSCT in various disease statuses, but one-way sensitivity analyses were performed separately in each status.

Table 3 Transition probabilities of subgroups

	Baseline value (plausible range)			
	Standard-risk	*High-risk*	*Lower age*	*Higher age*
HSCT in CR1	0.86 (0.81–0.92)	0.65 (0.54–0.77)	0.81 (0.76–0.86)	0.80 (0.72–0.87)
Alive at 10 years following HSCT in CR1	0.6 (0.53–0.68)	0.51 (0.4–0.66)	0.62 (0.55–0.69)	0.48 (0.39–0.58)
Alive at 10 years following HSCT after failure of HSCT in CR1	0.31 (0.24–0.38)	0.28 (0.13–0.43)	0.3 (0.21–0.39)	0.23 (0.11–0.35)
Alive at 10 years without relapse following CTx	0.27 (0.18–0.37)	0.13 (0.03–0.22)	0.19 (0.11–0.27)	0.25 (0.16–0.35)
NRM at 10 years following CTx	0.06 (0.02–0.11)	0.07 (0–0.14)	0.04 (0.01–0.08)	0.11 (0.05–0.18)
HSCT in CR2	0.68 (0.5–0.86)	0.58 (0.5–0.65)	0.66 (0.5–0.81)	0.65 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.23–0.61)	0.43 (0.22–0.84)	0.39 (0.26–0.58)	0.35 (0.19–0.64)
Alive at 10 years following HSCT after failure of HSCT in CR2[a]	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)
Alive at 10 years following HSCT in non-CR after relapse	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)

Abbreviations: CR, complete remission; CTx, chemotherapy; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
Transition probabilities that are not in Table 3 are the same as those mentioned in the whole population.
[a]As the number of patients who underwent HSCT in CR3 or more was not enough, the same rate of survival following HSCT in non-CR was used.

were alive at 10 years was determined on the basis of the literature.[15–17] We assigned a value of 100 to the utility for being alive without relapse at 10 years after chemotherapy alone, and a value of 0 to the utility for being dead in all situations. We assigned a fixed value of 98 to the utility for being alive without active GVHD at 10 years following HSCT, and assigned a value of 70 with a wide plausible range of 0–98 to the utility for being alive with active GVHD at 10 years. These utilities were determined on the basis of opinions of 10 doctors who were familiar with HSCT and the literature.[9,18]

Subgroup analyses were also performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years. Patients with a high white blood cell count (more than 30×10^9/l for B lineage and more than 100×10^9/l for T lineage) and/or with t(4;11) or t(1;19) were classified as a high-risk group, and all other patients were classified as standard-risk group. All TPs, based on the JALSG studies and the JSHCT data, were recalculated using the data of patients in each subgroup (Table 3). Other TPs and utilities were the same as those for the overall patient analyses.

Sensitivity analyses

To evaluate the robustness of the decision model, we performed one-way sensitivity analyses for all TPs, in which the decision tree was recalculated by varying each TP value in its plausible range, and confirmed whether the decision of the baseline analyses changed. In the analyses that included adjustments for QOL, the utility for being alive with active GVHD at 10 years was also subjected to a one-way sensitivity analysis.

We also performed a probabilistic sensitivity analysis using Monte Carlo simulation in which the uncertainties of all TPs were considered simultaneously.[19] The distribution of the random variables for each TP was determined to follow a normal distribution, with 95% of the random variables included in the plausible range. Following 1000 simulations based on the decision tree, the mean and s.d. of the expected value for each decision were calculated.

Results

Baseline analysis

The baseline analysis in the whole population without adjusting for QOL revealed an expected 10-year survival of 48.3% for the decision to perform allogeneic HSCT in first remission, which was better than that of 32.6% for the decision to continue chemotherapy. The decision to perform allogeneic HSCT continued to be superior even after adjusting for QOL (44.9% for HSCT vs 31.7% for chemotherapy, Table 4).

Table 4 Expected 10-year survival probabilities with and without adjusting for QOL

	Expected survival probability without a QOL adjustment		*Expected survival probability with a QOL adjustment*	
	HSCT (%)	*Chemotherapy (%)*	*HSCT (%)*	*Chemotherapy (%)*
All patients	48.3	32.6	44.9	31.7
Standard-risk patients	53.8	39.8	50.0	38.9
High-risk patients	38.0	25.0	35.4	24.1
Lower-aged patients[a]	53.1	32.9	49.3	31.9
Higher-aged patients[a]	40.7	33.4	37.8	32.8

Abbreviation: HSCT, hematopoietic stem cell transplantation; QOL, quality of life
[a]Lower-aged patients include those aged 35 years or younger. Higher-aged patients include those aged older than 35 years.

Sensitivity analysis

First, we performed one-way sensitivity analyses for all TPs in the decision model without adjusting for QOL. A better expected survival for the decision to perform HSCT was consistently demonstrated in all TPs within the plausible ranges. In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 48.3 and 2.6%, and those for chemotherapy were 32.7 and 3.4%, respectively.

Next, we performed one-way sensitivity analyses for all TPs and for the utility for being alive with active GVHD at 10 years in the decision model adjusted for QOL. Even in these analyses, the result of the baseline analysis did not reverse in all TPs. In addition, a higher expected survival probability for HSCT was retained, assuming that the utility for being alive with active GVHD ranged between 0 and 98 (Figure 2a). In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 44.8 and 2.6%, and those for chemotherapy were 31.8 and 3.4%, respectively.

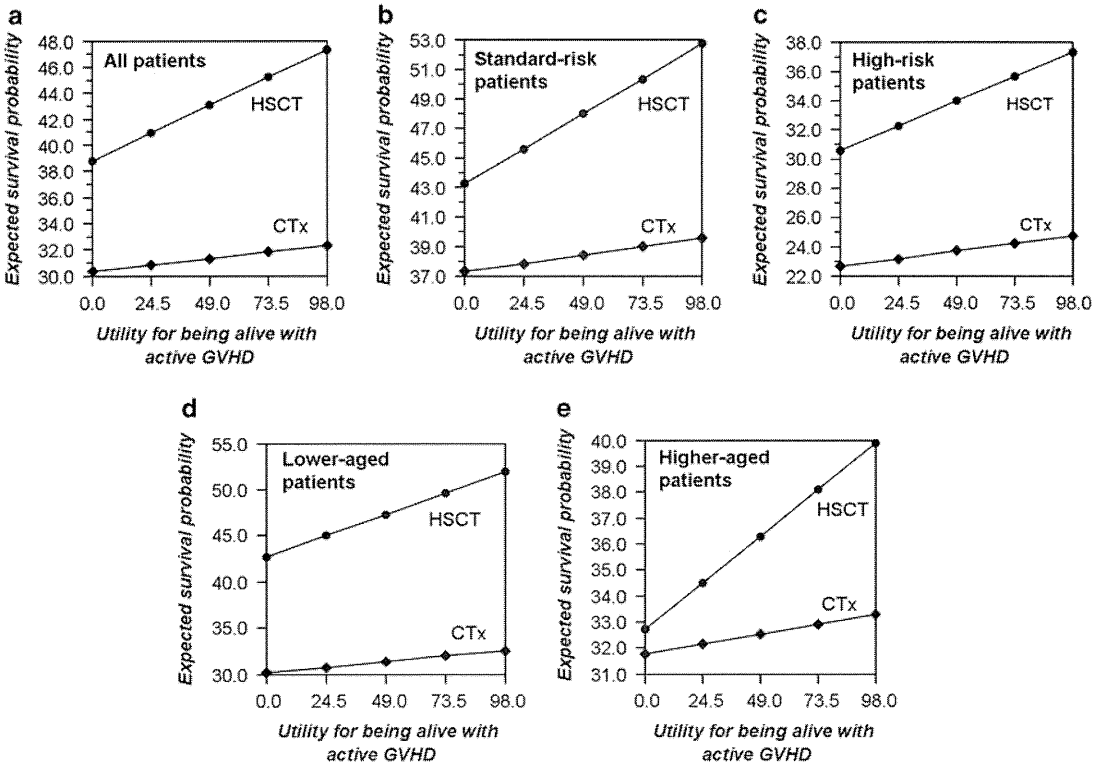

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently observed even with a wide plausible range of the utility in the whole population (**a**) and all subgroups (**b**–**e**).

Subgroup analyses

In subgroup analyses, both with and without adjustment for QOL, a better expected survival probability for HSCT was consistently observed in all subgroups (Table 4).

We also performed one-way sensitivity analyses in all subgroups. In the decision model without adjusting for QOL, varying each TP value in its plausible range did not affect the results of baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result of the baseline analysis reversed only if the probability of LFS at 10 years following chemotherapy in first remission was more than 0.334. Even in the decision model with adjustment for QOL, varying each TP value did not affect the result of the baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result reversed in favor of chemotherapy if the probability of LFS at 10 years without relapse following chemotherapy was more than 0.307 (Figure 3a) or the probability of overall survival at 10 years following HSCT in first remission was less than 0.413 (Figure 3b). On the other hand, non-relapse mortality at 10 years following chemotherapy did not affect the result. We also performed one-way sensitivity analyses for the utility of being alive with active GVHD ranging between 0 and 98. A higher expected survival probability for HSCT was retained in all subgroups (Figures 2b–e).

Discussion

Decision analysis is a statistical technique that aids the clinical decision-making process under uncertainty. This approach has also been used in situations in which a well-designed clinical trial is practically difficult to perform. In the present case, a prospective trial to randomly assign patients with ALL in first remission who have an HLA-matched sibling to undergo allogeneic HSCT or chemotherapy alone is practically difficult. Therefore, we tried to determine the optimal strategy in this clinical situation by using a decision analysis. We chose the 10-year survival probability as the primary outcome measure rather than life expectancy, as the cure rate, rather than how long they can survive, is important for young patients with acute leukemia to make a decision whether they should undergo allogeneic HSCT in first remission. When we performed the decision analysis using the 5-year survival probability as the primary outcome measure, however, the findings in this study did not change, as the survival curve nearly reaches a plateau after 5 years. Further, we adjusted for QOL by considering the presence or absence of persisting symptoms associated with chronic GVHD rather than by calculating quality-adjusted life years, as most patients who choose allogeneic HSCT may tolerate transiently impaired QOL and attach much importance to long-term QOL. Under these conditions, we decided to use a simple decision analysis model rather than a Markov model that allows probabilities and utilities to change with time, as the benefit of using a Markov model is limited in this situation. In addition, a large number of patients are required for the Markov model to define appropriate TPs that change with time. In this study, the number of patients was limited because we used data from the JALSG prospective studies to avoid biases of using retrospective data. We used the database of the JSHCT to calculate TPs in patients who underwent HSCT, because the number of patients who underwent HSCT was further limited in the JALSG prospective studies. However, outcomes after allogeneic HSCT in first remission were not significantly

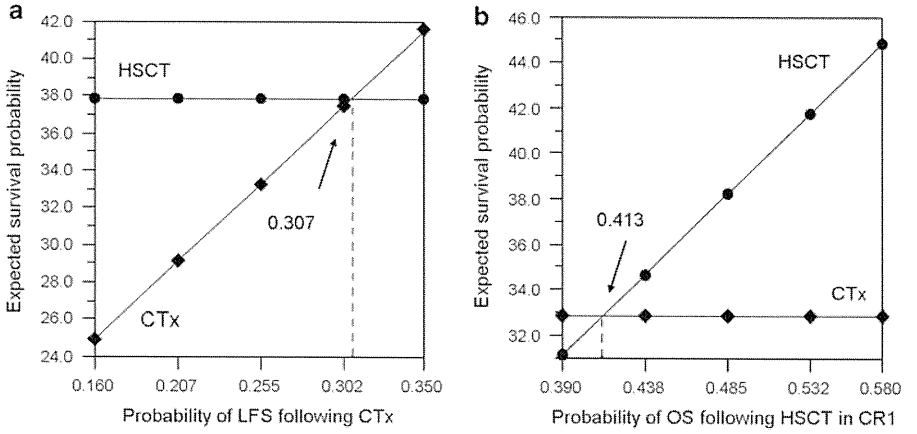

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy (CTx) was more than 0.307 (**a**), or the probability of overall survival at 10 years following allogeneic HSCT in first complete remission (CR1) was less than 0.413 (**b**).

different among the JALSG prospective studies and the JSHCT database (data not shown).

In our baseline analysis both with and without adjustment for QOL, the superiority of HSCT in first remission was demonstrated in the whole population and also in all subgroups. In the whole population, probabilistic sensitivity analysis using a Monte Carlo simulation also supported this result. However, in one-way sensitivity analyses, we should note that the decision model was sensitive to the probability of LFS following chemotherapy in first remission in higher-aged patients (Figure 3a). The adaptation of intensified chemotherapy according to pediatric regimens has led to improved outcomes in adolescents and young adults,[20] and even in older patients in recent trials,[21] and therefore this decision might change in the future.

The risk stratification we used in subgroup analyses was different from that used in the MRC/ECOG study.[8] Therefore, we added subgroup analyses according to the risk stratification used in the MRC/ECOG study. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior both in standard-risk (56.6 vs 36.2%) and high-risk (42.4 vs 33.3%) patients. With QOL adjustments, the similar tendency was observed in both standard-risk (52.6 vs 35.1%) and high-risk (39.4 vs 32.6%) patients. These findings were consistent with those based on our original risk stratification. In addition, we further subdivided patients into four different age categories: 15–25, 26–35, 36–45 and 46–54 years. The superiority of the decision to perform allogeneic HSCT in first remission was conserved in all age categories (data not shown).

A possible concern in this study was the long median duration of 152 days from achieving complete remission to allogeneic HSCT. In the current decision model, this long duration precluded allogeneic HSCT in first remission in about 20% of patients in the allogeneic HSCT branch (mainly because of early relapse), and thereby impaired the expected probability of survival for the decision to undergo allogeneic HSCT. In reality, a meta-regression analysis by Yanada *et al.*[3] revealed that compliance with allogeneic HSCT was significantly and positively correlated with survival.[3] Another fact to be noted is the low incidence of severe GVHD in Japanese patients, which might have favorably affected the decision to perform HSCT.[22] Therefore, the current conclusion should be cautiously applied to Western patients.

The QOL after HSCT is most strongly affected by the status of chronic GVHD, but it is difficult to determine the appropriate utility for each status of GVHD. Therefore, we performed a one-way sensitivity analysis with a wide plausible range of the utility for being alive with active GVHD. In our decision model, the superiority of HSCT was consistently observed regardless of the utility for being alive with active GVHD both in the whole population and in all subgroups (Figure 2).

In conclusion, to improve the long-term probability of survival, allogeneic HSCT in first remission is recommended for all adult patients with Ph-negative ALL who have an HLA-matched sibling. Even when we considered QOL, the superiority of HSCT was confirmed in the whole population and in all subgroups. However, this result might change by the adaptation of intensified chemotherapy, especially in higher-aged patients.

Conflict of interest

The authors declare no conflict of interest.

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Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study

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Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study

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We conducted a multi-institutional randomized study to determine whether high-dose daunorubicin would be as effective as standard-dose idarubicin in remission-induction therapy for newly diagnosed adult patients younger than 65 years of age with acute myeloid leukemia. Of 1064 patients registered, 1057 were evaluable. They were randomly assigned to receive either daunorubicin (50 mg/m^2 daily for 5 days) or idarubicin (12 mg/m^2 daily for 3 days) in combination with 100 mg/m^2 of cytarabine by continuous infusion daily for 7 days as induction therapy. Complete remission was achieved in 407 (77.5%) of 525 patients in the daunorubicin group and 416 (78.2%) of 532 in the idarubicin group ($P = .79$). Patients achieving complete remission received intensive postremission therapy that consisted of either 3 courses of high-dose cytarabine or 4 courses of standard-dose therapy. Overall survival rates at 5 years were 48% for the daunorubicin group and 48% for the idarubicin group ($P = .54$), and relapse-free survival rates at 5 years were 41% and 41% ($P = .97$), respectively. Thus, high-dose daunorubicin and standard-dose idarubicin were equally effective for the treatment of adult acute myeloid leukemia, achieving a high rate of complete remission and good long-term efficacy. This study is registered at http://www.umin.ac.jp/ctrj/ as C000000157. (*Blood*. 2011;117(8): 2358-2365)

Introduction

The combination of anthracycline and cytarabine (Ara-C) with or without other antileukemia drugs is a standard induction therapy for acute myeloid leukemia (AML),[1-3] and a combination of daunorubicin at a dose of 45 to 50 mg/m^2 given daily for 3 days and Ara-C at a dose of 100 to 200 mg/m^2 given daily for 7 days generally has been used. In the late 1980s, however, idarubicin was introduced into clinics, and 3 randomized studies comparing idarubicin with daunorubicin reported significantly higher complete remission (CR) rates in favor of idarubicin.[4-6] A meta-analysis also confirmed a superior effect of idarubicin at a dose of 10 to 12 mg/m^2 for 3 days versus daunorubicin at a dose of 45 to 60 mg/m^2 for 3 days in the achievement of CR.[7] Nevertheless, the long-term follow-up of the above-mentioned 3 randomized studies comparing idarubicin with daunorubicin revealed that the idarubicin group had better overall survival (OS) than the daunorubicin group in only 1 study.[8]

The Japan Adult Leukemia Study Group (JALSG) used idarubicin and Ara-C as induction therapy in the AML95 and AML97 studies,[9-11] after idarubicin was registered and approved for the national health insurance system in 1995. Both studies resulted in satisfactorily high CR rates (80% and 79%, respectively); however, these CR rates were not superior to those of our earlier AML87, AML89, and AML92 studies, which used daunorubicin in combination with other antileukemia drugs.[12-14] In these 3 previous studies,

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daunorubicin and other drugs were administered in a response-oriented individualized manner; that is, additional drugs were given for a few days when the bone marrow at day 8 was not hypoplastic, containing a substantial number of blasts. Therefore, the total doses of daunorubicin administered during the first course of induction therapy were 240 to 280 mg/m^2 given for more than 5 to 7 days, which was more than the conventional dose of 40 to 60 mg/m^2 given for 3 days. Usui et al also reported that the optimal dose of daunorubicin in their induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days).[15]

Because there had been no prospective randomized study comparing a higher dose of daunorubicin with the standard dose of idarubicin (12 mg/m^2) in adult AML, in the present multi-institutional randomized study, we prospectively compared idarubicin (12 mg/m^2 for 3 days) with daunorubicin (50 mg/m^2 for 5 days), in combination with Ara-C (100 mg/m^2 for 7 days), as induction therapy for previously untreated adult AML. High-dose daunorubicin resulted in the same CR rate and predicted 5-year OS compared with standard-dose idarubicin.

Methods

Patients

From December 2001 to December 2005, 1064 newly diagnosed adult patients 15 to 64 years of age with de novo AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears from all registered patients were sent to Nagasaki University and examined by May-Giemsa, peroxidase, and esterase staining. Next, diagnosis was reevaluated by the central review committee. Patients with the FAB M3 subtype were not registered in the present study. Eligibility criteria included adequate function of liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lung and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome, but they were eligible if they had no definite diagnosis of myelodysplastic syndrome confirmed by bone marrow histologic analysis even when they had a previous history of hematologic abnormality. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[16] The study was approved by the institutional review boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Treatments

Patients were randomly assigned by use of a centralized computer system to receive either idarubicin or daunorubicin. Randomization was stratified by age (younger or older than 50 years) and type of AML (FAB classification). All patients received 100 mg/m^2/d Ara-C by 24-hour continuous infusion from days 1 to 7. In the idarubicin group, patients received 12 mg/m^2/d idarubicin for 3 days, and in the daunorubicin group, they received 50 mg/m^2/d daunorubicin for 5 days. If patients did not achieve CR by the first course, the same induction therapy was repeated after an approximately 3- to 4-week interval. If patients did not achieve CR with 2 courses, they were judged as failure cases.

All patients who achieved CR were again randomized to receive either 4 courses of conventional consolidation therapy or 3 courses of high-dose Ara-C therapy. In the conventional consolidation-therapy group, the first course consisted of mitoxantrone (7 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The second course consisted of daunorubicin (50 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The third course consisted of aclarubicin (20 mg/m^2 by 30-minute infusion on days 1 to 5) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The fourth course consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5), etoposide (100 mg/m^2 by 1-hour infusion on days 1 to 5), vincristine (0.8 mg/m^2 by bolus injection on day 8), and vindesine (2 mg/m^2 by bolus injection on day 10). Each consolidation was administered as soon as possible after the neutrophils, white blood cells (WBCs), and platelets recovered to more than 1.5×10^9/L, 3.0×10^9/L, and 100×10^9/L, respectively. In the high-dose Ara-C group, 3 courses of 2.0 g/m^2 Ara-C were given by 3-hour infusion every 12 hours on days 1 to 5. Each course was administered 1 week after the neutrophils, WBCs, and platelets recovered to the above counts.

The best supportive care, including administration of antibiotics and platelet transfusions, was given as indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

After completion of consolidation therapy, no patients received further chemotherapy. Allogeneic stem cell transplantation (SCT) was offered during the first CR to patients 50 years of age or younger and with a histocompatible donor in the intermediate or adverse cytogenetic risk groups.

Definitions and study end points

Responses were evaluated according to the recommendations of the International Working Group.[17] CR was defined as the presence of all of the following: fewer than 5% blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts to more than 1.0×10^9/L and platelet counts to more than 100×10^9/L, and no evidence of extramedullary leukemia. Relapse after CR was defined as the presence of at least 1 of the following: reappearance of leukemic blasts in the peripheral blood, recurrence of more than 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy), and appearance of extramedullary leukemia.

This was a multi-institutional, randomized, phase 3 study with a 2×2 factorial design. The primary end point of the first randomization was CR rate. The result of the second randomization is reported here in part but will be presented fully in a separate paper. OS was calculated from the date of entry into the study until death due to any cause and was censored at the last follow-up. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR until the date of AML relapse or death of any cause and was censored at the last follow-up. Patients who underwent allogeneic SCT were not censored at the date of SCT.

Statistical analysis

This study was prospectively powered to demonstrate noninferiority of daunorubicin compared with idarubicin. With a sample size of 420 patients per group (840 in total), the study had a power of 90% at a 1% level of significance to demonstrate noninferiority (assuming an 80% CR rate for both groups). Statistical testing for the noninferiority trial was performed according to the method of Blackwelder.[18] The Kaplan-Meier method was used to estimate probabilities of OS and RFS.[19] To test factors that predict CR, the χ^2 test and Wilcoxon rank sum test were used for univariate analysis, and the multiple logistic regression model was used for multivariate analysis. For comparison of OS and RFS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis.[20,21] Cumulative rates of CR, neutrophil recovery, and platelet recovery were estimated according to the Kaplan-Meier method and were evaluated with the log-rank test. The JMP program (SAS Institute Inc) was used for these analyses. All analyses were performed according to the intention-to-treat principle. All statistical tests except the method of Blackwelder were 2-sided, and the significance level was set at .05.

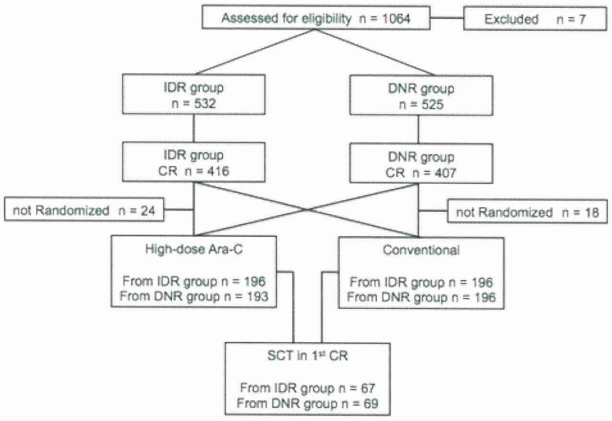

Figure 1. CONSORT flow diagram. IDR indicates idarubicin; DNR, daunorubicin; CR, complete remission; Ara-C, cytarabine; and SCT, stem cell transplantation.

Results

Patient characteristics

Among 1064 registered patients, 7 did not meet the inclusion criteria (misdiagnosis, 1; infectious complication, 1; without therapy, 1; and withdrawal of consent, 4). The study population thus comprised 1057 patients (Figure 1). Patient characteristics are presented in Table 1. Median age was 47 years (range, 15-64 years). Cytogenetics data were available for 1021 patients (96.6%). Among these, 247 (24.2%) were classified in the favorable-risk group, 681 (66.7%) in the intermediate-risk group, and 93 (9.1%) in the adverse group. Five hundred thirty-two patients were assigned to the idarubicin group and 525 to the daunorubicin group. The 2 groups were well balanced with regard to pretreatment characteristics such as age, initial WBC counts, FAB classification, and cytogenetic prognostic grouping.

Table 1. Patient characteristics

	IDR group (n = 532)	DNR group (n = 525)	*P*
Median age, y (range)	47 (15-64)	47 (15-64)	.781
≤ 50	310	306	
> 50	222	219	.996
Median WBC count, ×10⁹/L (range)	13.7 (0.1-382)	15.3 (0.1-334)	.769
≤ 20 × 10⁹/L	304	297	
20= ≤ 50 × 10⁹/L	95	104	
> 50 × 10⁹/L	125	121	
Unknown	8	3	.427
FAB type			
M0	30	30	
M1	95	94	
M2	232	233	
M4	100	100	
M5	56	51	
M6	17	16	
M7	2	1	.997
Cytogenetic group			
Favorable	128	119	
Intermediate	335	346	
Adverse	49	44	
Unknown	20	16	.561
MPO-positive blasts, %			
< 50	169	187	
≥ 50	307	292	
Unknown	56	46	.330
Performance status			
0, 1, 2	512	509	
3	20	16	.524

Values are number of patients unless otherwise indicated.

IDR indicates idarubicin; DNR, daunorubicin; WBC, white blood cell count; FAB, French-American-British classification; and MPO, myeloperoxidase.

Table 2. Results of induction therapy

	IDR group, n (%)	DNR group, n (%)
Patients	532	525
CR	416 (78.2)	407 (77.5)
CR by 1 course	341 (64.1)	321 (61.1)
CR by 2 courses	75 (14.1)	86 (16.4)
95% CI	74.5-81.5	73.8-80.9

IDR indicates idarubicin; DNR, daunorubicin; and CR, complete remission.

Response to induction therapy

Overall, of 1057 evaluable patients, 823 (77.9%) achieved CR. Of 532 patients in the idarubicin group, 416 (78.2%) achieved CR, and of 525 in the daunorubicin group, 407 (77.5%) obtained CR ($P = .79$). Noninferiority for the primary end point was assessed by determining whether the lower bound of the 95% confidence interval (CI) of the difference between the CR rates for the daunorubicin and idarubicin groups was less than −10%. The CR rate of the daunorubicin group was noninferior to that of the idarubicin group (Table 2). In the idarubicin group, 341 patients (64.1%) achieved CR after the first course, and in the daunorubicin group, 321 (61.1%) did so ($P = .39$). The average period to achieve CR was 33.8 days (95% CI 32.9 to 34.6 days) in the idarubicin group and 32.4 days (95% CI 31.6 to 33.2 days) in the daunorubicin group ($P = .038$). CR rates related to FAB classification, age, and cytogenetics are shown in Table 3. Although they were few, patients with FAB M6 responded better to idarubicin: 78% of 17 patients in the idarubicin group and 38% of 16 in the daunorubicin group achieved CR ($P = .037$). There were no differences in CR rate between the 2 groups in other FAB subtypes, cytogenetic risk groups, age, myeloperoxidase positivity of blasts, initial WBC count, or performance status (Table 3). Overall, logistic regression analysis revealed that induction regimen was not an independent prognostic factor but that cytogenetic group and percentage of myeloperoxidase-positive blasts were significant independent factors for achieving CR (Table 4). A cutoff value of WBCs at 20 or 50 × 10^9/L did not change the result.

OS and RFS

At a median follow-up of 48 months, 5-year predicted OS rates were 48% for the idarubicin group (95% CI 43% to 53%) and 48% for the daunorubicin group (95% CI 43% to 53%; $P = .54$; Figure 2A), and 5-year predicted RFS rates of CR patients were 41% (95% CI 36% to 46%) and 41% (95% CI 35% to 45%), respectively ($P = .97$; Figure 2B). Significant unfavorable prognostic features for OS by the Cox proportional hazard model were adverse cytogenetic risk group, age greater than 50 years, WBC count more than 20 × 10^9/L, myeloperoxidase-positive blasts less than 50%, and FAB classification of either M0, M6, or M7; for RFS, the significant unfavorable prognostic features were adverse cytogenetic risk group, WBC count more than 20 × 10^9/L, myeloperoxidase-positive blasts less than 50%, lactate dehydrogenase of 500 IU/L or more, and age greater than 50 years. Induction regimen was not an independent prognostic factor for either OS or RFS by this multivariate analysis.

Table 3. CR rates by induction therapy

	CR rate, %		
	IDR group (n = 532)	DNR group (n = 525)	*P*
FAB type			
M0	43	63	.195
M1	86	79	.236
M2	80	82	.718
M4	81	79	.86
M5	77	75	.96
M6	76	38	.037
M7	50	100	.999
Cytogenetic group			
Favorable	91	96	.134
Intermediate	79	76	.359
Adverse	51	43	.534
Unknown	50	69	.257
Age, y			
≤ 50	83	77	.108
> 50	73	78	.225
Myeloperoxidase-positive blasts, %			
< 50	68	66	.709
≥ 50	87	88	.699
WBC at diagnosis, $\times 10^9$/L			
≤ 20	79	76	.767
20= ≤ 50	82	82	.993
> 50	74	77	.824
Performance status			
0, 1, 2	79	78	.762
3	80	75	.999

CR indicates complete remission; IDR, idarubicin; DNR, daunorubicin; FAB, French-American-British classification; and WBC, white blood cell count.

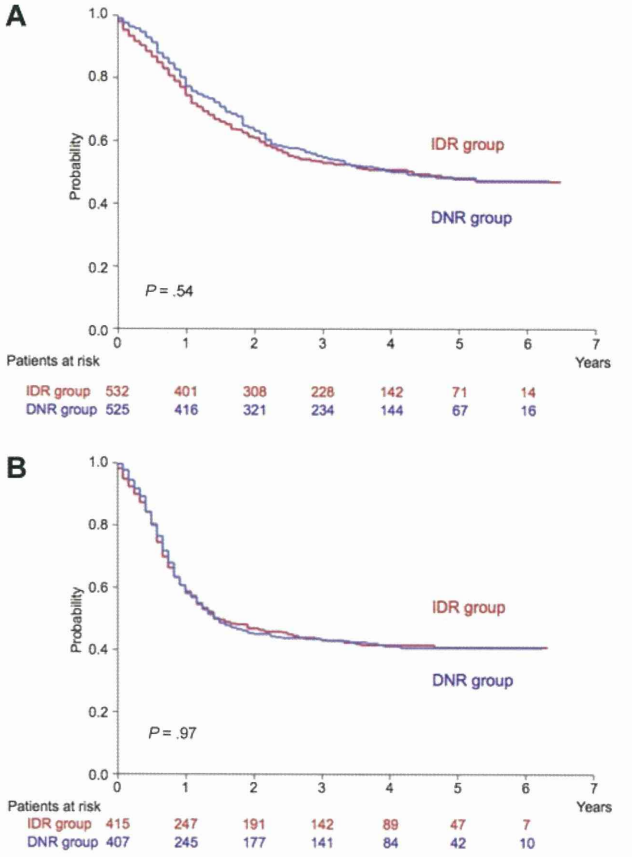

Figure 2. OS and RFS. (A) Predicted 5-year overall survival (OS) was 48% for the idarubicin group (IDR; n = 532; red line) and 48% for the daunorubicin group (DNR; n = 525; blue line; *P* = .54). (B) Predicted 5-year relapse-free survival (RFS) was 41% for the idarubicin group (IDR; n = 416; red line) and 41% for the daunorubicin group (DNR; n = 407; blue line; *P* = .97).

Adverse events

Patients receiving idarubicin required a slightly but significantly longer time to recover from neutropenia and thrombocytopenia. Median duration with a neutrophil count less than 1.0×10^9/L was 28 days for the idarubicin group and 27 days for the daunorubicin group ($P = .0011$; Figure 3A). Median duration with a platelet count less than 100×10^9/L was 25 days for the idarubicin group and 24 days for the daunorubicin group ($P = .0034$; Figure 3B). Sepsis occurred more frequently in the idarubicin group than in the daunorubicin group (8.7% and 4.9%, respectively; $P = .02$). Early death within 60 days occurred more frequently in the idarubicin group than in the daunorubicin group (4.7% and 2.1%, respectively; $P = .03$; Table 5).

Postremission therapy

Of the 823 CR patients, 781 were randomly assigned to receive either 4 courses of conventional standard-dose consolidation therapy (392 patients) or 3 courses of high-dose Ara-C therapy (389 patients), and 136 patients (16% of CR patients) underwent allogeneic SCT in the first CR. There was no significant difference in OS or RFS by postremission therapy between the idarubicin and daunorubicin groups (Table 6). In the idarubicin group, predicted 5-year OS rates were 57% for the conventional standard-dose consolidation arm (95% CI 49% to 65%) and 58% for the high-dose Ara-C arm (95% CI 51% to 66%; $P = .79$; Figure 4A). In the daunorubicin group, predicted 5-year OS rates were 56% (95% CI 48% to 63%) and 58% (95% CI 50% to 65%; $P = .71$; Figure 4B), respectively. If 2 groups were evaluated together, predicted 5-year OS rates were 56% (95% CI 51% to 62%) and 58% (95% CI 53% to 62%; $P = .95$), and predicted 5-year RFS rates were 39% (95% CI 34% to 44%) and 43% (95% CI 38% to 48%), respectively ($P = .72$). The detailed results of this consolidation phase will be reported in a separate paper.[22]

Table 4. Factors that predicted CR in all evaluable patients by multivariate analysis

Variables	Odds ratio	*P*
Cytogenetic group		
Favorable	10.39	< .0001
Intermediate	4.67	< .0001
Myeloperoxidase-positive blast ≥ 50%	2.64	< .0001
Induction therapy: IDR arm	0.97	.854

CR indicates complete remission; and IDR, idarubicin.

Discussion

The present randomized study demonstrates that if the dose intensity is increased appropriately, daunorubicin is as effective as a standard dose of idarubicin for adults less than 65 years of age

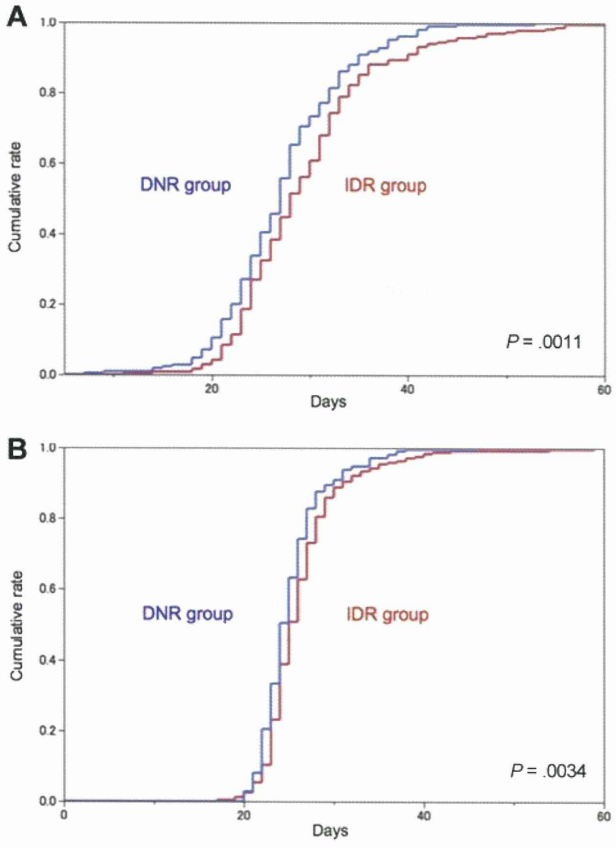

Figure 3. Hematologic recovery. (A) Day of recovery from neutropenia after the first induction course. Neutropenia was defined as neutrophil count $< 1.0 \times 10^9$/L. Median duration until recovery was 28 days for the idarubicin group (IDR; red line) and 27 days for the daunorubicin group (DNR; blue line; $P = .0011$). (B) Day of recovery from thrombocytopenia after the first induction course. Thrombocytopenia was defined as platelet count $< 100 \times 10^9$/L. Median duration until recovery was 25 days for the idarubicin group (IDR; red line) and 24 days for the daunorubicin group (DNR; blue line; $P = .0034$).

who have been newly diagnosed with AML. Remission-induction therapy with 50 mg/m^2 of daunorubicin for 5 days resulted in almost the same CR rate and long-term outcome as seen with 12 mg/m^2 of idarubicin for 3 days in combination with 100 mg/m^2 of Ara-C for 7 days. Generally, daunorubicin is used at a dose of 45 to 50 mg/m^2 for 3 days in combination with 100 to 200 mg/m^2 of Ara-C for 7 days, and 50% to 70% of newly diagnosed adult patients with AML achieve CR. As stated in the "Introduction," JALSG used a response-oriented individualized induction therapy in the AML87, AML89, and AML92 studies for AML, which permitted the additional daunorubicin and other antileukemia drugs

Table 5. Adverse events (World Health Organization grades 3 to 5) after the start of induction therapy

	IDR group, no. of patients (%)	DNR group, no. of patients (%)	*P*
Sepsis	46 (8.7)	26 (4.9)	.021
Early death*	25 (4.7)	11 (2.1)	.026
Bleeding	19 (3.6)	23 (4.4)	.532
Febrile neutropenia	416 (78.2)	406 (77.4)	.761
Acute cardiac toxicity	10 (1.9)	4 (0.8)	.112
Late-onset cardiac failure	2 (0.38)	2 (0.38)	.998

IDR indicates idarubicin; and DNR, daunorubicin.
*Death within 60 days after the start of induction therapy.

Table 6. Effect of induction therapy on outcome by postremission therapies

Consolidation arm	5-year OS		5-year RFS	
	IDR group	DNR group	IDR group	DNR group
Conventional standard-dose, %	57	56	41	37
P	.759		.332	
High-dose Ara-C, %	58	58	42	44
P	.725		.658	
Allogeneic SCT in first CR, %	59	59	58	64
P	.469		.394	

Number of patients in the conventional standard-dose arm was 196 in the IDR group and 196 in the DNR group; in the high-dose Ara-C arm, the numbers were 196 and 193, respectively; and in the SCT group, the numbers were 67 and 69, respectively, as shown in Figure 1.

OS indicates overall survival; RFS, relapse-free survival; IDR, idarubicin; DNR, daunorubicin; Ara-C, cytarabine; and CR, complete remission.

to be administered according to bone marrow status on day 8 or later.[12-14] The CR rates in these 3 studies ranged from 77% to 80%, and the median total dose of daunorubicin was 240 mg/m^2.

On the basis of these experiences and also because of the regulation of our national medical insurance system, we used a dose and schedule of daunorubicin of 50 mg/m^2 for 5 days, that is, a total dose of 250 mg/m^2. In addition,we avoided higher daily doses, such as 80 mg/m^2 for 3 days, because higher plasma concentration might cause more cardiotoxicity in older patients.[23]

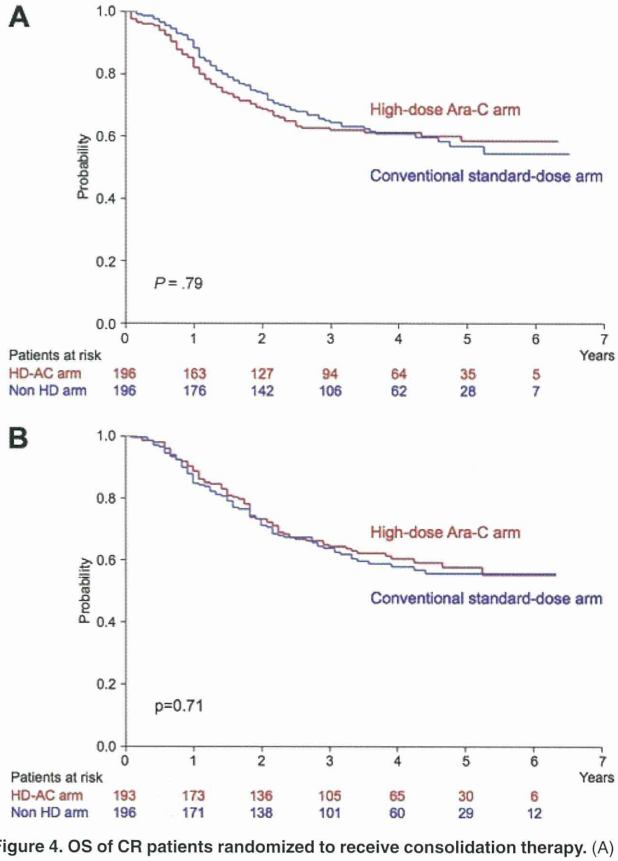

Figure 4. OS of CR patients randomized to receive consolidation therapy. (A) In the idarubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 196; red line) and 57% for the conventional standard-dose arm (n = 196; blue line; $P = .79$). (B) In the daunorubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 193; red line) and 56% for the conventional standard-dose arm (n = 196; blue line; $P = .71$). Ara-C indicates cytarabine; HD-AC arm, high-dose Ara-C arm; and Non HD arm, conventional standard-dose arm.

Three randomized studies in the early 1990s[4-6] and subsequent studies[24,25] and meta-analyses[7] reported a superior effect of idarubicin (12 to 13 mg/m^2 × 3 days) over that of daunorubicin (45 to 50 mg/m^2 × 3 days), in combination with Ara-C, and AML patients receiving idarubicin obtained 70% to 80% CR without a significant increase in toxic mortality, whereas those receiving daunorubicin achieved 58% to 65% CR.[4-6] However, because the duration of neutropenia and thrombocytopenia was longer in the idarubicin groups, it was questioned whether the doses used in these comparisons were equivalent in terms of levels of toxicity and whether any observed advantage represented an inherent biological advantage of idarubicin rather than biological dose equivalence.[1,2]

In these randomized studies, Wiernik et al reported that patients with initial WBC counts > 50 × 10^9 cells/L obtained only 32% CR by the daunorubicin regimen compared with 68% CR by the idarubicin regimen, whereas patients with WBC counts < 50 × 10^9/L obtained 65% and 69% CR, respectively.[5] Berman et al also reported that patients in the idarubicin group did well regardless of their initial WBC count, whereas patients in the daunorubicin group had a decreased response rate as the WBC count increased.[4] In the present study, however, a total of 250 mg/m^2 of daunorubicin resulted in almost the same CR rate as a total dosage of 36 mg/m^2 of idarubicin regardless of initial WBC counts and other prognostic factors such as cytogenetics, age, and FAB classification except M6. Although among patients with FAB M6, 16 patients in the daunorubicin group had a significantly lower CR rate than 17 patients in the idarubicin group, we have no clear explanation for this observation, because the small number of patients made further analysis difficult. Thus, the increased total dosage of daunorubicin administered in 5 days would be responsible for almost the same satisfactory CR rate and long-term outcome as idarubicin administered in 3 days in the present study. As for adverse events, the recovery from neutropenia and thrombocytopenia was slightly but significantly delayed in the idarubicin group, and sepsis and early mortality occurred more frequently in the idarubicin group, as shown in Figure 3 and Table 5.

Before we initiated the present AML201 study, there was no evidence that a higher dose of daunorubicin was more effective than its standard dose because of the lack of a prospective randomized study. In the sequential studies reported by Southwest Oncology Group, however, the CR rate with daunorubicin at a dose of 70 mg/m^2 was better than that with 45 mg/m^2.[26,27] Very recently, 2 groups reported that a higher dose of daunorubicin improved the CR rate and OS in prospective randomized studies.[28,29] A collaborative group composed of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology, the German AML Study Group, and the Swiss Group for Clinical Cancer Research compared 3-day daunorubicin at 90 mg/m^2 with 3-day daunorubicin at 45 mg/m^2, in combination with 7-day Ara-C, in elderly patients 60 to 83 years of age who had AML or high-risk refractory anemia and reported a higher CR rate for the escalated-treatment group (52% vs 35%, $P = .002$).[28] Although survival end points did not differ significantly overall, among patients 60 to 65 years of age, the CR rate (73% vs 51%) and OS rate (38% vs 23%) were significantly higher for the 90-mg/m^2 group. The Eastern Cooperative Oncology Group also compared 3-day daunorubicin at 90 mg/m^2 with 3-day daunorubicin at 45 mg/m^2, in combination with 7-day Ara-C, in patients 17 to 60 years of age with AML and reported a higher CR rate (70.6% vs 57.3%, $P < .001$) and longer OS (median 23.7 vs 15.7 months, $P = .003$) for the high-dose group.[29] Given these previous reports and the present report, the optimal total dose of daunorubicin is still to be explored but may rest somewhere between 250 and 270 mg/m^2. Because we used the FAB classification in the present study, we did not include either patients with 20% to 30% of blasts in the bone marrow or those with refractory anemia with excess blasts; therefore, it is unclear whether the present result is applicable to those patients.

Idarubicin is a derivative of daunorubicin and differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. In vitro and preclinical data have shown that idarubicin is more lipophilic, is faster in cellular uptake, exhibits increased cellular retention, is lower in susceptibility to P-glycoprotein–dependent resistance, and is less cardiotoxic than daunorubicin. Both idarubicin and daunorubicin undergo conversion to their respective alcohol metabolites, idarubicinol and daunorubicinol. Unlike the latter, idarubicinol has a prolonged plasma half-life and is thought to have a pharmacologic advantage.[30-33]

The pediatric Berlin-Frankfurt-Münster group previously compared idarubicin 12 mg/m^2 for 3 days with daunorubicin 30 mg/m^2 twice daily for 3 days, in combination with Ara-C and etoposide, and reported almost the same CR rates (85% vs 86%, respectively) and predicted 5-year event-free survival (55% vs 49%, respectively, $P = .29$) in newly diagnosed childhood AML.[34] Furthermore, daunorubicin at a dose of 60 mg/m^2 for 3 days and idarubicin at a dose of 12 mg/m^2 for 3 days achieved similar CR rates in the studies by Eastern Cooperative Oncology Group that consisted of a large number of adult patients.[35,36]

Recently, the French Acute Leukemia Association reported a randomized study comparing standard doses of idarubicin (12 mg/m^2 for 3 days) with high doses of daunorubicin (80 mg/m^2 for 3 days) or idarubicin (12 mg/m^2 for 4 days) for remission induction in newly diagnosed elderly patients 50 to 70 years of age (median 60 years old) with AML.[37] CR rates were significantly higher for the standard-dose idarubicin group (83%) than for the high-dose daunorubicin group (70%, $P = .007$) but not for the high-dose idarubicin group (78%, $P = .12$). Although OS, relapse incidence, and event-free survival were not different among the 3 arms of the study, daunorubicin (80 mg/m^2 for 3 days) did not improve the CR rate of elderly AML patients to the level of the standard-dose idarubicin regimen.

With regard to adverse events, recovery from myelosuppression was faster and sepsis was less frequent in the daunorubicin group. Both acute and late-onset cardiotoxicity were reported only in a small number of patients in both groups. Given that there was no increase in severe cardiac toxicities in patients receiving high-dose daunorubicin (90 mg/m^2 for 3 days) compared with standard-dose daunorubicin (45 mg/m^2 for 3 days) in the Eastern Cooperative Oncology Group study (7.9% and 7.2%, respectively),[29] daunorubicin may not necessarily be administered for 5 days as in the present study (50 mg/m^2 for 5 days), although further follow-up observation is needed for late-onset cardiotoxicity.

Since the landmark study of the Cancer and Leukemia Group B,[38] it has been believed that high-dose Ara-C is superior to consolidation therapy with intermediate (400 mg/m^2 for 5 days) or conventional (100 mg/m^2 for 5 days) doses of Ara-C. In the present study, we prospectively compared high-dose Ara-C with consolidation therapy that included a conventional dose of Ara-C and non–cross-resistant agents. Our results clearly demonstrate that there is no difference in RFS and OS between the 2 consolidation arms, regardless of whether idarubicin or daunorubicin is used as induction chemotherapy.

In conclusion, the intensified dose of daunorubicin in the present setting, that is, 50 mg/m^2 for 5 days, proved to be biologically equivalent in terms of efficacy and no more toxic in terms of myelosuppression than the standard dose and schedule of idarubicin, that is, 12 mg/m^2 for 3 days, for remission-induction therapy in newly diagnosed younger patients (15 to 64 years old, median 47 years) with AML.

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Authorship

Contribution: S.O. designed and performed research, collected and interpreted data, and wrote the manuscript; S.M. designed and performed research, analyzed data, and participated in writing the manuscript; H.F., H.K., K.S., N.U., H.O., K.M., C.N., Y.M., A.F., T. Nagai, T.Y., M. Taniwaki, M. Takahashi, F.Y., Y.K., N.A., H.S., and H.H. performed research; S.H. analyzed data; K.O. and T. Naoe conducted and performed research; and R.O. conducted research, interpreted data, and participated in writing the manuscript.

For a complete list of the members of the JALSG, see the supplemental Appendix (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

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