Table 2 Mortality rates of bacteremia/fungemia

Organism	No. of deaths/no. of patients (%)				
	AML-87/-89	AML-92	AML-95	AML-97	Total
Gram-positive bacteria	7/27 (25.9)	5/28 (17.9)	2/21 (9.5)	3/44 (6.8)	17/120 (14.2)
Staphylococcus aureus (MSSA)	2/4	0/2	0/2	0/1	2/9 (22.2)
Staphylococcus aureus (MRSA)	–	3/5	1/3	1/7	5/15 (33.3)
Staphylococcus epidermidis	1/5	0/7	0/3	1/14	2/29 (6.9)
Streptococcus/Enterococcus sp.	2/11	0/6	0/6	1/13	3/36 (8.3)
Other GPB	2/7	2/8	1/7	0/9	5/31 (16.1)
Gram-negative bacteria	5/28 (17.9)	3/24 (12.5)	4/17 (23.5)	1/19 (5.3)	13/88 (14.8)
Pseudomonas aeruginosa	3/16	2/14	2/9	1/10	8/49 (16.3)
Other GNB	2/12	1/10	2/8	0/9	5/39 (12.8)
Fungi	6/11 (54.5)	0/7 (0)	0/4 (0)	1/8 (12.5)	7/30 (23.3)
Candida sp.	4/9	0/4	0/3	0/5	4/21 (19.0)
Other fungi	2/2	0/3	0/1	1/3	3/9 (33.3)
Polymicrobial	0/2 (0)	2/2 (100)	0/1 (0)	0/3 (0)	2/8 (25.0)
Total	18/68 (26.5)	10/61 (16.4)	6/43 (14.0)	5/74 (6.8)	39/246 (15.9)

Table 3 Pathogens causing pneumonia

Organism	Total (%)
Gram-positive bacteria	32 (26.0)
Staphylococcus aureus (MSSA)	9
Staphylococcus aureus (MRSA)	7
Coagulase-negative *staphylococci*	7
Streptococcus sp.	6
Enterococcus	3
Gram-negative bacteria	29 (23.6)
Pseudomonas aeruginosa	15 (12.2)
Pseudomonas cepacia	5
Enterobacter cloacae	3
Stenotrophomonas maltophilia	2
Other GNB	4
Fungi	44 (35.8)
Candida	10 (8.1)
Candida albicans	4
Candida krusei	1
Aspergillus	23 (18.7)
Muncor	2
Fungi not identified	4
Polymicrobial[a]	18 (14.6)
Total	123 (100)

[a]*H. influenzae* + *Acinetobacter calcoaceticus*, *Stenotrophomonas maltophilia* + *Aspergillus*, *S. maltophilia* + *Achromobacter* + *E. cloacae*, *C. tropicalis* + *S. maltophilia*, *Ps. aeruginosa* + *C. albicans*, Viridans streptococci + *S. maltophilia*, *Candida* + *S. maltophilia*, Viridans streptococci + *Candida*, *S. maltophilia* + *Ps. aeruginosa*, *S. maltophilia* + *C. albicans*, *Ps. cepacia* + *Ps. aeruginosa* + *S. epidermidis*, *E. cloacae* + *K. pneumoniae* + *Ps. cepacia* + *Flavobacterium meningosepticum* + *E. faecalis*, *A. xylosoxidans* + MRSA, *A. calcoaceticus* + *Moraxella*, *Ps. aeruginosa* + *C. parapsilosis*, MRSA + fungi, MRSA + *Aspergillus*, *E. cloacae* + *Ps. aeruginosa*, in one each

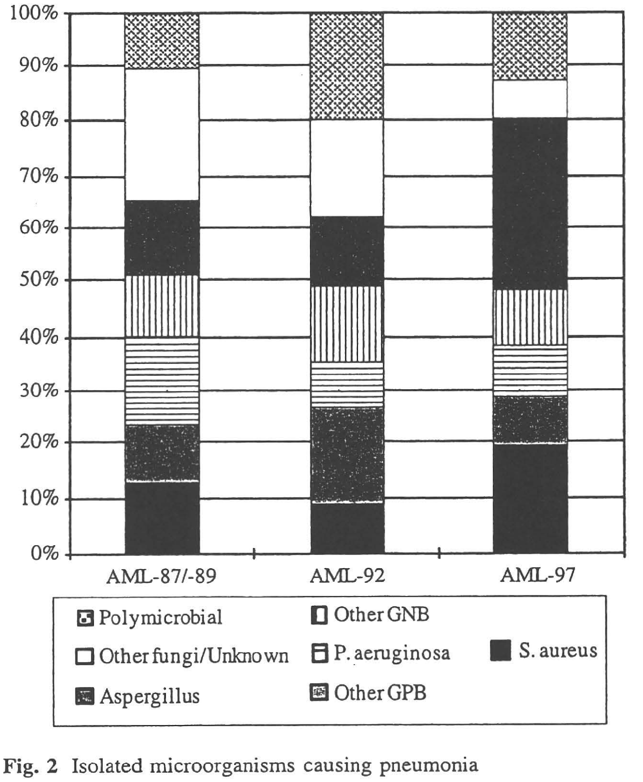

Fig. 2 Isolated microorganisms causing pneumonia

than that of microbiologically documented pneumonia (22.8 vs. 33.9%, $P = 0.05$).

4 Discussion

Bacteremia/fungemia and pneumonia complicating AML during remission induction therapy were analyzed among

Table 4 Mortality rates of pneumonia

Category	No. of deaths/no. of patients (%)				
	AML-87/-89	AML-92	AML-95[a]	AML-97	Total (%)
Microbiologically documented	15/47 (31.9)	18/44 (40.9)	–	8/30 (26.7)	41/121[b] (33.9)
Gram-positive bacteria	4/11	3/12		1/9	8/32 (25.0)
Staphylococcus aureus (MSSA)	3/6	0/2		0/1	3/9 (33.3)
Staphylococcus aureus (MRSA)	–	2/2		1/5	3/7 (42.9)
Other GPB	1/5	1/8		0/3	2/16 (12.5)
Gram-negative bacteria	5/13	4/10		3/5	12/28 (42.9)
Pseudomonas aeruginosa	3/8	2/4		2/3	7/15 (46.7)
Other GNB	2/5	2/6		1/2	5/13 (38.5)
Fungi	6/18	6/13		4/12	16/43 (37.2)
Candida sp.	3/6	2/6		1/2	6/14 (42.9)
Aspergillus sp.	2/7	3/6		3/10	8/23 (34.8)
Other fungi	1/5	1/1			2/6 (33.3)
Polymicrobial	0/5	5/9		0/4	5/18 (27.8)
Clinically documented	26/95 (27.4)	17/61 (27.9)	–	9/72 (12.5)	52/228[b] (22.8)
Total	41/142 (28.9)	35/105 (33.3)	11/66 (16.7)	17/102 (16.7)	104/415 (25.1)

[a] Microbiological data were not available in AML-95

[b] The prognosis of 2 patients with microbiologically documented pneumonia and 8 patients with clinically documented pneumonia were unknown

15 years based on the JALSG patients. With regard to bacteremia/fungemia, an increase in GPB has been noted in the literature in recent years [1, 2]. The current analysis indicated that the incidence of bacteremia due to GPB has been stable or slightly increased by period, while a decline in bacteremia due to GNB and fungemia was marked. One reason for this decrease might be the result of prophylaxis with fluoroquinolone and FLCZ. As of 2001, more than 90% of physicians conducted antibacterial or antifungal prophylaxis [11, 12]. With regard to the significance of antibacterial and antifungal prophylaxis, there were no strong recommendations in the guidelines of IDSA because improved prognosis had not necessarily been achieved and an increase in resistant microorganisms was feared [8, 9, 13]. However, the most recent meta-analysis of fluoroquinolone has provided results indicating the efficacy of this prophylaxis [21]. FLCZ or ITCZ are recommended to use for antifungal prophylaxis in case of severe neutropenia such as hematopoietic stem cell transplantation (HSCT) and AML [22, 23]. Albeit a retrospective study, the decrease of bacteremia due to GNB and fungemia in our results supports this efficacy. Moreover, another reason is that onset of bacteremia due to GNB was inhibited by the start of early empiric antibiotic therapy [8–10, 13, 24]. From the questionnaire analysis, 50% of physicians used combination therapy with a third/fourth generation cephalosporin or a carbapenem plus an aminoglycoside. Thirty-five percent of them used monotherapy with a third/fourth generation cephalosporin or a carbapenem [11, 12]. Both regimens were proved to be equally effective for empiric therapy for febrile neutropenia (FN) in Japan [24].

With regard to the prognosis for bacteremia/fungemia, the current results indicated a considerably lower mortality rate than that generally reported [1, 2]. The reason for this is that complete remission is now achieved with intensive chemotherapy for AML in about 80% of patients [15–19], so neutrophils recover and immunity improves in many patients. The use of G-CSF in recent series of patients might be another explanation for favorable outcome. Bacteremia/fungemia in which the course of the underlying illness cannot be controlled is still presumed to have a poor prognosis. Especially when seen in terms of incidence, GPB is crucial to future control measures, but there is no valid evidence regarding prevention of bacteremia due to GPB. In Japan, there is a restriction prohibiting the use of VCM if MRSA is not detected. However, there is a considerable possibility that this drug would be effective when initial empiric therapy was ineffective.

Another option for persistent febrile neutropenic patients is antifungal empiric therapy. This approach is recommended in IDSA and Japanese FN guidelines [8–10, 13] when fever does not respond to antibacterial agents after 72–96 h. This might be another reason for decreased incidence of fungemia in this study although was not effective for preventing IPA. An increase of IPA has been emphasized in the past, but many of these reports were primarily in the area of HSCT [25, 26]. In the current analysis, an increase of IPA was observed for AML as well.

Although definitive diagnosis of IPA is difficult, these patients are diagnosed comprehensively by attending physician primarily through fungal detection from sputum in combination with galactomannan antigen [27], β-D-glucan [28], or fungal DNA detection [29] and diagnostic imaging [30]. Moreover, there were additional 5 patients in whom the attending physician diagnosed as suspected IPA in AML-97. The prognosis for IPA in patients with hematologic malignancy was more favorable than that in the area of HSCT [25, 26, 31]. This is probably due to the recovery of neutrophils like that seen in bacteremia/fungemia. However, the mortality of IPA was still high in this study (34.8%). In the current study period, AMPH was the only therapeutic agent used to treat IPA, and Micafungin (MCFG) and Voriconazole (VRCZ) were not used. New antifungal agents such as MCFG, VRCZ, liposomal AMPH, and ITCZ injection might be much effective for treating IPA [31, 32].

The incidence of pneumonia due to other causative microorganisms and unknown etiology has declined in recent years. The fact that about 80% of facilities in Japan currently use a clean room or a clean bed equipped with HEPA filters may also be associated with the decline in pneumonia [11, 12]. The mortality has also improved, but not at a satisfactory level. The incidence of pneumonia is especially prevalent in the elderly [7], and patients in whom the causative microorganism is unknown account for two-third. The development of new diagnostic methods and appropriate use of antibiotics based on the PK/PD might improve the prognosis of pneumonia.

The current analysis clarified the fact that the control of bacteremia/fungemia is now clearly close to reaching a satisfactory level during remission induction phase of AML. Improvement in the management of pneumonia is currently desired.

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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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Keywords: decision analysis; acute lymphoblastic leukemia; allogeneic hematopoietic stem cell transplantation; HLA-matched sibling donor; first remission

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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,

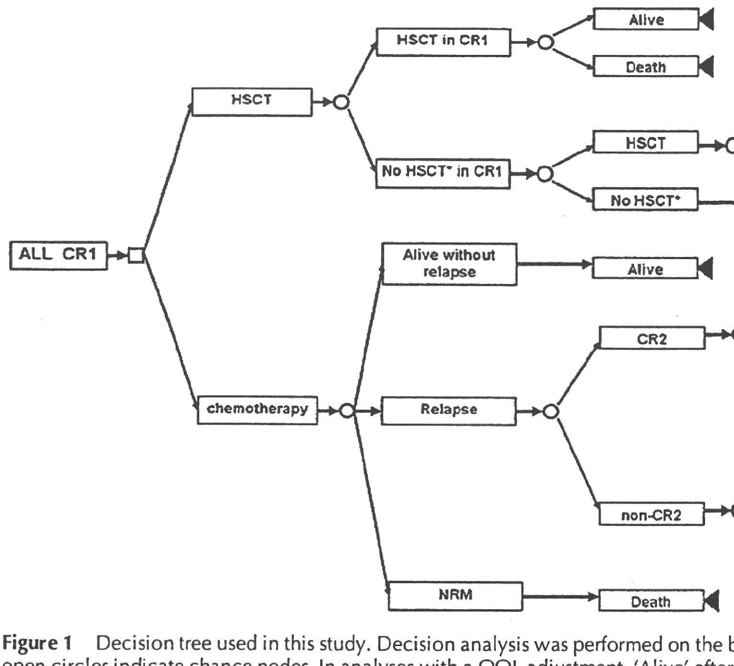

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic 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.

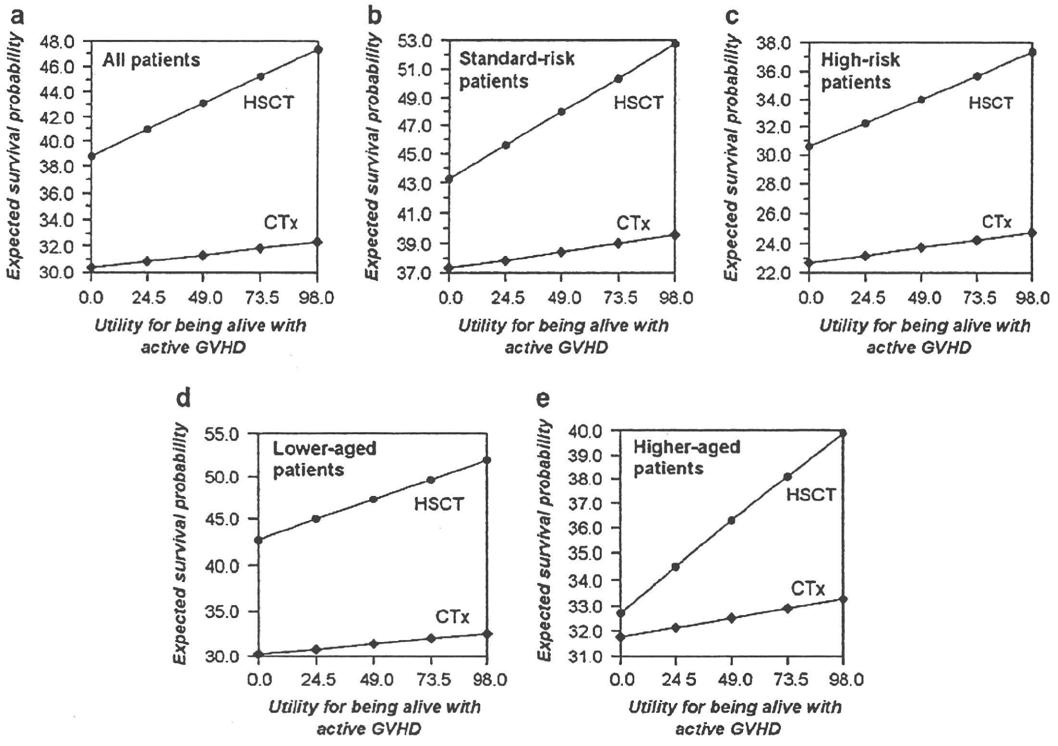

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently 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

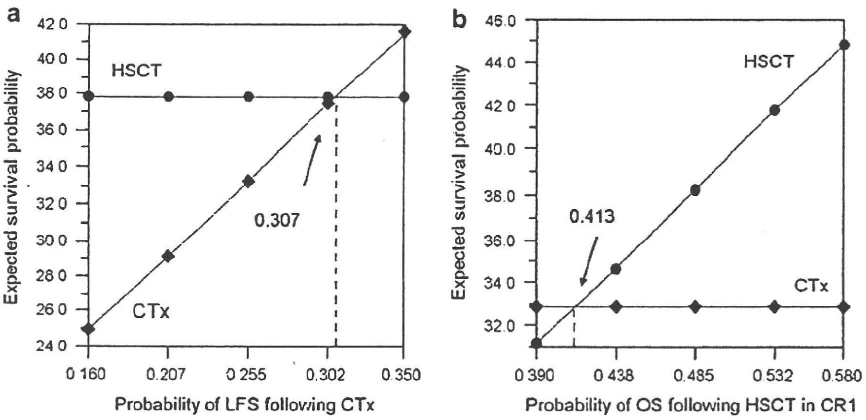

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy (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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ORIGINAL ARTICLE

Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study

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Abstract We prospectively compared allogeneic hematopoietic stem cell transplantation (allo-HSCT) with chemotherapy as a post-remission therapy in a multicenter trial (JALSG AML97) of adult patients with intermediate or poor risk acute myeloid leukemia (AML). Of 503 patients aged 15–50 years old registered between December 1997 and July 2001, 392 achieved complete remission (CR). CR patients classified in the intermediate or poor risk group using a new scoring system were tissue typed. Seventy-three with and 92 without an HLA-identical sibling were assigned to the donor and no-donor groups. Of 73 patients in the donor group, 38 (52%) received allo-HSCT during CR1 and 17 (23%) after relapse. Intention-to-treat analysis revealed that the relapse incidence was reduced in the donor group (52 vs. 77%; $p = 0.008$), and the disease-free survival (DFS) improved (39 vs. 19%; $p = 0.016$), but overall survival (OS)

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was not significantly different (46 vs. 29%; $p = 0.088$). The OS benefit was seen in the patients aged 36–50 years old (49 vs. 24%; $p = 0.031$), suggesting an advantage of allo-HSCT among older patients with leukemia that is more resistant to chemotherapy than that among younger patients.

Keywords AML · Allogeneic hematopoietic stem cell transplantation · Post-remission chemotherapy

1 Introduction

Around 70–80% of newly diagnosed patients with adult acute myeloid leukemia (AML) achieve complete remission (CR) when treated with cytarabine (AraC) and anthracycline, usually daunorubicin (DNR) or idarubicin (IDR). However, only about one-third of these patients remain disease free for more than 5 years [1–5]. Intensified post-remission chemotherapy has improved the survival rates of patients with AML, especially of younger patients [6]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be the most intensive post-remission treatment consisting of high-dose chemoradiotherapy and allo-immune mechanisms. However, the powerful anti-leukemic effects of this treatment are counterbalanced by a high incidence of treatment-related mortality (TRM). Thus, allo-HSCT has not always been considered superior to chemotherapy [7, 8]. Intensified chemotherapy with high-dose Ara-C confers promising results on good risk patients [9] for whom allo-HSCT is currently abstained in the first CR (CR1). The Japan Adult Leukemia Study Group (JALSG) AML97 protocol committee circulated a questionnaire among the institutions participating in JALSG regarding their policy about indications for allo-HSCT among AML patients in CR1. The findings revealed that good risk patients in CR1 did not undergo an allo-HSCT at most of these institutions. Cytogenetic profile has been widely used to classify the patients with AML [7–13]; however, cytogenetic studies are not always foolproof. The JALSG established a scoring system that adopted significant factors including cytogenetic results from previous JALSG AML trials [14]. We applied this scoring system to stratify patients and conducted a prospective, multicenter cooperative study (AML97) to compare allo-HSCT with chemotherapy among intermediate and poor risk patients with AML in CR1.

2 Patients and methods

2.1 Patients and study design

The JALSG AML97 study was implemented between December 1997 and July 2001 at 103 institutions where the ethical committees approved the protocol. Adult patients aged from 15 to 64 years newly diagnosed with de novo AML according to the French–American–British (FAB) classification at each institution were eligible, but those with acute promyelocytic leukemia (APL) were excluded. Peripheral blood and bone marrow smears of the registered patients were stained with May-Giemsa, peroxidase, and esterase at Nagasaki University and subsequently reviewed by a central review committee. All patients provided written informed consent to participate before registration in this study.

The chemotherapeutic design of AML97 has been described elsewhere in detail [15]. In short, all the patients were treated with the same induction therapy consisted of AraC (100 mg/m^2, continuous infusion, days 1–7) and IDR (12 mg/m^2 days 1–3). If the patients did not achieve remission after the first induction therapy, then the same therapy was given again. For patients who did not achieve a CR even after second induction therapy, no further treatment was defined in this study. In the comparison between allo-HSCT and chemotherapy as post-remission therapy, these patients were not included in the analysis. All patients who achieved CR were randomized to receive either 4 courses of consolidation therapy without maintenance therapy (group A) or the conventional JALSG post-remission regimen with maintenance therapy (group B) [3]. The results of the two post-remission chemotherapeutic strategies (group A vs. group B) were comparable [15]. The CR patients were classified into good, intermediate or poor risk groups according to the scoring system described below. Intermediate or poor risk patients younger than 50 years old with living siblings were tissue typed. Patients with an HLA-identical sibling were assigned to undergo allo-HSCT soon after three courses of consolidation therapy (donor group), and those without living or HLA-identical siblings were assigned to the no-donor group that continued receiving chemotherapy.

Patients in the donor group with AST or ALT values fourfold higher than the normal range, serum bilirubin and creatinine more than 2 mg/dl, ejection fraction based on an echocardiogram of less than 50% or oxygen saturation according to pulse oximetry of less than 90% were ineligible for allo-HSCT, but were analyzed as a donor group one in an intention-to-treat fashion. Conditioning before transplantation and prophylaxis for graft-versus-host disease was performed according to each institutional standard. Either allogeneic peripheral blood or bone marrow was allowed to be the stem cell source.

2.2 Scoring system

We collected clinical and laboratory data (except for APL) from previous JALSG AML trials (AML87, $n = 234$

Table 1 JALSG scoring system

Scoring system		
System 1		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	≤2 × 10^9/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
No. of induction	1	+1
t(8;21) or inv(16)	+	+1
Total score		
Good risk group		8–10
Intermediate risk group		5–7
Poor risk group		0–4
System 2		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	≤2 × 10^9/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
Total score		
Good risk group		7–8
Intermediate risk group		4–6
Poor risk group		0–3

MPO myeloperoxidase, *WBC* white blood cell

patients; AML89, $n = 311$; AML92, $n = 986$), and then selected significant factors for achieving CR, disease-free survival (DFS) and overall survival (OS) using multivariate analysis [14]. According to the weight of significance, myeloperoxidase positivity of blasts, patient age, and WBC count at diagnosis were valued at 2 points, and FAB subtypes, performance status, numbers of inductions required to achieve CR, and favorable karyotypes of t(8;21) or inv(16) were valued at 1 point (Table 1, system 1). When we originally planned to use this system, cytogenetic data were not always available at diagnosis. Thus, we designed the system 2 that could be applied even without a cytogenetic data.

2.3 Statistical analysis

The aim of this study was to compare the efficacy of allo-HSCT and chemotherapy as a post-remission treatment, by evaluating DFS and OS rate. Forty-two patients were estimated for an evaluation of the primary endpoint of this study. The JALSG data management committee collected the clinical data from all participating institutions, then fixed them and analyzed the OS of each risk group in July 2004 and the relapse rate (RR), DFS, OS and TRM of the donor and no-donor groups in January 2009. The OS, DFS, RR and TRM were measured from the date of CR. The event for OS was death due to all causes, and patients were censored at the last observation date if alive. The events of DFS were death during CR or relapse. The RR was defined as the cumulative probability of relapse, censoring at death in CR. The events of TRM comprised death before relapse. We estimated OS, DFS, RR and TRM with their respective standard errors using the Kaplan–Meier method [16]. We compared the OS, DFS, RR and TRM between the patients with and without a donor using the log-rank test. Furthermore, the hazard ratio and the 95% confidence interval (CI) of the OS, DFS, RR and TRM were calculated using Cox regression analysis. The Wilcoxon rank-sum test was used for the continuous data, such as age and WBC count, while the Chi-square test was used for the ordinal data, such as the risk group and the frequency of allo-HSCT. All analyses were performed on the intention-to-treat principal with all patients in their allocated arms. Adding to the prospective comparison of the efficacy between allo-HSCT and chemotherapy, we also retrospectively performed subgroup analysis by age. Statistical analyses were conducted using the SAS software package (SAS Institute, Inc, Cary, NC).

3 Results

3.1 Study patients and genetical allocation

Five hundred and three de novo AML patients aged from 15 to 50 years participated in the AML97 comparison of allo-HSCT with chemotherapy as a post-remission therapy. Of 392 patients achieved CR, 62 patients were excluded from the analysis because of insufficient data mainly deficient clinical data at diagnosis which were essential to verify their classification. Three hundred and thirty evaluable patients were classified into the good ($n = 149$), intermediate ($n = 162$) or poor risk ($n = 19$) groups using the scoring system described above (Fig. 1). The 5-year OS

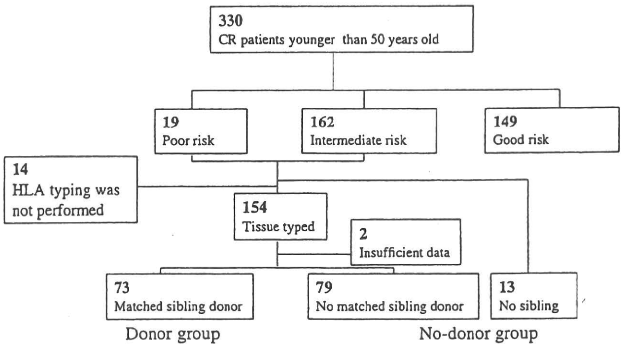
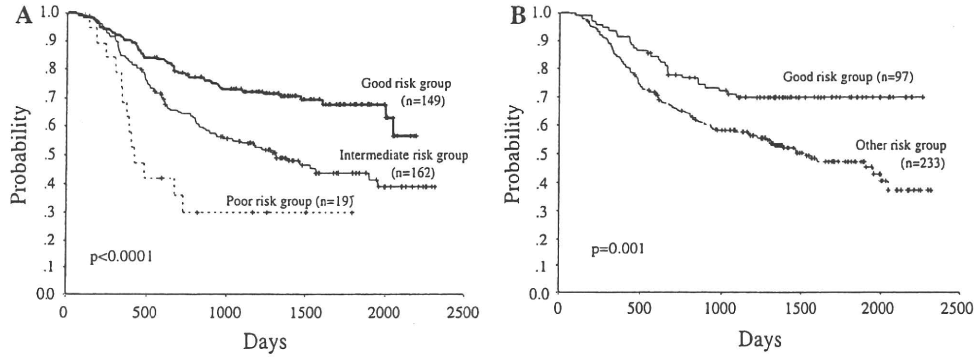


Fig. 1 Overview of patients included in analysis by risk classification, HLA typing, and donor availability

Fig. 2 Overall survival of patients in CR according to JALSG scoring system (**a**) and by cytogenetic studies (**b**)



rates of the CR patients with good, intermediate and poor risk were 68, 44 and 30%, respectively [hazard ratio (HR), 0.51 (good vs. intermediate) and 0.25 (good vs. poor), respectively; 95% confidential interval (CI), 0.35–0.73 (good vs. intermediate) and 0.14–0.48 (good vs. poor); $p < 0.0001$; Fig. 2a]. Among the intermediate and poor risk patients with living siblings, 154 patients and their siblings were examined for their HLA types. Seventy-three of these patients had an HLA-identical sibling and were assigned to the donor group. Thirteen patients with no siblings and 79 patients without an HLA-identical sibling were assigned to the no-donor group (92 patients). Finally, one patient in donor group and one patient in no-donor group were excluded from the analysis because of their insufficient data of survival (Fig. 1). The follow-up durations of the donor and no-donor groups were 1854 days (range 163–3176 days) and 1010 days (range 93–3008 days), respectively.

3.2 Patient characteristics of donor versus no-donor groups

Table 2 shows the characteristics of patients in the donor and no-donor groups. The distributions of these features were comparable in both groups with respect to age, gender, initial WBC count, MPO positivity of blasts, FAB subtype, performance status, prognostic risk according to JALSG score, presence of favorable cytogenetic abnormalities, and the groups of post-remission chemotherapy.

3.3 Donor group

Fifty-six patients (76%) in the donor group actually underwent allo-HSCT (Table 2). Thirty-eight patients (52%) received an allo-HSCT during CR1 at a median of 159 days (range 43–314 days) from CR1. Eighteen patients underwent allo-HSCT after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 183 days (range 39–757 days) and 248 days (range 157–973 days), respectively. Thirty and 24 patients were transplanted after undergoing a conditioning regimen with or without total body irradiation (TBI), respectively, and conditioning information was not available for 2 patients. The sources of transplanted stem cells were bone marrow cells ($n = 26$), peripheral blood cells ($n = 27$) and bone marrow cells together with peripheral blood cells ($n = 2$). Twenty-nine of the 56 patients in the donor group who underwent allo-HSCT remain alive. Twenty patients died of recurrent leukemia and 7 of transplant-related causes. Seventeen patients allocated to the donor group did not receive a transplantation for the following reasons; patients' refusal ($n = 6$), donors' refusal to donate ($n = 2$), physician's decision ($n = 1$), disease progression before transplantation ($n = 2$), donor health problems ($n = 2$) and unknown reasons ($n = 4$).

3.4 No-donor group

Of the 92 patients in the no-donor group, 42 eventually underwent HSCT (Table 2): autotransplantation ($n = 3$), allo-HSCT from HLA mismatched-related donors ($n = 4$), allo-HSCT from an HLA matched-unrelated donor ($n = 28$), and allo-HSCT from an HLA-mismatched unrelated donor ($n = 7$). Eleven patients underwent a transplantation during CR1 from an unrelated donor or mismatched-related donor at a median of 281 days (range 170–1700 days) from CR1, significantly later than those transplanted during CR1 in the donor group ($p < 0.001$). Thirty-one patients received a transplantation after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 329 days (range 92–876 days) and 519 days (range 167–1373 days), respectively.

3.5 Comparison of donor versus no-donor groups

The actual risk of relapse at 8 years was significantly lower in the donor group than in the no-donor group (52 vs. 77%, respectively, HR, 0.58; 95% CI, 0.39–0.88; $p = 0.008$; Table 3). The TRM did not significantly differ between the donor and the no-donor groups (16 vs. 17%, respectively, HR, 0.97; 95% CI, 0.34–2.80; $P = 0.959$; Table 3). Seven

Table 2 Patients' characteristics

	Donor	No-donor	p
Total number	73	92	
Age			
Median (range)	37 (16–50)	36 (15–50)	0.60[a]
15–35 years	33	46	
36–50 years	40	46	0.54[b]
Sex			
M/F	44/29	45/47	0.15[b]
WBC at diagnosis (10^9/l) (range)	3.8 (0.05–36.8)	5.1 (0.14–45.0)	0.16[a]
MPO positivity of blasts (range)	30 (0–100)	50 (0–100)	0.18[a]
FAB classification			
M0	4	6	
M1	18	25	
M2	22	24	
M4	20	23	
M5	7	14	
M6	1	0	
M7	1	0	0.67[b]
Performance status			
0–1	66	84	
2–3	7	8	0.70[b]
Risk classification by JALSG scoring system			
Intermediate	64	84	
Poor	9	8	0.45[b]
Cytogenetics			
t(8;21) or inv(16)	4	4	0.74[b]
Chemotherapy group			
Group A	38	42	
Group B	30	47	0.28[c]
Not randomized	5	3	
Allogeneic transplant			
During CR1	38	11	
		9 from UD	
		1 from MUD	
		1 from MRD	
After relapse	18	31	
No transplant	17	50	

UD HLA-matched unrelated donor, *MUD* HLA-mismatched unrelated donor, *MRD* HLA-mismatched related donor, *WBC* white blood count, *MPO* myeloperoxidase

[a] Mann–Whitney test

[b] Chi-square test

[c] Chi-square test excluding non-randomized

patients in the donor group and four in the no-donor group died of transplant-related causes during CR1. The lower RR in the donor group resulted in a significantly better DFS compared with the no-donor group (39 vs. 19%, respectively, HR, 0.63; 95% CI, 0.44–0.92; $P = 0.016$; Table 3; Fig. 3). The significant superiority of DFS in the donor group translated into a higher OS rate, but the difference in OS between the two groups did not reach statistical significance (46 vs. 29%, HR, 0.70; 95% CI, 0.47–1.06; $p = 0.088$; Table 3; Fig. 4).

The donor/no-donor analysis was performed on the intention-to-treat principal, which may underestimate the beneficial effect of allo-HSCT probably because of low compliance of transplantation. The 8-year DFS and OS of the recipients actually transplanted during CR1 ($n = 38$) in the donor group were significantly better than those of the patients not transplanted in the no-donor group ($n = 50$); 58 versus 27%, HR, 0.36; 95% CI, 0.20–0.66; $p < 0.001$, and 61 versus 24%, HR, 0.36; 95% CI, 0.19–0.68; $p = 0.001$, respectively.

Table 3 Effects of donor availability on outcome in donor and no-donor groups

Outcome	Donor			No-donor			p	HR (95% CI)
	n	No. of events	Probability of outcome at 8 years ±SE (%)	n	No. of events	Probability of outcome at 8 years ±SE (%)		
All patients	73			92				
RR		36	52 ± 6		67	77 ± 5	0.008	0.58 (0.39–0.88)
TRM		7	16 ± 6		7	17 ± 7	0.959	0.97 (0.34–2.80)
DFS		44	39 ± 6		74	19 ± 4	0.016	0.63 (0.44–0.92)
OS		37	46 ± 7		61	29 ± 6	0.088	0.70 (0.47–1.06)
Age ≤35	33			46				
RR		17	52 ± 9		31	70 ± 7	0.309	0.74 (0.41–1.33)
TRM		2	12 ± 8		3	15 ± 8	0.785	0.78 (0.13–4.71)
DFS		20	39 ± 9		34	26 ± 7	0.366	0.78 (0.45–1.35)
OS		18	42 ± 10		27	35 ± 9	0.860	0.95 (0.52–1.72)
Age >35	40			46				
RR		19	52 ± 9		36	85 ± 6	0.006	0.46 (0.26–0.81)
TRM		5	19 ± 8		4	19 ± 11	0.962	1.03 (0.27–3.92)
DFS		24	39 ± 8		40	12 ± 5	0.012	0.52 (0.31–0.87)
OS		19	49 ± 9		34	24 ± 7	0.031	0.54 (0.31–0.95)

RR relapse rate, *DFS* disease-free survival, *TRM* treatment-related mortality, *OS* overall survival

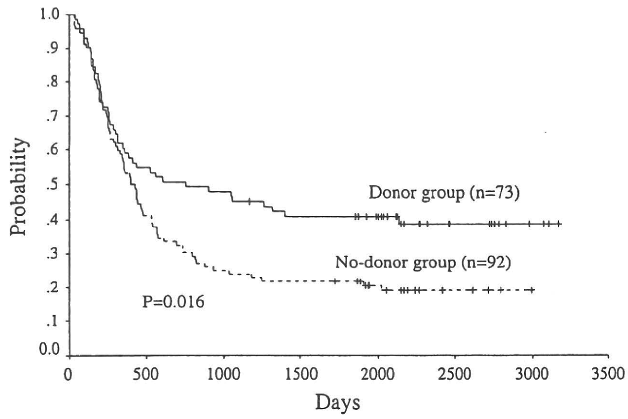


Fig. 3 Disease-free survival in donor and no-donor groups

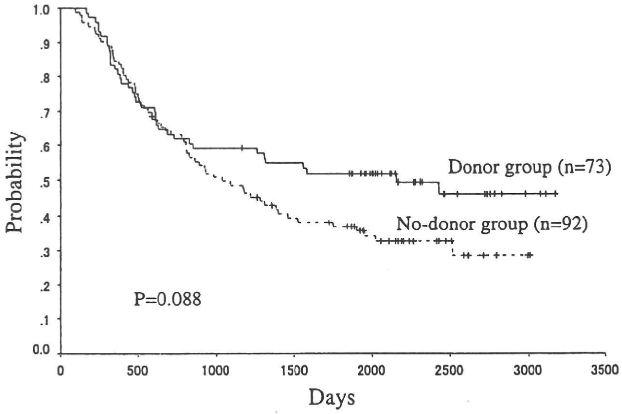


Fig. 4 Overall survival in donor and no-donor groups

3.6 Subset analysis according to patient age

The OS of the patients younger than 35 years of age were comparable between the donor and the no-donor groups (Fig. 5a). However, the OS of the patients aged >35 in the donor group was significantly better compared with the no-donor group (49 vs. 24%, respectively, HR, 0.54; 95% CI, 0.31–0.95; $p = 0.031$; Table 3; Fig. 5b). The RR, TRM, DFS and OS in the donor group were comparable between the two age categories (Table 3; Fig. 5c). In contrast, OS and DFS were marginally worse in the no-donor group of patients aged >35 than ≤35 years (Table 3; Fig. 5d). The distribution of the cytogenetic profile, risk by the JALSG scoring system, myeloperoxidase positivity of blasts, WBC count, FAB classification and performance status at diagnosis did not significantly differ between the two age categories in the no-donor group (data not shown).

4 Discussion

Many clinical trials have compared allo-HSCT with chemotherapy as a post-remission therapy for the patients with AML during CR1. Most of these targeted all patients in CR1 as a single population without prospective stratification by the prognostic factors. Thus, patients were simply assigned into the allo-HSCT or the chemotherapy groups according to donor availability [7, 10, 17, 18]. Here, we

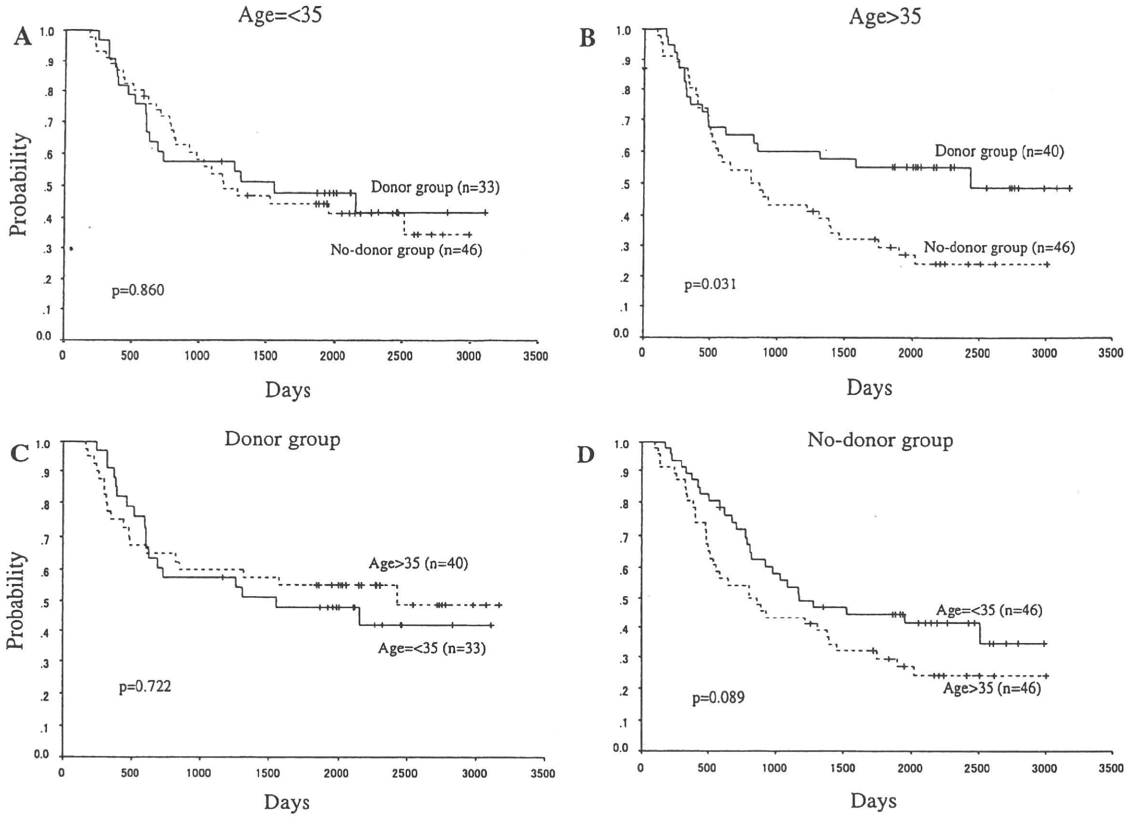


Fig. 5 Overall survival of patients according to age (**a** and **b** ≤35 and >35 years, respectively) and donor availability (**c** and **d**, donor and no-donor groups, respectively)

prospectively compared the effectiveness of allo-HSCT with chemotherapy among patients who were stratified into intermediate or poor risk groups according to JALSG scoring, which constitutes a new means of predicting the prognosis of AML. When this study was planned, as the availability of the cytogenetic study was expected to be variable, and the JALSG scoring system was revealed to be useful to stratify the patients, we adopted a scoring system to select the intermediate and poor risk patients. In contrary to our expectation, cytogenetic studies were performed in 99.2% of the registered patients and the results were available in 97% of the patients. Of 330 CR patients younger than 50 years old, cytogenetic studies disclosed that 97 had good prognostic chromosomal abnormalities, i.e., t(8;21) or inv(16). The OS was significantly better among patients with than without good prognostic cytogenetic profiles (70 vs. 47% at 5 years, with HR, 0.51; 95% CI, 0.34–0.77; $p = 0.001$; Fig. 2b). According to JALSG scoring, 87, 10 and 0 patients with good prognostic cytogenetic abnormalities corresponded to the good, intermediate and poor risk groups, respectively. More good risk patients were selected using this scoring system than by that using karyotype of AML cells alone and about 10% of patients who might be classified into the good risk group by cytogenetic profiles entered the comparison groups by the JALSG scoring system. The JALSG scoring system, which resembles the index used in the Bordeaux Grenoble Marseille Toulouse (BGMT) intergroup study [18], obviously separated patients with a good prognosis who should be excluded from the transplantation trials.

Allo-HSCT prevents AML relapse through intensive cytoreduction using high-dose chemoradiotherapy and graft-versus-leukemia effects. However, previous trials have not always shown advantages of this strategy on the survival of AML patients in CR1. Some studies have not found a benefit of allo-HSCT either on DFS or OS [7, 8], and some showed an advantage only on DFS [10, 17] compared with chemotherapy/auto-transplantation. Retrospective subgroup analysis and meta-analysis have shown a better OS in the donor group [10, 13, 19, 20], demonstrating the importance of limiting the indication of allo-HSCT for only the patients with an intermediate or poor risk.

The following issues should be considered regarding the prospective comparison of allo-HSCT with chemotherapy: assignment of patients according to sibling donor availability [21], low compliance of allo-HSCT for patients in the donor group, and allo-HSCT performed in the no-donor group from unrelated donors. We could compare the effectiveness of treatment strategies using the intention-to-treat analysis. However, the intrinsic issues of this type of trial and recent advances in alternative stem cell sources will cause difficulties with future prospective comparison of allo-HSCT and chemotherapy using a similar study design.

Although the comparison was performed among patients in the intermediate and poor risk groups, the benefit of allo-HSCT was not significant in OS. Low compliance of allo-HSCT during CR1 in the donor group (52% in the current trial) and allo-HSCT in the no-donor group (total 45%; 11% during CR1) appeared to make the efficacy of allo-HSCT underestimated, especially with regard to OS. However, survival was significantly better among older patients in the donor group (Table 3; Fig. 5b), which seemed to contradict previous findings [19]. Age usually adversely affects allo-HSCT outcome, but it was not associated with the decrease of OS in the donor group in the present study (Table 3; Fig. 5c). Low incidence of TRM probably allowed the powerful anti-leukemic effect of allo-HSCT to function properly, indicating the advantage of allo-HSCT especially among older patients with leukemia that was more resistant to chemotherapy than that among younger patients [1] shown in the no-donor group (Fig. 5d), and caused a contrary result from HOVON/SAKK study. The recent reduction in TRM seemed to contribute much to these results as suggested by others [22, 23]. Different population of the cohorts selected by JALSG scoring and by cytogenetic profiles might also have influenced the present findings.

Molecular markers can be very useful for selecting patients who will most likely benefit from allo-HSCT during CR1 among those with a normal karyotype, which comprises the largest group of patients with AML [24]. The overall safety of allo-HSCT obviously needs improvement, and also patients with chemotherapy-resistant AML who could benefit from allo-HSCT should be identified. Thus, stratification of patients with AML should be improved using a combination of leukemic cell karyotype and, genetic markers and also other clinical findings.

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