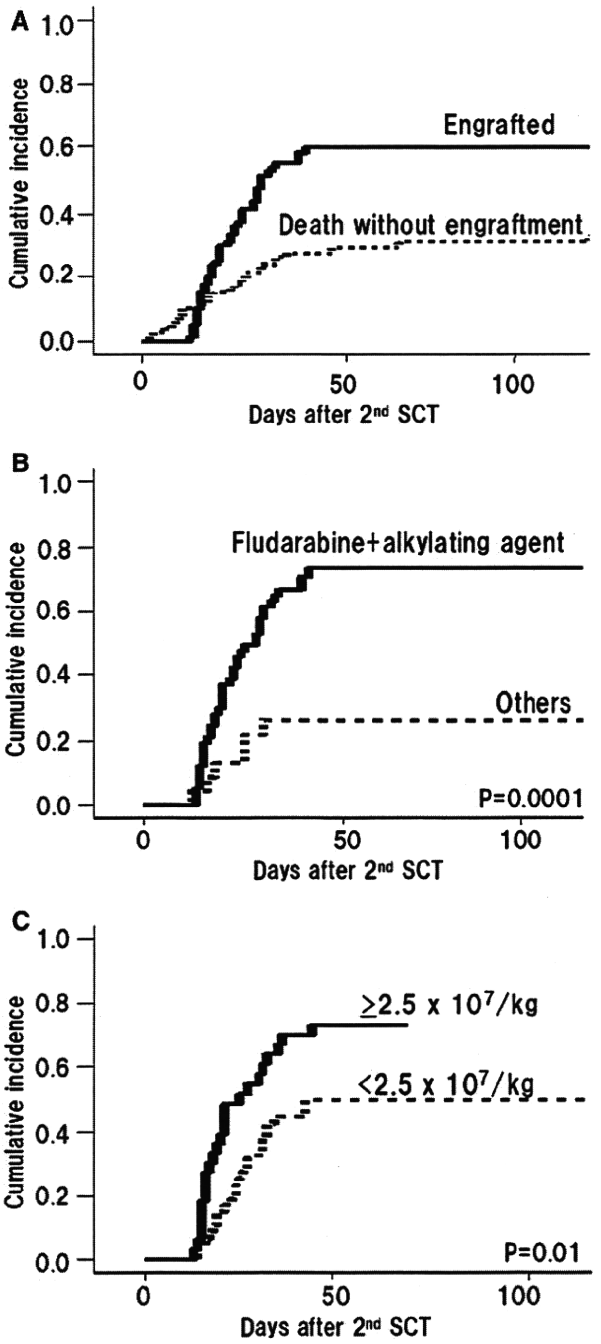

Figure 1. Cumulative incidence of neutrophil engraftment. (A) The cumulative incidences of neutrophil engraftment (solid line) and death without engraftment (dotted line) are shown. (B) The cumulative incidence of neutrophil engraftment was higher in patients who received alkylating agent–containing regimen (solid line) than in those who did not (dotted line) ($P = .0001$). (C) The cumulative incidence of neutrophil engraftment was higher in patients who received graft containing TNC $\geq 2.5 \times 10^7$/kg than in those who did not ($P = .01$).

The incidence of neutrophil engraftment was higher in patients who received alkylating agents including melphalan, busulfan, and cyclophosphamide as part of conditioning for the second SCT (73% versus 26%, $P = .0001$), as shown in Figure 1B. The engraftment rate was similar among the 3 types of conditioning regimens that included alkylating agents. The incidence of neutrophil engraftment was higher when patients received 2-4 Gy TBI (71% versus 50%, $P = .03$). The engraftment rate was higher in patients who received graft containing a higher number of TNC $\geq 2.5 \times 10^7$/kg than in those who received $< 2.5 \times 10^7$/kg (73% versus 50%, $P = .01$) (Figure 1C). When 2.0×10^7/kg was used as a cutoff for TNC, the engraftment rate tended to be higher in patients who received graft that contained higher TNC (65% versus 36%, $P = .08$). The standard-risk group at the first SCT was also associated with a higher neutrophil engraftment than the high-risk group (70% versus 43%, $P = .02$). The number of $CD34^+$ cells was evaluated in 68 patients with a median of 0.6×10^5/kg (range: 0.1-4.22), and this was not associated with the neutrophil engraftment rate. In 14 patients who received MTX for GVHD prophylaxis after the second SCT, neutrophil engraftment was delayed (median 31 days; range: 14-44 days) compared to those who did not receive MTX (median 21 days; range: 13-42 days), although the ultimate engraftment rates were similar (50% versus 61%, $P = .26$). In 8 patients who received ATG for the second SCT, 3 (38%) achieved neutrophil engraftment. Anti-HLA antibody was examined before the second SCT in 28 patients. In 9 patients with positive anti-HLA antibody, only 2 (22%) achieved engraftment and 6 (67%) died within 28 days after RICBT. Among 47 patients who obtained neutrophil engraftment, with chimerism analyses available in 44 patients at a median of 30 days (range: 12-119), 42 patients (95%) achieved complete donor chimerism, and 2 continued to show mixed chimerism. Among 61 patients who survived for more than 28 days, 31 patients (51%) achieved platelet engraftment that was more than 20,000/μL, and subsequently 27 patients (44%) obtained platelet engraftment more than 50,000/μL. The median day of last platelet transfusion was 53 days (range: 15-197) after the second SCT.

RRT and aGVHD (Table 3)

Grade 3 or 4 RRT excluding febrile neutropenia was recognized in 48 patients (60%) after the second SCT, which included toxicities associated with stomatitis (n = 8), liver damage (n = 20), diarrhea (n = 11), renal and bladder (n = 10), heart (n = 8), lung (n = 21), and central nervous system (CNS) (n = 18). The details of CNS complication were limbic encephalitis including HHV-6 encephalitis (n = 8), brain hemorrhage (n = 3), cerebral aspergillosis (n = 2), and others (n = 5). TRM was 75% in 48 patients who developed grade 3 or 4 organ toxicities, and 28% in the remaining 32 patients without grade 3 or 4 organ toxicities after the second SCT. The probabilities of grades II-IV and III-IV aGVHD were 25% and 11%, respectively,

Table 3. Outcomes after the Second SCT (RICBT)

Parameters	n = 80
The engraftment rate in 61 patients surviving >28 days	45 (74%)
GF in 61 patients surviving >28 days	13 (21%)
Grade 3-4 organ toxicities*	48 (60%)
Documented infection	58 (63%)
CMV antigenemia	36 (45%)
Acute GVHD	
Grade II-IV	20 (25%)
Grade III-IV	9 (11%)
Relapse	12 (15%)
Death	51 (64%)
The median day of death after second SCT	37 days (range: 2-611)
Causes of death	
Infection	33 (65%)
Bacterial	14
Fungal	6
Viral	8
Complex or unknown	5
Relapse	6 (12%)
Acute GVHD	1 (2%)
Other†	11 (22%)

SCT indicates stem cell transplantation; RICBT, reduced-intensity cord blood transplantation; GF, graft failure; CMV, cytomegalovirus; GVHD, graft-versus-host disease.
*Grade of organ toxicities was evaluated by the CTCAE v3.0 [40].
†Other causes included cerebral hemorrhage (n = 3), multiorgan failure (n = 2), thrombotic microangiopathy (n = 2), veno-occulusive disease of the liver (n = 1), interstitial pneumonitis (n = 1), heart failure (n = 1), and secondary malignancy (n = 1).

and only 1 patient who had grade IV aGVHD died of GVHD.

TRM, Relapse, and Causes of Death (Table 3)

Fifty-one patients (64%) died at a median of 37 days (range: 2-611) after the second SCT. The cumulative incidence of TRM was 45%, 56%, and 61% at day 100, 1 year, and 2 years, respectively (Figure 2A), and infection was the most frequent cause of death. Notably, death that was directly related to bacterial infection occurred during prolonged neutropenia in the first 2 months after the second SCT. In 11 patients with grade 3 or 4 carryover organ toxicities at the second SCT, 8 (73%) died of TRM (Figure 2B). TRM was higher in patients who received an oral busulfan-based regimen (72%) than in those who received melphalan-based (50%) or cyclophosphamide-based (53%) regimens. Underlying malignancy relapsed in 12 patients (16%) at a median of 158 days (range: 22-781) after the second SCT, and 3 patients received a third SCT after relapse. Overall, 6 patients died of disease recurrence.

Survival

The median follow-up time in the surviving patients was 325 days (range: 89-1069) after the second SCT. The Kaplan-Meier curves of OS and PFS of all 80 patients are shown in Figure 3A. The estimated

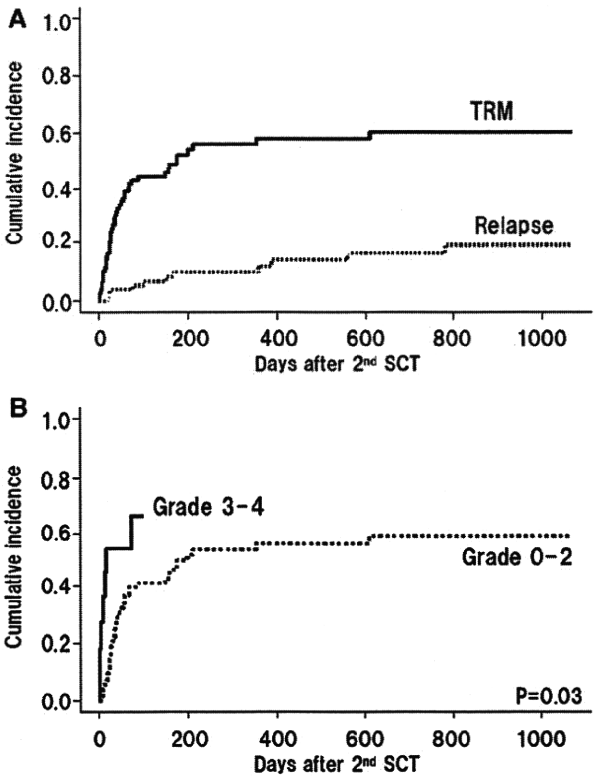

Figure 2. Cumulative incidence of transplantation-related mortality (TRM) and relapse. (A) The cumulative incidences of TRM (solid line) and relapse (dotted line) are shown. (B) The cumulative incidence of TRM was higher in patients who had grade 3 or 4 carryover organ toxicity before the second SCT (solid line) than in those who did not (dotted line) ($P = .03$).

rates of OS and PFS at 1 year after the second SCT were 33% and 29%, respectively. The OS was worse in 11 patients who had grade 3 or 4 carryover organ toxicities at the second SCT compared to the other 69 patients. OS was significantly better in patients who had standard-risk disease at the first SCT than in those who had high-risk disease (Figure 3B).

Factors Associated with Engraftment and OS

In a univariate analysis, standard risk at the first SCT, PS 0-1 at the second SCT, conditioning that included alkylating agents or 2-4 Gy TBI, and a higher dose of infused TNC ($\geq 2.5 \times 10^7$/kg) were significantly associated with a higher probability of engraftment. Carryover organ toxicities ($P = .09$) and infection at the second SCT ($P = .07$) were also included in a multivariate analysis. The type of engraftment failure after first SCT did not have an influence on outcome after the second SCT (primary versus secondary). As a result, higher TNC dose ($\geq 2.5 \times 10^7$/kg: hazard ratio [HR] = 2.14, 95% confidence interval [CI], 1.29-3.52; $P = .003$), conditioning that included alkylating agents (HR = 3.70, 95% CI, 1.51-9.09; $P = .005$), and standard risk at first SCT (HR = 2.04, 95% CI, 1.06-3.85; $P = .03$)

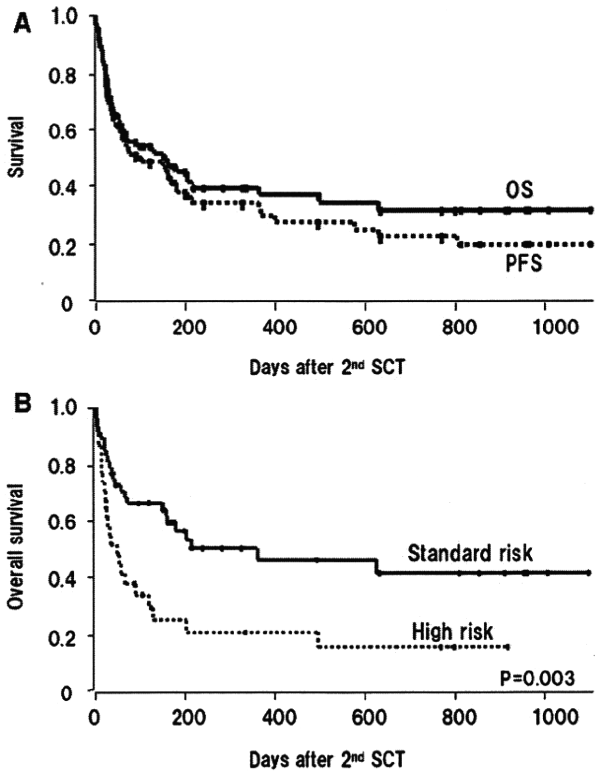

Figure 3. OS and PFS. (A) The Kaplan-Meier estimates of OS (solid line) and PFS (dotted line) are shown. (B) OS in patients who were high risk at the first SCT (dotted line) was lower than that in those who were standard risk (solid line) ($P = .003$).

remained significant in the multivariate Cox proportional hazards regression analysis (Table 4). In a multivariate Cox proportional hazards regression analysis of OS, high-risk disease at the first SCT (HR = 2.14, 95% CI, 1.20-3.81; $P = .01$) and grade 3 or 4 carryover organ toxicities at the second SCT (HR = 2.84, 95% CI, 1.33-6.06; $P = .007$) were associated with an increased risk of poor OS (Table 5).

DISCUSSION

Based on data obtained from this large cohort of patients, we showed that neutrophil engraftment can be achieved in >70% of adult patients who received RICBT as salvage therapy for GF. Although our cohort was composed of rather older patients, the engraftment rate was comparable to that reported in primary CBT [17,18,29,34]. Considering the poor PS and carryover infection and organ toxicities, salvage therapy with RICBT is a feasible option that gave a 1-year OS of 33%. Nevertheless, this procedure is still associated with a high rate of TRM (45% at day 100), 60% of which was related to infectious complications, and we performed analyses to identify the risk factors for engraftment and survival.

Guardiola et al. [22] reported in 82 patients with various hematological diseases who underwent second allogeneic SCT that the neutrophil engraftment rate and 3-year OS were 70% and 30%, respectively. They showed that a longer intertransplant interval of ≥80 days was associated with a higher neutrophil engraftment rate and survival in a multivariate analysis. McCann et al. [19] also reported that a longer interval of ≥60 days was associated with a higher engraftment rate and OS in 41 patients with aplastic anemia. In our study, we did not find any association between interval and neutrophil engraftment or OS, and this discrepancy may be because of differences in the cohorts of patients evaluated. In the report by Guardiola et al. [22], the proportions of patients who experienced secondary GF and who received transplant from an HLA-matched sibling donor were much higher than in our study (66% versus 20%, 78% versus 6%, respectively). Grandage et al. [25] reported successful engraftment in 12 patients who underwent a second SCT from the same unrelated donor after GF. In the current study, however, it was not possible to perform a second SCT using an unrelated BM donor because most patients had poor PS, organ toxicities, or infections with prolonged cytopenia (ANC $<100/mm^3$).

Our data confirmed that a higher number of infused CB cells (TNC $\geq 2.5 \times 10^7$/kg) was associated with a higher probability of neutrophil engraftment after the second RICBT ($P = .01$), which was consistent with previous reports [4,42]. Because the median body weight of patients in this study was 55 kg, CB units containing $>2.0 \times 10^7$/kg were available in >80% of patients. A double cord blood unit strategy might be favorable as previous reported, because a higher cell dose was associated with better survival [43]. Although in a previous study by Wagner et al. [44], the total number of $CD34^+$ cells was reported to be a major determinant of neutrophil recovery after CBT, our present findings did not confirm this point. Another discrepancy with previous reports [44] is that HLA disparity between the donor and recipient was not related to the engraftment rate in our study. We also examined the effect of HLA mismatch with serological HLA-A, B and allele DRB1 except for 5 patients whose allele typing was not performed. However, the results remained unchanged, and there was no impact on engraftment and OS.

The need for an intensive immunosuppressive conditioning regimen before the second SCT for GF depends on the mechanism of GF, and we found that a fludarabine-based regimen that included alkylating agents was associated with a higher neutrophil engraftment rate. Whereas the use of cytotoxic drugs is not mandatory before stem cell boost for patients who have poor graft function [23,24], intensive immunosuppressive conditioning is essential to suppress residual host T and natural killer cells to

Table 4. Univariate and Multivariate Analysis of Factors Predicting Engraftment after the Second SCT

Covariates	Proportion (%)*	Univariate	Multivariate	
		P	Hazard Ratio (95% CI)	P
Disease risk at the first SCT†		.02		.03
Standard risk	70		2.04 (1.06-3.85)	
High risk	43		1.00	
Type of graft failure		.57		—
Primary	58		—	
Secondary	56		—	
Interval between the first SCT and second SCT		.87		—
<50 days	60		—	
≥50 days	59		—	
PS		.01		—
0-1	81		—	
2-4	46		—	
Carryover organ toxicities at the second SCT‡		.09		—
Grade 0-2	65		—	
Grade 3-4	27		—	
Carryover infection at the second SCT		.07		—
Febrile neutropenia/none	69		—	
Documented infection	51		—	
Conditioning§		.0001		.005
Alkylating agent–containing	73		3.70 (1.51-9.09)	
Other	26		1.00	
TBI		.03		—
2-4 Gy TBI	71		—	
No TBI	50		—	
TNC of the CB		.01		.003
≥2.5 × 10^7/kg	73		2.14 (1.29-3.52)	
<2.5 × 10^7/kg	50		1.00	

SCT indicates stem cell transplantation; PS, performance status; TBI, total-body irradiation; TNC, total nucleated cells; CB, cord blood; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; CML, chronic myelogeneous leukemia; MDS, myelodysplatic syndrome; RAEB, refractory anemia with excess blasts; CI, confidence interval.

Other covariates examined included sex, patient age, conditioning of the first SCT, use of methotrexate as GVHD prophylaxis, and numbers of selorogic HLA mismatch in graft-versus-host and host-versus-graft directions.

*Proportions of patients who achieved neutrophil engraftment.

†Standard risk included acute leukemia and non-Hodgkin lymphoma in any complete remission, CML in any chronic phase, and aplastic anemia. High risk included all other types of leukemia and non-Hodgkin lymphoma categories, and MDS-RAEB.

‡Grade of organ toxicities was evaluated by the CTCAE v3.0 [40].

§Alkylating agents included melphalan, busulfan, and cyclophosphamide. Other conditioning included fludarabine alone and a combination of fludarabine plus thiotepa or etoposide.

overcome immunologic rejection [21,26,45]. As previously reported in patients with aplastic anemia [19,46], the addition of 2-4 Gy TBI to the RIC regimen increased the probability of engraftment in a univariate analysis, although it did not have a significant effect in a multivariate analysis. In our preliminary data, 6 of the 10 patients who received second CBT without cytotoxic conditioning regimen (ie, ATG only, steroid only, etc.) experienced GF again after second SCT. Whereas the addition of alkylating agent and low-dose TBI to the conditioning regimen for the second RICBT enhanced neutrophil engraftment, it did not affect the overall outcomes in our study. To determine the best conditioning regimen for salvage RICBT after GF, further studies to evaluate regimens including fludarabine plus melphalan or cyclophosphamide with or without 2-4 Gy TBI will be required.

In our study, the TRM early after the second RICBT was extremely high (45% at day 100), mainly because of infectious complications, which was consistent with previous reports on CBT [5,17,29,30,47]. This is probably because of a prolonged period of severe neutropenia before and after the second RICBT in patients complicated with GF, which incubated carryover infections. To reduce the incidence of infection-related TRM, frequent monitoring and extensive treatment including granulocyte transfusion to support the intertransplant period may be needed [48]. Alternatively, the earlier application of RICBT while patients are still in better condition without infection may be preferred to reduce TRM.

When patients require a second SCT for GF, the selection of the donor source is critical. Based on the feasibility of second RICBT in our study, we suggest that CB carries the highest priority for selection because of its ready availability. Although the possibility of a second SCT or boost of stem cells from the same related donor of the first SCT has been reported [19,22], 75% of our patients had undergone CBT at the first transplant, which reflects the difficulty of finding a suitable donor. Another possibility is a second SCT from a haploidentical related donor [49,50]. The more rapid neutrophil engraftment after SCT using PBSC

Table 5. Univariate and Multivariate Analysis of Overall Survival after the Second SCT

Covariates	proportion at 1 Year (%)	Univariate P	Multivariate Hazard Ratio (95% CI)	Multivariate P
Disease risk at the first SCT*		.03		.01
Standard risk	50		1.00	
High risk	26		2.14 (1.20-3.81)	
Type of graft failure		.87		—
Primary	36		—	
Secondary	39		—	
Interval between the first SCT and second SCT		.38		—
<50 days	40		—	
≥50 days	31		—	
PS		.2		—
0-1	39		—	
2-4	35		—	
Carryover organ toxicities at the second SCT†		.001		.007
Grade 0-2	41		1.00	
Grade 3-4	0		2.84 (1.33-6.06)	
Carryover infection at the second SCT		.14		—
Febrile neutropenia/none	46		—	
Documented infection	27		—	
Conditioning‡		.69		—
Alkylating agent–containing	35		—	
Other	40		—	
TBI		.56		—
2-4 Gy TBI	37		—	
No TBI	37		—	
TNC of the CB		.77		—
≥2.5 × 10^7/kg	41		—	
<2.5 × 10^7/kg	33		—	

SCT indicates stem cell transplantation; PS, performance status; TBI, total-body irradiation; TNC, total nucleate cells; CB, cord blood; GVHD, graft-versus-host disease; HLA. human leukocyte antigen; CML, chronic myelogeneous leukemia; MDS, myelodysplatic syndrome; RAEB, refractory anemia with excess blasts; CI, confidence interval.

Other covariates examined included sex, patient age, conditioning of the first SCT, use of methotrexate as GVHD prophylaxis, and numbers of serological HLA mismatch in graft-versus-host and host-versus-graft directions.

*Standard risk included acute leukemia and non-Hodgkin lymphoma in any complete remission, CML in any chronic phase, and aplastic anemia. High risk included all other types of leukemia and non-Hodgkin lymphoma categories, and MDS-RAEB.

†Grade of organ toxicities was evaluated by the CTCAE v3.0. [40].

‡Alkylating agents included melphalan, busulfan, and cyclophosphamide. Other conditioning included fludarabine alone and a conbination of fludarabine plus thiotepa or etoposide.

from a haploidentical donor may decrease the risk of infectious complications in patients suffering from GF. However, compared to CBT, the feasibility of this procedure has not yet been established and the incidence of acute GVHD increases. In addition, collection of autologous stem cells prior to CBT might be an option to salvage a fraction of patients who experienced GF as previously reported [51]. Nevertheless, further studies are warranted to determine which types of transplant, CBT or SCT from a haploidentical related donor, can achieve better outcomes for patients suffering from GF.

This study has several inherent limitations. First, the patients and transplantation characteristics including the conditioning regimen, GVHD prophylaxis, and supportive care varied among the different centers. Second, the timing of and general conditions at the second RICBT differed among patients. Third, there may be unrecognized biases because only successful cases may have been collected. Finally, the duration of follow-up for patients in this study was too short to draw any definite conclusions. Nevertheless, the large cohort of 80 patients who received RICBT as salvage therapy for GF in the current study allowed us to make several clinically relevant observations.

In conclusion, we suggest that salvage therapy with a second RICBT is a feasible therapeutic option for patients who are suffering from GF. To achieve stable neutrophil engraftment after the second RICBT, conditioning with fludarabine plus alkylating agents and the infusion of CB containing ≥2.5 × 10^7/kg cells are preferable. A high TRM early after RICBT emphasizes the need for the earlier application of RICBT while patients still have better PS and have not yet acquired infection and organ toxicity. Prospective trials are needed to determine the ultimate utility of rescue RICBT using a fludarabine-based regimen including alkylating agents for patients suffering from GF.

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AUTHORSHIP STATEMENT

F. Waki and T. Fukuda played a major role in designing and performing the research, verifying the integrity of and analyzing the data, and writing the manuscript. Y. Kanda played a major role in the statistical analyses and in developing the concept of the research. K. Masuoka, T. Yamashita, A. Wake, and S. Takahashi designed the research and contributed vital data to generate the final database. Y. Takaue and S. Taniguchi designed the research and contributed to writing or interpreting relevant parts of the manuscript. All other coauthors contributed vital data to generate the final database and interpreted relevant parts of the manuscript.

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APPENDIX

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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,

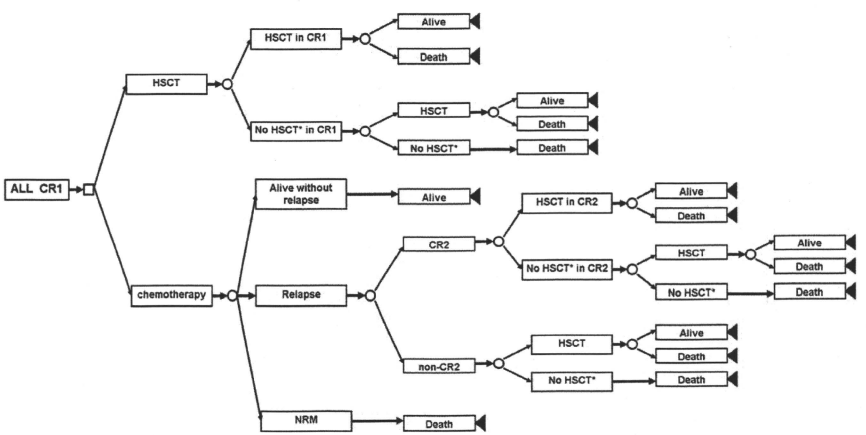

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic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

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.

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 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.

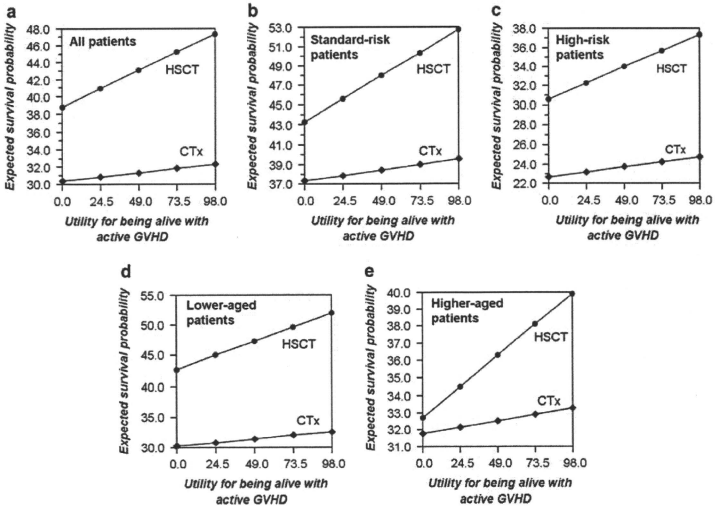

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently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

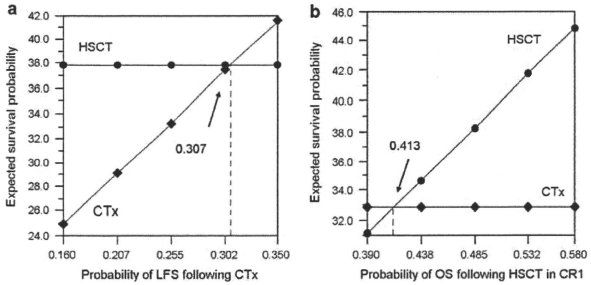

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy (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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Association between serum high-molecular-weight adiponectin level and the severity of chronic graft-versus-host disease in allogeneic stem cell transplantation recipients

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Association between serum high-molecular-weight adiponectin level and the severity of chronic graft-versus-host disease in allogeneic stem cell transplantation recipients

(Running title)

Association between adiponectin and chronic GVHD

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Abstract

Recently, a growing body of evidence has suggested that adiponectin, which is secreted by adipose tissues, plays a critical role in obesity-related and autoimmune diseases. We compared the concentrations of adiponectin among 26 normal subjects and 34 allogeneic stem cell transplantation recipients. The concentrations of adiponectin were significantly higher in recipients with cGVHD than those in subjects without cGVHD (21.7±11.0 vs 9.1±6.1 μg/ml in females ($P<0.001$), and 10.1±6.8 vs 4.3±2.9 μg/ml in males ($P=0.003$)). Multivariate analysis revealed that a higher concentration of adiponectin was associated with female gender (β-coefficient 8.2, $P<0.0001$) and the severity of cGVHD (β-coefficient 6.6, 12.7, and 15.6, $P <0.01$, each for mild, moderate, and severe cGVHD, respectively). In addition, adiponectin levels increased as cGVHD progressed, decreased as cGVHD improved, and did not change with stable cGVHD. In conclusion, adiponectin was associated with the severity of cGVHD, and might play a role in the pathophysiology of cGVHD.

Introduction

Chronic graft-versus-host disease (cGVHD) is a major problem following allogeneic stem cell transplantation (allo-SCT), and dramatically impairs the recipient's quality of life [1,2]. Clinical symptoms of cGVHD resemble those of autoimmune diseases, including scleroderma and sicca syndrome. Therefore, an immune abnormality similar to that in autoimmune diseases may play a role in the development of cGVHD, although the actual pathophysiology remains unknown [3]. In cGVHD, inflammatory cytokines that modulate T and B cells, such as tumor necrosis factor alpha (TNF-α) and soluble B-cell activation factor, have been well investigated [4,5]. However, it remains to be elucidated whether other endocrine substances may play a role in cGVHD. Recently, it has been revealed that adiponectin, an adipokine that is secreted by adipose tissues, is associated with immunity and inflammation, and may play a critical role in both obesity-related and autoimmune diseases [6-11]. Therefore, we compared the serum adiponectin levels among allo-SCT recipients and normal subjects to assess the association between adiponectin and cGVHD.

Patients and methods

We retrospectively reviewed the clinical records of 34 patients (21 with myeloid, 11 with lymphoid malignancies, and 2 with aplastic anemia) who received allo-SCT between March 2008 and March 2010 and who survived for at least 180 days after SCT. The diagnosis and the severity of cGVHD were determined based on the NIH classification [12]. In addition, we collected data regarding age, gender, and BMI of these patients as well as those of 26 normal healthy subjects as a control.

We measured the serum concentrations of high-molecular-weight (HMW) adiponectin by an enzyme-linked immunosorbent assay according to the manufacturer's instructions (Fujirebio Inc., Tokyo, Japan). To compare HMW-adiponectin levels among groups, we used the first samples obtained at least 6 months after SCT, and performed Student's t-test / ANOVA for categorical variables, and a regression analysis for continuous variables. Thereafter, multiple regression analysis was performed with backward stepwise selection. Furthermore, we calculated the ratios of later-to-prior HMW-adiponectin between each pair of consecutive samples in the same patients, and assessed the impact of the clinical changes in cGVHD on HMW-adiponectin concentrations using ANOVA after logarithmic conversion among recipients grouped according to worsening, stable, and improving cGVHD. Statistical significance was defined as a two-sided P-value of <0.05. This study was approved by the institutional review board of Jichi Medical University and all patients gave written informed consents for the cryopreservation and analyses of blood samples in accordance with the Declaration of Helsinki.

Results and discussion

Patient characteristics

The characteristics of the 34 allo-SCT recipients are presented in Table 1. Of these, 22 had cGVHD at the sampling, including 7 and 4 with moderate and severe cGVHD respectively. Sampling was performed at a median 189 days after SCT (range: 177-434 days). Their median age was 38.5 years (range: 16-65). Their median weight loss after SCT and median BMI at sampling were 4.1 kg (range: -16.9-26.5 kg) and 20.3 (15.3-34.6), respectively. The 26 normal healthy subjects included 11 males and 15 females. Their median age and BMI were 40 years (range: 28-68) and 21.71 (range: 17.31-29.47), respectively.

Comparison of the concentrations of HMW-adiponectin

Gender and BMI are known to be associated with the concentration of adiponectin [13]. Therefore, HMW-adiponectin levels were compared among groups stratified according to gender and BMI (Figure 1-A and 1-B). The concentrations of HMW-adiponectin were significantly higher in recipients with cGVHD than those in subjects without cGVHD (21.7±11.0 vs 9.1±6.1 μg/ml in females ($P<0.001$), and 10.1±6.8 vs 4.3±2.9 μg/ml in males ($P=0.003$), respectively, Figure 1-A). The concentration of HMW-adiponectin was inversely correlated with BMI ($R^2=0.20$, $P=0.0003$). Furthermore, the HMW-adiponectin levels in recipients with cGVHD were higher than those in normal subjects and recipients without cGVHD in each stratified BMI group (Figure 1-B).

When we analyzed only allo-SCT recipients, a univariate analysis revealed that a high HMW-adiponectin level was associated with female gender, low BMI, the presence and the severity of cGVHD, gut involvement and steroid administrations. Multiple regression analysis revealed that a high HMW-adiponectin level was associated with female gender, steroid administrations, and the severity of cGVHD among allo-SCT recipients (Table 1). When the 26 normal subjects were included, it was further confirmed that a high