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,

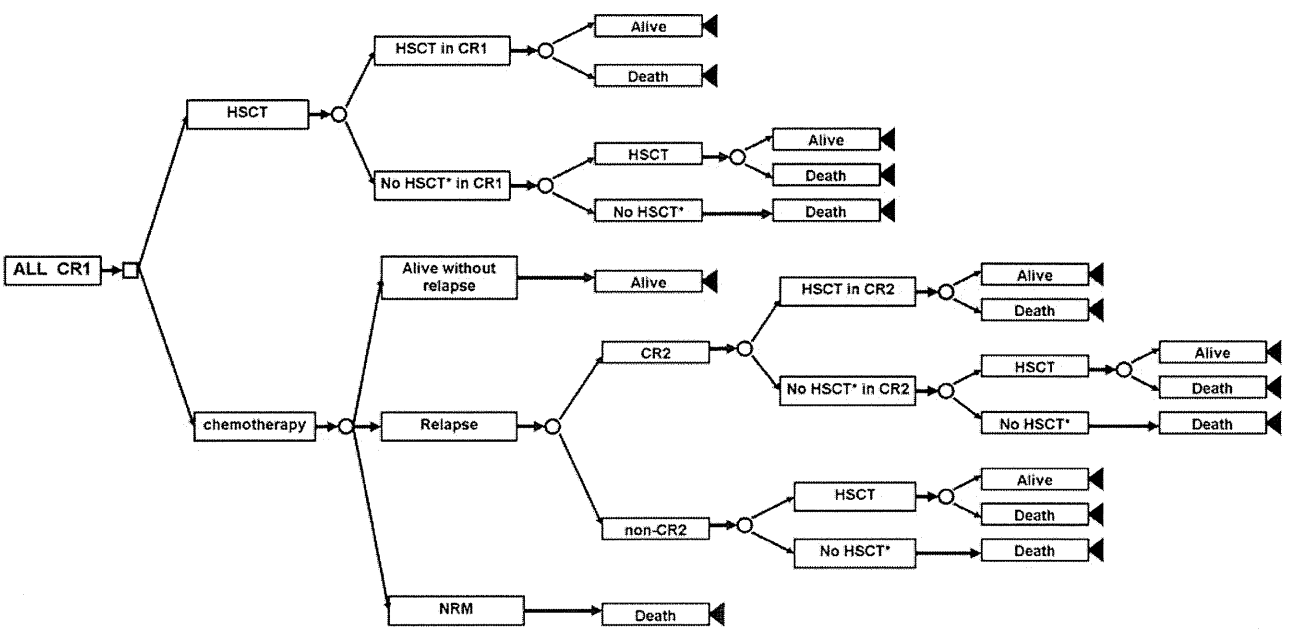

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic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

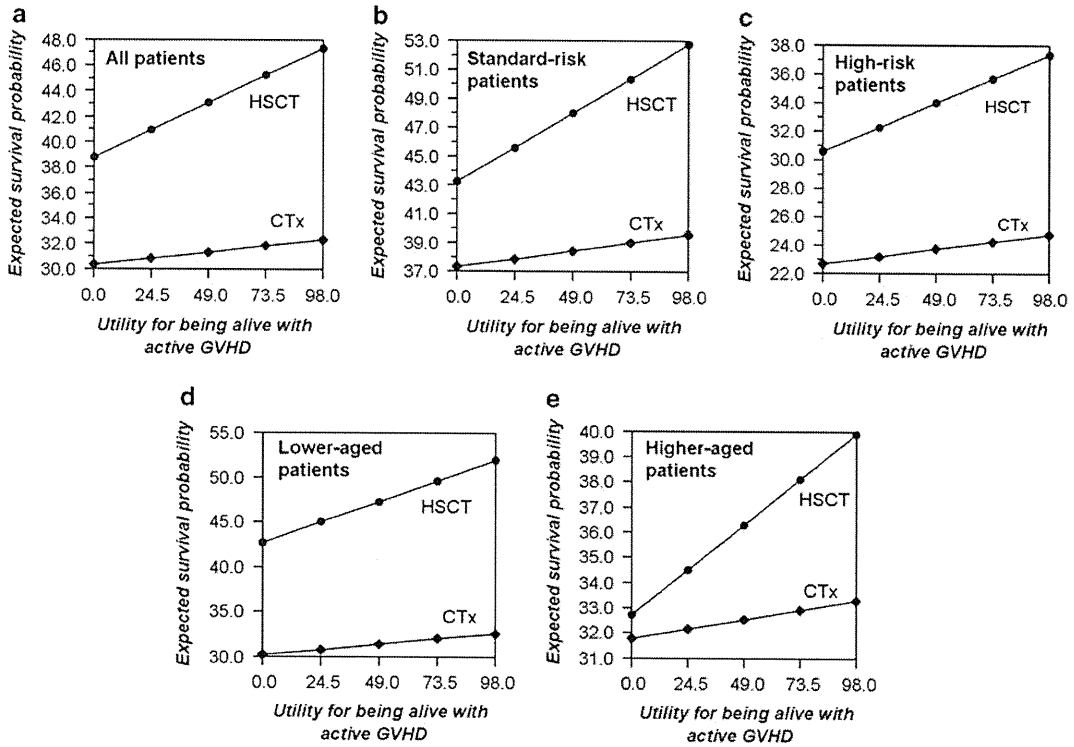

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently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

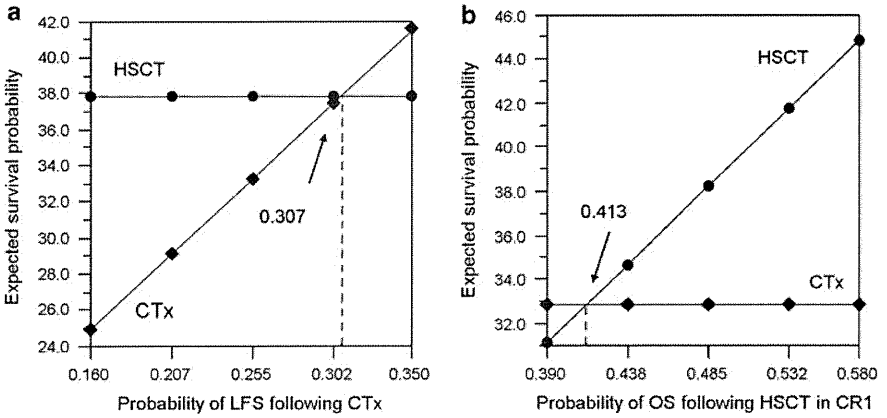

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy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

Acknowledgements

We thank all staff of the JALSG centers and the JSHCT centers for providing excellent patient care and reporting clinical data.

References

1 Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2006, 133–141.
2 Sebban C, Lepage E, Vernant JP, Gluckman E, Attal M, Reiffers J *et al.* Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol* 1994; **12**: 2580–2587.
3 Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. *Cancer* 2006; **106**: 2657–2663.
4 Takeuchi J, Kyo T, Naito K, Sao H, Takahashi M, Miyawaki S *et al.* Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and

maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. *Leukemia* 2002; **16**: 1259–1266.
5 Takeshita A, Ohnishi K, Miyazaki Y, Jnnai I, Miyawaki S, Takahashi M *et al.* P-Glycoprotein is related to the achievement of complete remission but not to disease-free survival in adult acute lymphoblastic leukemia: A Prospective Analysis in the JALSG-ALL97 Study. *Blood* 2004; **104**: (311A) (abstract 1095).
6 Atsuta Y, Suzuki R, Yoshimi A, Gondo H, Tanaka J, Hiraoka A *et al.* Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. *Int J Hematol* 2007; **86**: 269–274.
7 Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *Hematology Am Soc Hematol Educ Program* 2009, 371–381.
8 Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK *et al.* In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008; **111**: 1827–1833.
9 Sung L, Buckstein R, Doyle JJ, Crump M, Detsky AS. Treatment options for patients with acute myeloid leukemia with a matched sibling donor: a decision analysis. *Cancer* 2003; **97**: 592–600.
10 Pidala J, Anasetti C, Kharfan-Dabaja MA, Cutler C, Sheldon A, Djulbegovic B. Decision analysis of peripheral blood versus bone marrow hematopoietic stem cells for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2009; **15**: 1415–1421.
11 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; **18**: 695–706.
12 Tavernier E, Boiron JM, Huguet F, Bradstock K, Vey N, Kovacsovics T *et al.* Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia* 2007; **21**: 1907–1914.
13 Thomas DA, Kantarjian H, Smith TL, Koller C, Cortes J, O'Brien S *et al.* Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. *Cancer* 1999; **86**: 1216–1230.
14 Cornelissen JJ, van der Holt B, Verhoef GE, van't Veer MB, van Oers MH, Schouten HC *et al.* Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood* 2009; **113**: 1375–1382.
15 Kiss TL, Abdolell M, Jamal N, Minden MD, Lipton JH, Messner HA. Long-term medical outcomes and quality-of-life assessment of patients with chronic myeloid leukemia followed at least 10 years after allogeneic bone marrow transplantation. *J Clin Oncol* 2002; **20**: 2334–2343.
16 Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. *J Clin Oncol* 2005; **23**: 6596–6606.
17 Fraser CJ, Bhatia S, Ness K, Carter A, Francisco L, Arora M *et al.* Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood* 2006; **108**: 2867–2873.
18 Lee SJ, Kuntz KM, Horowitz MM, McGlave PB, Goldman JM, Sobocinski KA *et al.* Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. *Ann Intern Med* 1997; **127**: 1080–1088.
19 Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making* 1985; **5**: 157–177.
20 Litzow MR. Evolving paradigms in the therapy of Philadelphia chromosome-negative acute lymphoblastic leukemia in adults. *Hematology Am Soc Hematol Educ Program* 2009, 362–370.
21 Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E *et al.* Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009; **27**: 911–918.
22 Morishima Y, Morishita Y, Tanimoto M, Ohno R, Saito H, Horibe K *et al.* Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings; possible role of genetic homogeneity. The Nagoya Bone Marrow Transplantation Group. *Blood* 1989; **74**: 2252–2256.

Int J Hematol (2011) 93:523–531
DOI 10.1007/s12185-011-0817-8

ORIGINAL ARTICLE

Use of mycophenolate mofetil in patients received allogeneic hematopoietic stem cell transplantation in Japan

Minako Iida · Takahiro Fukuda · Kazuhiro Ikegame · Satoshi Yoshihara · Hiroyasu Ogawa · Shuichi Taniguchi · Akiyoshi Takami · Yasunobu Abe · Masayuki Hino · Tetsuya Etou · Yasunori Ueda · Toshiaki Yujiri · Toshimitsu Matsui · Atsuo Okamura · Junji Tanaka · Yoshiko Atsuta · Yoshihisa Kodera · Ritsuro Suzuki

Received: 14 September 2010 / Revised: 15 March 2011 / Accepted: 15 March 2011 / Published online: 5 April 2011

Abstract We evaluated the use of mycophenolate mofetil (MMF) after hematopoietic stem cell transplantation (HSCT) in Japan from 1999 to 2008. MMF was administered to 301 patients, including 157 for the prevention of graft-versus-host disease (GVHD), 94 for the treatment of acute GVHD and 50 for the treatment of chronic GVHD. The three most common doses were 500 mg twice daily, 250 mg three times daily and 1,000 mg twice daily, given to 63, 54 and 45 patients, respectively. The incidence of grade II–IV acute GVHD was 30.0% and grade III–IV was 20.0% in the GVHD prevention group. Among treated patients, disappearance or improvement of subjective symptoms occurred in 57.0% of acute GVHD patients and in 52.0% of chronic GVHD patients. With regard to safety, the following major adverse events (grade 3 or more) were recorded: 31 infections, 31 neutropenia, 28 thrombocytopenia, 25 diarrhea and 1 renal disorder. A total of 116 patients developed grade 3 or 4 adverse events, but 79 were successfully treated with supportive treatment. Thus, our findings suggest that MMF is safe and effective for the

M. Iida · Y. Atsuta · R. Suzuki
Department of HSCT Data Management and Biostatistics, Nagoya University School of Medicine, Nagoya, Japan

M. Iida (✉) · Y. Kodera
Department of Promotion for Blood and Marrow Transplantation, Aichi Medical University School of Medicine, 21, Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan
e-mail: miida@aichi-med-u.ac.jp

T. Fukuda
Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan

K. Ikegame · S. Yoshihara · H. Ogawa
Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

S. Taniguchi
Department of Hematology, Toranomon Hospital, Tokyo, Japan

A. Takami
Department of Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Y. Abe
Department of Medicine and Bioregulatory Science, Graduate School of Medical Science, Kyusyu University, Fukuoka, Japan

M. Hino
Department of Hematology, Osaka City University Graduate School of Medicine, Osaka, Japan

T. Etou
Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan

Y. Ueda
Department of Hematology, Kurashiki Central Hospital, Okayama, Japan

T. Yujiri
Third Department of Internal Medicine, Yamaguchi University School of Medicine, Yamaguchi, Japan

T. Matsui · A. Okamura
Department of Hematology, Kobe University Graduate School of Medicine, Hyogo, Japan

J. Tanaka
Department of Hematology, Hokkaido University Hospital, Sapporo, Japan

prevention and treatment of GVHD in patients who have received an allogeneic stem cell transplant.

Keywords Mycophenolate mofetil (MMF) · Allogeneic stem cell transplantation · GVHD

1 Introduction

Acute and chronic graft-versus-host disease (GVHD) are important complications following allogeneic hematopoietic stem cell transplantation (HSCT) that can be prevented or treated by immunosuppressive agents such as cyclosporine, tacrolimus, steroids or other therapies [1–3]. Some patients, however, do not respond to these conventional treatments. It is well recognized that mycophenolate mofetil (MMF) is widely used in countries outside Japan, and numerous reports have documented its efficacy for prophylaxis and treatment of GVHD [4–13].

In Japan, MMF is only approved as an immunosuppressant drug for organ transplantation (e.g., renal transplantation) and has not been approved for prophylactic or therapeutic use for GVHD in the field of HSCT. As there have been several reports of experimental MMF use for HSCT in Japan [14, 15], we conducted a nationwide survey to determine the efficacy and safety of MMF in the Japanese population.

2 Patients and methods

2.1 Study design

We retrospectively collected data on MMF use after allogeneic HSCT from related donors. Questionnaires were sent to 228 institutes registered with the Japan Society for Hematopoietic Cell Transplantation (JSHCT). A total of 57 surveys were returned detailing 301 patients undergoing MMF treatment. Data regarding the purpose of treatment, dosage, length of treatment, presence or absence of subjective symptoms of GVHD, GVHD grade and stage (before and after treatment), decrease or increase in concomitant immunosuppressants, effects, adverse events and outcomes were collected. Basic information for each transplantation was extracted from the Transplant Registry Unified Management Program (TRUMP) system, which is a registry used for Japanese patient outcomes [16]. Several demographic data were not available due to the lack of patient entry into the TRUMP system. The effects of MMF with regard to subjective symptoms (none, disappearance, improvement, no change and ingravescence) and the use of steroids (none, withdrawal, dose reduction, no change and dose increase) were assessed by physicians. Adverse events were evaluated by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, ver.3). This study was approved by the ethical committees of the Japan Society of Hematopoietic Cell Transplantation and the Nagoya University School of Medicine.

2.2 Statistics

Correlations between the two subgroups were examined using the χ^2 test and Fisher's exact test. P values of less than 0.05 obtained in two-sided tests were considered statistically significant. The data were analyzed with STATA version 10 statistical software (STATA Corp, TX).

3 Results

3.1 Patient background

Patient background data are summarized in Table 1. Patient age ranged from 12 to 70 years (median 41) at the time of transplantation, and there were 173 (57.5%) male and 128 (42.5%) female patients. Among the 301 patients, 97 (32.2%) received a transplant from HLA-matched donor, and 182 (60.5%), from HLA-mismatched donors. Of the HLA-mismatched donors, 66 (36.3%) were 1 locus, 46 (25.3%) were 2 loci and 55 (30.2%) were 3 loci mismatched. There were also 22 patients (7.3%) with missing HLA data. Among the 157 patients who received MMF for GVHD prophylaxis, 119 (75.8%) received a transplant from an HLA-mismatched donor, and among the 50 patients who received MMF as a treatment for chronic GVHD, 17 (34.0%) received a transplant from an HLA-mismatched donor. The graft source was peripheral blood stem cells (PBSCs) in 176 patients, bone marrow (BM) in 101 patients and PBSCs plus BM in 2 patients. The preconditioning regimen was myeloablative in 91 patients and non-myeloablative in 166 patients. Table 1 shows that the primary disease was hematological malignancy in the majority of patients (94.4%) with aplastic anemia or other diseases accounting for the remainder of the patients. Among the patients with the hematological malignancies, 65.9% (162/246, which is clear data of disease status) were in non-complete remission at the time of transplantation.

3.2 MMF administration

The aim of MMF administration was GVHD prevention in 157 patients, acute GVHD treatment in 94 patients and chronic GVHD treatment in 50 patients (Table 1). The daily MMF dosage varied from 250 to 3,000 mg, and the number of doses per day ranged from 1 to 8. The most common dosages and frequencies of MMF administration were

Table 1 Patient characteristics

Variables	Number
Patient number	301
Median age (range)	41 (12–70)
Male/female	173/128
Disease[a]	
Acute myeloid leukemia	78 (46)
Acute lymphoblastic leukemia	66 (44)
Chronic myelogenous leukemia	15 (11)
Myelodysplastic/myeloproliferative syndrome	39 (12)
Malignant lymphoma	75 (41)
Multiple myeloma	11 (8)
Aplastic anemia	3
Other diseases	14 (11)
Purpose of MMF	
GVHD prophylaxis	157
aGVHD treatment	94
cGVHD treatment	50
Graft source[b]	
Bone marrow (BM)	101
Peripheral blood stem cell (PBSC)	176
Both BM and PBSC	2
Donor type[b]	
Matched related	97
Mismatched related	182
1 locus mismatch	66
2 loci mismatch	46
3 loci mismatch	55
Unknown	15

[a] Numbers in parenthesis indicate those of not in complete remission

[b] Twenty-two data were missing for graft source and donor type

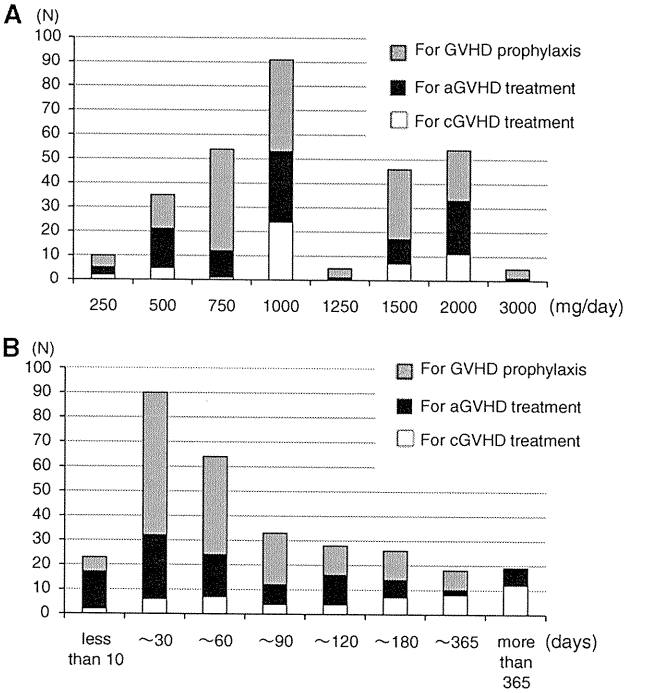

Fig. 1 **a** Initial dose of MMF. MMF was given at a variety of doses ranging from 250 mg per day to 3,000 mg per day. The most common dose was 500 mg twice a day ($N = 67$ among 91 patients taking 1,000 mg per day). **b** Dosing period of MMF. MMF was given for a variety of dosing periods (median 45 days)

500 mg two times per day, 250 mg three times per day and 1,000 mg two times per day given to 63 patients (20.9%), 54 patients (17.9%) and 45 patients (15.0%), respectively. Consequently, 91 patients received 1,000 mg of MMF per day, and 54 patients, 750 or 2,000 mg per day. 59 patients were treated with a daily dose higher than 2,000 mg. There was no consistent pattern between the length and purpose of treatment. MMF administration was discontinued within 30 days in 113 patients (38.4%); however, 19 patients received MMF for more than a year (Fig. 1). Most patients (289 patients, 96.0%) were given MMF concurrently with other immunosuppressants (e.g., cyclosporine, tacrolimus or steroids), and only 12 patients (4%) received MMF alone.

3.3 Adverse events

Adverse events (AEs) associated with MMF administration are listed in Table 2. The major events were neutropenia, infection, thrombocytopenia and myelosuppression. Only three patients (1.7%) developed renal insufficiency with a grade 1, 2 or 4 increase in creatinine. Eighteen patients (6.0%) died from AEs associated with MMF (Table 3). The primary causes of death were infections in 11 patients (including 5 patients with pneumonia, 4 with sepsis and 2 with invasive *Aspergillus* infection), neutropenia in 3 patients, myelosuppression in 2 patients, 1 thrombocytopenia and 1 brain hemorrhage. There were 44 grade 4 AEs: 25 of these patients (56.8%) improved and 15 (34.1%) remained unchanged, but 4 (9.1%) eventually died. The incidence of AEs of grade 3 or higher (except infection) increased in accordance with the daily dosage of MMF (Fig. 2), but most of these AEs improved (Table 4).

3.4 Efficacy of MMF

Among the 157 patients who received MMF for GVHD prophylaxis, the incidences of grade II–IV and grade III–IV acute GVHD were 29.7% (43/145) and 20.0% (29/145), respectively. Limited and extensive chronic GVHD occurred in 21 (18.6%) and 30 (26.6%) patients, respectively ($N = 113$). No significant differences were found in the incidence of grade II–IV acute GVHD between HLA-matched and mismatched transplant patients ($9/25 = 36.0$ vs. $33/113 = 29.2\%$, $P = 0.63$), and no significant differences were noted between these two groups with regard to the

Table 2 Adverse events whose relationships to MMF were not necessarily denied

Adverse events: all (grade 3–5)	GVHD prophylaxis ($N = 157$)		aGVHD treatment ($N = 94$)		cGVHD treatment ($N = 50$)		Total ($N = 301$)	
	N	%	*N*	%	*N*	%	*N*	%
Infection	6 (5)	3.8 (3.2)	16 (13)	17.0 (13.8)	9 (8)	18.0 (16.0)	31 (26)	10.3 (8.6)
Diarrhea	6 (5)	3.8 (3.2)	16 (10)	17.0 (10.6)	3 (3)	6.0 (6.0)	25 (18)	8.3 (6.0)
Nausea	7 (2)	4.5 (1.3)	6 (4)	6.4 (4.3)	3 (0)	6.0 (0)	16 (6)	5.3 (2.0)
Vomiting	2 (0)	1.3 (0)	2 (0)	2.1 (0)	1 (0)	2.0 (0)	5 (0)	1.7 (0)
Neutropenia	5 (5)	3.2 (3.2)	21 (20)	22.3 (21.3)	5 (5)	10.0 (10.0)	31 (30)	10.3 (10.0)
Thrombocytopenia	5 (5)	3.2 (3.2)	18 (15)	19.1 (16.0)	5 (5)	10.0 (10.0)	28 (25)	9.3 (8.3)
Myelosuppression	7 (7)	4.5 (4.5)	10 (7)	10.6 (7.4)	4 (4)	8.0 (8.0)	21 (18)	7.0 (6.0)
Gastrointestinal bleeding	3 (2)	1.9 (1.3)	3 (3)	3.2 (3.2)	0 (0)	0 (0)	6 (5)	20.0 (1.7)
Constipation	1 (0)	0.6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0.3 (0)
Others	5 (3)	3.2 (1.9)	7 (3)	7.4 (3.2)	3 (2)	6.0 (4.0)	15[a] (8[b])	5.0 (2.7)

Numbers in parenthesis indicate those for grade 3 or more toxicity

[a] Others: liver dysfunction (3), creatine kinase elevation (2), hair loss, hemorrhage cystitis

[b] Others: hypocalcemia, brain hemorrhage, septic shock, creatine kinase elevation, abdominal pain, TMA, diabetes mellitus, engraft failure

Table 3 Cause of death potentially associated with MMF

	Number
Infection	11
Pneumonia	5
Bacterial	2
MRSA	1
Fungal	1
CMV	1
Sepsis	4
Invasive *Aspergillus* infection	2
Neutropenia	3
Myelosuppression	2
Thrombocytopenia	1
Brain hemorrhage	1
Total	18

incidence of grade III–IV acute GVHD (6/25 = 24.0 vs. 22/113 = 19.5%, $P = 0.59$). The incidence of chronic GVHD, however, tended to be lower in the HLA-mismatched transplant group (14/23 = 60.9 vs. 35/83 = 42.2%, $P = 0.16$; Fig. 3), although this finding was not statistically significant. The incidences of grade II–IV and III–IV acute GVHD were lower in the subgroup of patients receiving 2,000 mg of MMF daily than in the subgroup receiving 1,000 mg daily (28.6 vs. 37% and 14.3 vs. 28.6% for grade II–IV and III–IV acute GVHD, respectively), although these differences were not statistically significant ($P = 0.51$ and 0.22, respectively). No dose effect was found for chronic GVHD prevention ($P = 0.72$).

Among the 94 patients in the acute GVHD treatment group, subjective symptoms disappeared in 27 (28.7%) and improved in 28 (29.8%). Symptoms remained unchanged in 17 patients (18.1%) and worsened in 22 patients (23.4%). Within this treatment group, 52 patients (55.3%) experienced improvement in their acute GVHD grade. Treatment with combined immunosuppressants was discontinued in 5 patients (5.3%) and reduced in 51 patients (54.3%). Among the 50 patients who received MMF as a treatment for chronic GVHD, the drug was effective against subjective symptoms (i.e., resulted in resolution or improvement) in 52.0% (10.0 and 42.0% experiencing resolution and improvement, respectively). Five patients (10.0%) discontinued combined immunosuppressants, and 29 (58.0%) reduced their dosage. The dosage remained unchanged in 14 patients (28.0%) and increased in only 2 patients (4%) (Fig. 4). In the acute GVHD treatment group, the effectiveness of MMF was higher among patients who had received HLA-matched transplants; however, this difference was not statistically significant for all items evaluated (58–70 vs. 32–69%, $P = 0.18$–0.60). In the chronic GVHD treatment group, the efficacy of MMF against subjective symptoms was higher in the HLA-matched subgroup than in the HLA-mismatched subgroup (17/33 = 51.5 vs. 3/9 = 33.3%, respectively, $P = 0.45$). In contrast, the rate of dosage reduction or discontinuation for combined immunosuppressants was higher in the HLA-mismatched subgroup than in the HLA-matched subgroup (7/9 = 77.8 vs. 21/33 = 63.6%, respectively, $P = 0.69$).

To assess the efficacy of MMF with regard to total daily dosage, we selected two subgroups: the most frequent dosage (1,000 mg per day) and the maximum dosage (more than 2,000 mg per day). The efficacy rate for every acute GVHD survey item was virtually identical between the 1,000 mg per day ($N = 28$) and 2,000 mg per day ($N = 23$) subgroups

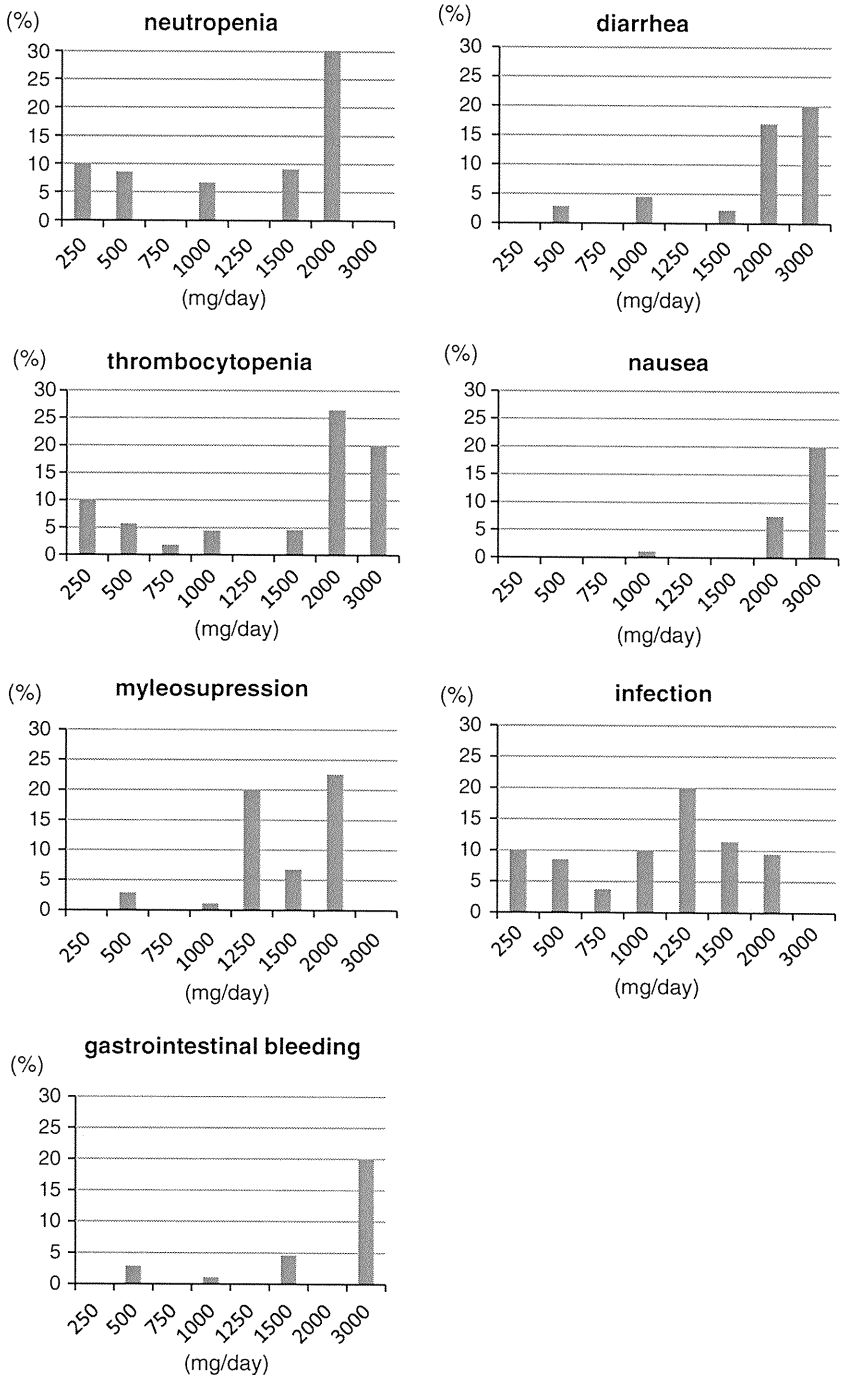

Fig. 2 Frequency of adverse events (grades 3–5) separated by total daily dose. High doses of MMF resulted in higher rates of hematological and gastrointestinal adverse events. Infections developed at all doses of MMF

(47.8–70.8 vs. 33.3–72.7%, respectively, $P = 0.06$-0.97). Among chronic GVHD patients, no difference in dose efficacy was observed between the two dosage subgroups ($N = 24$ in the 1,000 mg per day group and $N = 11$ for patients taking more than 2,000 mg per day, $P = 0.83$–0.91).

3.5 Transplantation outcome

In the GVHD prevention group, engraftment was seen in 122 of 134 evaluable patients (91.0%). Among all 301 patients, 62 (20.7%) relapsed and 169 (56.2%) died after transplantation. The overall survival rate was 41.9% at a median follow-up of 3 years. The main causes of death included disease recurrence in 33 patients (responsible for 19.5% of patient mortality), infection in 26 patients (15.4%), acute GVHD in 26 patients (15.4%) and chronic GVHD in 7 patients (4.1%). Among the 26 deaths due to acute GVHD, 18 patients were in the acute GVHD treatment group. Among the seven patients who died due to chronic GVHD, four were in the chronic GVHD treatment group.

Table 4 Rate of recovery from the adverse events in grades 3–4

	1,000 mg/day ($N = 91$)	More than 2,000 mg/day ($N = 59$)	Total ($N = 301$)
Infection	1/4 (25%)	1/2 (50%)	12/16 (75%)
Diarrhea	3/4 (75%)	7/10 (70%)	10/16 (63%)
Nausea	0/1 (0%)	4/5 (80%)	4/6 (67%)
Neutropenia	6/6 (100%)	12/15 (80%)	24/27 (89%)
Thrombocytopenia	3/4 (75%)	5/14 (36%)	11/24 (46%)
Myelosuppression	1/1 (100%)	8/11 (73%)	12/16 (75%)
Gastrointestinal bleeding	1/1 (100%)	0/1 (0%)	2/5 (40%)

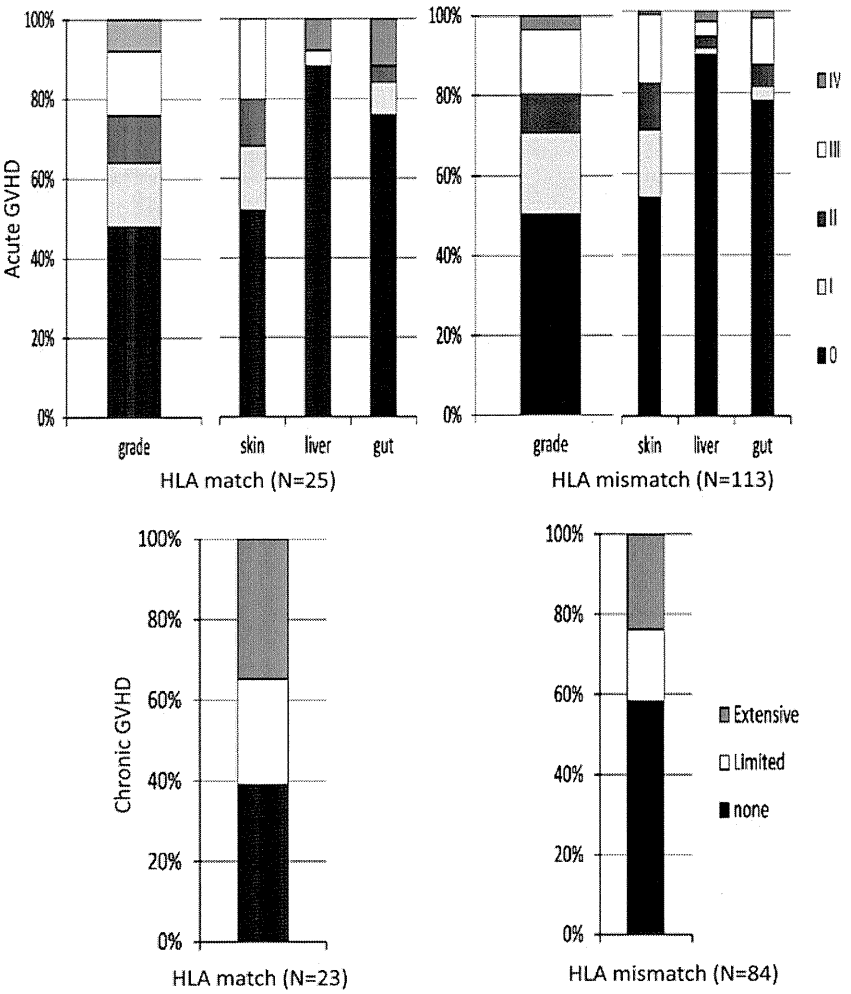

Fig. 3 Incidence of GVHD with prophylactic MMF use. The incidences of grade II–IV acute GVHD were 36.0 and 29.2% in the HLA-matched and -mismatched subgroups, respectively. In contrast, the incidence of chronic GVHD in the HLA-mismatched subgroup was lower (42.2%) than in the HLA-matched subgroup (60.9%)

4 Discussion

GVHD is one of the leading complications following allogeneic HSCT and is associated with morbidity and mortality. Calcineurin inhibitors and steroids are widely used for GVHD prevention and treatment, but several other immunosuppressive agents have been used for these purposes overseas [17–19]. Since 1997, many promising reports have compared MMF with conventional immunosuppressants [4–13]. In particular, reports focused on GVHD prevention are becoming increasing common due to the use of alternative donor sources [20]. Our current survey demonstrates that the efficacy rate of MMF is approximately 60% for the treatment of acute and chronic GVHD. Furthermore, our results also reveal that MMF is effective for the prevention of GVHD. Especially in HLA-mismatched patients, the frequency of grade III–IV acute GVHD was 20.3%, which was lower than the previous report subjected to HLA-mismatched transplants among Japanese populations [21]. As the efficacy of MMF was

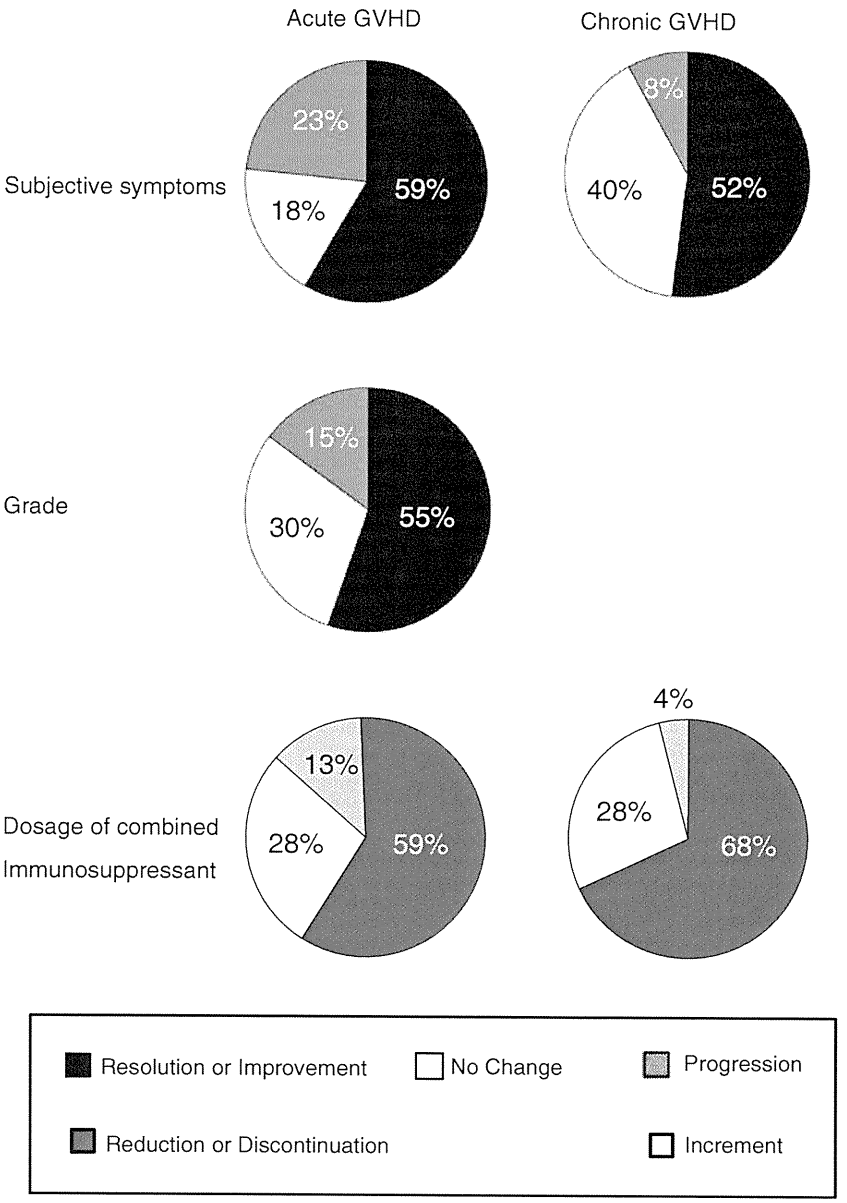

Fig. 4 Response of acute and chronic GVHD during therapeutic MMF use. Subjective symptoms of acute and chronic GVHD resolved in 59 and 52% of the cases, respectively, following the administration of MMF. In addition, 55% of the acute GVHD patients improved the grade of their disease. Finally, 60 and 68% of the acute and chronic GVHD patients, respectively, reduced or discontinued their use of combined immunosuppressant therapy

higher in patients receiving 2,000 mg per day than in those receiving 1,000 mg per day for chronic GVHD prevention, MMF doses of more than 2,000 mg per day are recommended for Japanese patients if the AEs are manageable.

Whether MMF is superior to existing immunosuppressants is a topic of continuing debate. Most previous reports on MMF have been promising, and the response rates for acute and chronic GVHD range from 47 to 71 and 26 to 76.9%, respectively, under various conditions [4, 6, 9–11, 17, 20]. On the other hand, one report suggested that MMF causes no significant improvement in the prevention of GVHD compared to cyclosporine and methotrexate (62 vs. 70%) [12]. Furthermore, another report showed that addition of MMF to an immunosuppressive regimen to control chronic GVHD had no effect (success rate of 15%) [22]. The results in this survey are not statistically different between using MMF and using cyclosporine or tacrolimus as reported in the previous report for the prevention and treatment of GVHD. We would like to emphasize, however, that the patient population in this study consisted mostly of HLA-mismatched donors and non-complete remission recipients (60.5 and 65.9%, respectively; Table 1). Even in this situation, MMF showed comparable efficacy. Therefore, we would like to conclude that MMF has a certain role for immunosuppressants.

Several reports have noted that the incidence of renal damage attributed to MMF (0–12.5%) is lower than that reported for other immunosuppressants like calcineurin inhibitors [4, 5, 11, 12, 23–25]. Our analysis revealed that the incidence of renal insufficiency (serum creatinine > 2 mg/dl)

was 1%. Serum creatinine > 2 mg/dl due to treatment with calcineurin inhibitors can be as high as 50–60 and 56–67% for cyclosporine and tacrolimus, respectively [26, 27]. Thus, MMF will be especially useful for patients with poor renal function.

In conclusion, MMF is tolerable and effective in Japanese patients who have received HSCT. Further studies are warranted to identify suitable candidates and appropriate therapeutic combinations of MMF for the prophylaxis and treatment of GVHD following allogeneic HSCT.

Acknowledgments This work was supported in part by Health and Labour Sciences Research Grants for Clinical Cancer Research from the Ministry of Health, Labour and Welfare, Japan. The authors would like to thank the staff of the Data Center of the Japan Society for Hematopoietic Cell Transplantation and the following collaborating institutions for providing patient data and specimens: Hokkaido University, Sapporo Hokuyu Hospital, Sapporo City General Hospital, Hakodate Municipal Hospital, Aomori Prefectural Central Hospital, Tsukuba University, Gunma University, Saitama Medical University International Medical Center, Chiba University, Jikei University Kashiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keio University, Tokyo Women's Medical University, Kyorinn University, Toranomon Hospital, Tokai University, St. Marianna University Yokohama City Seibu Hospital, Nagaoka Red Cross Hospital, Kouseiren Takaoka Hospital, Kanazawa University, Yamanashi Prefectural Central Hospital, Shinshu University, Nagano Red Cross Hospital, Gifu University, Hamamatsu Medical University, Nagoya University, National Hospital Organization Nagoya Medical Center, Konan Kosei Hospital, Mie University, Yamada Red Cross Hospital, Shiga University, Kyoto University, Kyoto Prefectural University, Kinki University, Osaka City University, Osaka City General Hospital, Matsushita Memorial Hospital, Osaka Medical College, Kitano Hospital, Hyogo College of Medicine, Kobe University, Kurashiki Central Hospital, Hiroshima University, National Hospital Organization Kure Medical Center, Yamaguchi University, Tokushima University, Tokushima Red Cross Hospital, Kagawa University, Ehime Prefectural Central Hospital, Ehime University, Kyushu University First Department of Internal Medicine, Kyusyu University Third Department of Internal Medicine, Hamanomachi Hospital, National Organization Kyusyu Cancer Center, Nagasaki University, Sasebo City General Hospital, Oita University, Kyusyu University Hospital at Beppu, Imamura Bun-in Hospital and Kagoshima University.

References

1. Goker H, Haznedaroglu IC, Chao NJ. Acute graft-vs-host disease: pathobiology and management. Exp Hematol. 2001;29:259–77.
2. Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood. 1990;76:1464–72.
3. Martin PJ, Carpenter PA, Sanders JE, Flowers ME. Diagnosis and clinical management of chronic graft-versus-host disease. Int J Hematol. 2004;79:221–8.
4. Basara N, Blau WI, Kiehl MG, Romer E, Rudolphi M, Bischoff M, et al. Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. Transplant Proc. 1998;30:4087–9.
5. Basara N, Blau WI, Kiehl MG, Schmetzer B, Bischoff M, Kirsten D, et al. Mycophenolate mofetil for the prophylaxis of acute GVHD in HLA-mismatched bone marrow transplant patients. Clin Transplant. 2000;14:121–6.
6. Basara N, Blau WI, Romer E, Rudolphi M, Bischoff M, Kirsten D, et al. Mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant patients. Bone Marrow Transplant. 1998;22:61–5.
7. Bolwell B, Sobecks R, Pohlman B, Andresen S, Rybicki L, Kuczkowski E, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. Bone Marrow Transplant. 2004;34:621–5.
8. Bornhauser M, Schuler U, Porksen G, Naumann R, Geissler G, Thiede C, et al. Mycophenolate mofetil and cyclosporine as graft-versus-host disease prophylaxis after allogeneic blood stem cell transplantation. Transplantation. 1999;67:499–504.
9. Busca A, Saroglia EM, Lanino E, Manfredini L, Uderzo C, Nicolini B, et al. Mycophenolate mofetil (MMF) as therapy for refractory chronic GVHD (cGVHD) in children receiving bone marrow transplantation. Bone Marrow Transplant. 2000;25:1067–71.
10. Kim JG, Sohn SK, Kim DH, Lee NY, Suh JS, Lee KS, et al. Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. Eur J Haematol. 2004;73:56–61.
11. Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. Bone Marrow Transplant. 1999;24:517–20.
12. Nash RA, Johnston L, Parker P, McCune JS, Storer B, Slattery JT, et al. A phase I/II study of mycophenolate mofetil in combination with cyclosporine for prophylaxis of acute graft-versus-host disease after myeloablative conditioning and allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2005;11:495–505.
13. Neumann F, Graef T, Tapprich C, Vaupel M, Steidl U, Germing U, et al. Cyclosporine A and mycophenolate mofetil vs cyclosporine A and methotrexate for graft-versus-host disease prophylaxis after stem cell transplantation from HLA-identical siblings. Bone Marrow Transplant. 2005;35:1089–93.
14. Okamura A, Yamamori M, Shimoyama M, Kawano Y, Kawano H, Kawamori Y, et al. Pharmacokinetics-based optimal dose-exploration of mycophenolate mofetil in allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2008;88:104–10.
15. Takami A, Mochizuki K, Okumura H, Ito S, Suga Y, Yamazaki H, et al. Mycophenolate mofetil is effective and well tolerated in the treatment of refractory acute and chronic graft-versus-host disease. Int J Hematol. 2006;83:80–5.
16. Atsuta Y, Suzuki R, Yoshimi A, Gondo H, Tanaka J, Hiraoka A, et al. Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. Int J Hematol. 2007;86:269–74.
17. Alousi AM, Weisdorf DJ, Logan BR, Bolanos-Meade J, Carter S, Difronzo N, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood. 2009;114:511–7.
18. Lee SJ, Vogelsang G, Gilman A, Weisdorf DJ, Pavletic S, Antin JH, et al. A survey of diagnosis, management, and grading of chronic GVHD. Biol Blood Marrow Transplant. 2002;8:32–9.
19. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9:215–33.
20. Furlong T, Martin P, Flowers ME, Carnevale-Schianca F, Yatscoff R, Chauncey T, et al. Therapy with mycophenolate

mofetil for refractory acute and chronic GVHD. Bone Marrow Transplant. 2009;44:739–48.
21. Kanda Y, Chiba S, Hirai H, Sakamaki H, Iseki T, Kodera Y, et al. Allogeneic hematopoietic stem cell transplantation from family members other than HLA-identical siblings over the last decade (1991–2000). Blood. 2003;102:1541–7.
22. Martin PJ, Storer BE, Rowley SD, Flowers ME, Lee SJ, Carpenter PA, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. Blood. 2009;113:5074–82.
23. Arai S, Vogelsang GB. Management of graft-versus-host disease. Blood Rev. 2000;14:190–204.
24. Bornhauser M, Thiede C, Schuler U, Platzbecker U, Freiberg-Richter J, Helwig A, et al. Dose-reduced conditioning for allogeneic blood stem cell transplantation: durable engraftment without antithymocyte globulin. Bone Marrow Transplant. 2000;26:119–25.
25. Krejci M, Doubek M, Buchler T, Brychtova Y, Vorlicek J, Mayer J. Mycophenolate mofetil for the treatment of acute and chronic steroid-refractory graft-versus-host disease. Ann Hematol. 2005;84:681–5.
26. Nash RA, Antin JH, Karanes C, Fay JW, Avalos BR, Yeager AM, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood. 2000;96:2062–8.
27. Ratanatharathorn V, Nash RA, Przepiorka D, Devine SM, Klein JL, Weisdorf D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood. 1998;92:2303–14.

Int J Hematol (2010) 92:351–359
DOI 10.1007/s12185-010-0657-y

ORIGINAL ARTICLE

Use of foscarnet for cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation from a related donor

Maiko Asakura · Kazuhiro Ikegame · Satoshi Yoshihara · Shuichi Taniguchi · Takehiko Mori · Tetsuya Etoh · Akiyoshi Takami · Takashi Yoshida · Takahiro Fukuda · Kazuo Hatanaka · Heiwa Kanamori · Toshiaki Yujiri · Yoshiko Atsuta · Hisashi Sakamaki · Ritsuro Suzuki · Hiroyasu Ogawa

Received: 15 February 2010 / Revised: 30 June 2010 / Accepted: 26 July 2010 / Published online: 7 August 2010

Abstract Foscarnet is an active agent against cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation (HSCT), as well as ganciclovir. We investigated the usefulness of foscarnet in patients who underwent related allogeneic HSCT. Foscarnet was used in 320 patients with a median age of 45 years (range 15–72). The purpose of administration was CMV disease in 65, preemptive use in 248 and prophylaxis in 7. Totally, 194 patients had a history of prior ganciclovir treatment. The reason for foscarnet use was insufficient therapeutic effect of prior ganciclovir in 99, and adverse event including myelosuppression in 95. The response rate in symptom was 52% for the CMV disease patients. Antigenemia disappeared in 77% of the preemptive treatment and improved in 13% of the patients. No outbreak of CMV disease was recognized. The total effectiveness of therapeutic and preemptive use was significantly higher for patients without prior ganciclovir (91 vs. 76%, $P = 0.001$). Adverse events of grade 3 or higher were recognized in 24%, including electrolyte abnormalities in 11%, neutropenia in 8%, and thrombocytopenia in 8%. Renal damage was only observed in 3% of patients. Foscarnet was concluded to be a safe and effective anti-CMV agent and to be a suitable alternative to ganciclovir.

Keywords Cytomegalovirus infection · Foscarnet · Blood and marrow transplantation · Efficacy · Adverse reaction

M. Asakura · Y. Atsuta · R. Suzuki (✉)
Department of HSCT Data Management and Biostatistics, Nagoya University School of Medicine, 1-1-20 Daiko-minami, Higashi-ku, Nagoya 461-0047, Japan
e-mail: r-suzuki@med.nagoya-u.ac.jp

K. Ikegame · S. Yoshihara · H. Ogawa
Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

S. Taniguchi
Department of Hematology, Toranomon Hospital, Tokyo, Japan

T. Mori
Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

T. Etoh
Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan

A. Takami
Department of Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

T. Yoshida
Hematology Department, Toyama Prefectural Hospital, Toyama, Japan

T. Fukuda
Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan

K. Hatanaka
Department of Internal Medicine, Rinku General Medical Center, Izumisano, Japan

H. Kanamori
Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan

T. Yujiri
Third Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan

H. Sakamaki
Department of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

1 Introduction

Cytomegalovirus (CMV) disease is one of the most important infectious complications after allogeneic hematopoietic stem cell transplantation (HSCT), which influences the outcome of the transplantation. The presence of graft-versus-host disease and steroid therapy are associated with the occurrence of CMV infection or reactivation. Ganciclovir is used as a first-line agent for both prophylaxis and the treatment of CMV disease [1–5]. However, approximately one-third of patients receiving ganciclovir develop drug-induced neutropenia or thrombocytopenia [6–9]. Therefore, ganciclovir is unsuitable for use in patients with poor bone marrow function. Another problem is ganciclovir resistant CMV [10–12].

For such cases, foscarnet is an important alternative agent that demonstrates anti-viral activity against all known herpes viruses including CMV [11, 13–15]. In early studies, the dose-limiting toxicities of foscarnet were found to be nephrotoxicity and neurotoxicity, which were seen in up to 50% of patients [16, 17]. Two randomized controlled trials (RCT) comparing the usefulness of preemptive foscarnet versus ganciclovir have been performed for CMV antigenemia [18, 19]. These studies revealed that the effectiveness of foscarnet was equivalent to that of ganciclovir. Adverse reactions and treatment-related mortality of foscarnet were also the same as those of ganciclovir. Renal dysfunction was only noted in 5% of the patients that received foscarnet [19].

The use of foscarnet has also been reported in cord blood transplantation, which is more complicated by viral infection [20]. These studies including the RCT only involved patients who had received foscarnet as an initial therapy. Therefore, we conducted a nationwide study in Japan of the use of foscarnet against CMV infection after related HSCT to investigate the current status, and compared its efficacy and toxicity in patients with and without prior ganciclovir use.

2 Patients and methods

2.1 Study design

This study is a retrospective survey investigating the use of foscarnet after stem cell transplantation. The subjects of this study were patients who received foscarnet after receiving allogeneic transplantation from a related donor in the period from 1998 to 2008. We performed a questionnaire at institutions carrying out allogeneic stem cell transplants in Japan. Data regarding the presence of CMV disease, CMV antigenemia, the reason for foscarnet use, the dose and duration of foscarnet, the effectiveness of therapy, and adverse events were collected. The obtained data were combined with data from the national registry of the Japan Society of Hematopoietic Cell Transplantation, which was collected by the TRUMP system [21]. This study was approved by the Ethical Committees of the Japan Society of Hematopoietic Cell Transplantation and Hyogo College of Medicine.

2.2 CMV antigenemia assay

Cytomegalovirus antigenemia was measured as described previously [22, 23]. Briefly, peripheral white blood cells were attached to slides by cytocentrifugation and stained with HRP-C7 (Teijin, Tokyo, Japan) or C10/C11 (Biotest, Dreieich, Germany) monoclonal antibodies. The number of positive cells was counted per 50,000 attached cells for HRP-C7 and per 150,000 applied cells for C10/C11. The examination was performed in duplicate, and the mean was used for further analyses.

2.3 Definition of CMV disease and infection

CMV diseases were defined as any organ infections by CMV, ideally proven by histopathologic examinations. They include gastroenteritis, pneumonia, retinitis, hepatitis, encephalitis, and cystitis. Patients who presented with interstitial pneumonia accompanied by CMV antigenemia were also diagnosed with CMV disease (pneumonia). For patients who presented with antigenemia and simultaneous diarrhea, gastrointestinal endoscopy and biopsy were recommended, but those who could not receive such diagnostic procedure were regarded as suspicious CMV disease (gastroenteritis). Both CMV antigenemia and CMV disease were regarded as CMV infection.

2.4 Type of therapy

The administration of anti-viral agents for patients without any CMV disease but accompanied by CMV antigenemia with or without febrile complications was defined as preemptive therapy in this study. Therapy of CMV disease was defined as CMV treatment. The use of anti-viral agents for those without antigenemia or CMV disease was regarded as prophylaxis.

2.5 Statistics

Pairwise comparisons were performed using the χ^2 test and Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. The Kruskal–Wallis test was used to compare multiple groups. P values of <0.05 obtained in 2-sided tests were considered statistically significant. Data were analyzed with the STATA version 11 statistical software (STATA Corp, TX, USA).

3 Results

3.1 Patient characteristics

The background data of 320 patients are shown in Table 1. There were 171 males and 149 females. Their median age was 45 years, and the ages of the patients ranged from 15 to 72 years. The underlying disease of patients was acute myeloid leukemia (AML) in 110, acute lymphoblastic leukemia (ALL) in 59, chronic myelogenous leukemia (CML) in 18, myelodysplastic syndrome (MDS)/myeloproliferative disorder (MPD) in 42, chronic lymphocytic leukemia (CLL) in 2, non-Hodgkin lymphoma (NHL) in 51, Hodgkin lymphoma (HL) in 4, adult T cell lymphoma (ATL) in 16, multiple myeloma (MM) in 10, aplastic anemia (AA) in 6 and 1 each for renal cell carcinoma and virus associated hemophagocytic syndrome. Several demographic data were not available due to the lack of patient entry to the TRUMP system. CMV antibody was positive in both the patient and donor in 189 pairs (59%), in the patient only in 22 cases (7%), and in the donor only in 8 cases (3%), and it was negative in both patient and donor in 4 pairs (1%). Of 289 patients with evaluable data, 113 patients received bone marrow (BM) as a graft, 172 received peripheral blood stem cell (PBSC), and 4 received both BM and PBSC. HLA was matched in 108 of 268 patients but was mismatched in the remaining 160 (155 with serological mismatch and 5 with allele mismatch).

Table 1 Patient characteristics

Variables	Number
Patient number	320
Median age (range)	45 (15–72)
Male/female	171/149
Disease	
Acute myeloid leukemia	110
Acute lymphoblastic leukemia	59
Chronic myelogenous leukemia	18
Myelodysplastic/myeloproliferative syndrome	42
Chronic lymphocytic leukemia	2
Non-Hodgkin lymphoma	51
Hodgkin lymphoma	4
Adult T cell leukemia	16
Multiple myeloma	10
Aplastic anemia	6
Other diseases	2
CMV serology	
Donor +/Patient +	189
Donor +/Patient −	8
Donor −/Patient +	22
Donor −/Patient −	4
Graft source	
Bone marrow (BM)	113
Peripheral blood stem cell (PBSC)	172
Both BM and PBSC	4
Donor type	
Matched related	108
Mismatched related	160

3.2 CMV infection

Foscarnet was administered for CMV disease in 65 patients (20%), including 46 with gastroenteritis, 12 with pneumonia, 2 with retinitis, and one each for hepatitis, encephalitis, and cystitis. Each one other patient developed pneumonia and retinitis accompanied by simultaneous gastroenteritis. On the other hand, 248 (78%) were preemptively treated (only complicated with CMV antigenemia), and 7 (2%) were prophylactically treated. Before foscarnet administration, 194 (61%) patients had received ganciclovir, and one of the patients was treated with cidofovir after ganciclovir use. The reason for changing the anti-viral agent to foscarnet was insufficient therapeutic effect in 99 patients and adverse events due to preceding ganciclovir including myelosuppression in 95 patients. In 126 patients who had not received any anti-viral premedication, foscarnet was used because of poor bone marrow function in 116.

A total of 208 patients (67%) received steroid therapy at the time of foscarnet initiation. The rate of patients under steroid use was 58% for CMV disease, 70% for preemptive foscarnet, and 43% for prophylaxis, but the difference was not significant ($P = 0.08$).

3.3 Dosage of foscarnet

The initial dose of foscarnet ranged from 7 mg/kg to 216 mg/kg (median 88 mg/kg, Fig. 1). The dose was

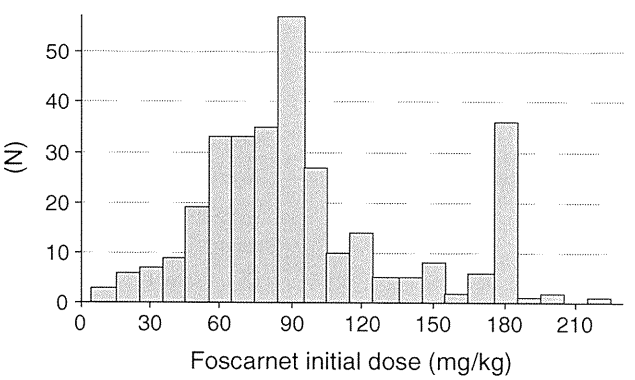

Fig. 1 Initial dose of foscarnet. Foscarnet was given at a variety of doses ranging from 7 to 216 mg/kg (median 88 mg/kg). Two peaks at 90 and 180 mg/kg were seen in the histogram

significantly higher in the patients who had received prior ganciclovir (range 10–216 mg/kg, median 91 mg/kg) than those who had not (range 7–180 mg/kg, median 72 mg/kg) ($P < 0.0001$). The median dose in the preemptive, treatment, and prophylactic groups was 89, 90, and 63 mg/kg, respectively; i.e., it was significantly lower in the prophylactic use group ($P = 0.05$). The initial dose of foscarnet did not have any correlation with creatinine clearance calculated from serum creatinine level and age by the Modification of Diet in Renal Disorder (MDRD) formula ($r = 0.21$, Fig. 2). The duration of foscarnet use ranged from 1 to 163 days (median 20 days) and was significantly shorter for patients who had received prior ganciclovir than those who had not (median 17 vs. 22 days, $P = 0.05$). As there were two peaks at 90 and 180 mg/kg in the dose of foscarnet administered, 5 dose categories (0–39, 40–79, 80–99, 100–159, and 160–220) were defined, and the efficacy and toxicity of foscarnet were estimated according to this categorization.

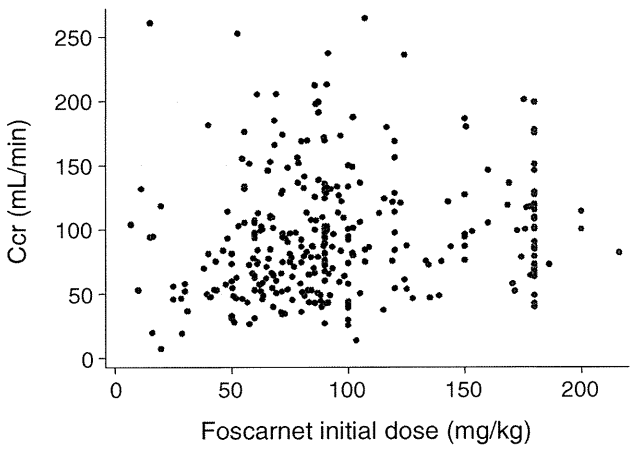

Fig. 2 Relationship between the initial dose of foscarnet and creatinine clearance. Creatinine clearance was calculated from serum creatinine level and age by the Modification of Diet in Renal Disorder (MDRD) formula [Ccr for male = $0.741 \times 175 \times (\text{age})^{(-0.203)} \times (\text{serum creatinine})^{(-1.154)}$, Ccr for female = $0.741 \times 175 \times (\text{age})^{(-0.203)} \times (\text{serum creatinine})^{(-1.154)} \times 0.742$]. No correlation was found ($r = 0.21$)

3.4 Efficacy

Among 65 patients with CMV disease, the symptoms disappeared in 5 (8%) and improved in 28 (44%), no change was seen in 20 (32%), and the symptoms worsened in 10 (16%) (Table 2). One patient was not evaluable with regards to their response, and another patient did not have any symptoms at the initiation of foscarnet because of the effect of prior ganciclovir use. The effectiveness (resolved or improved) was higher in those who did not receive ganciclovir, but the difference was not statistically significant (71 vs. 46%, $P = 0.10$). When the effectiveness in symptom was compared between HLA-matched and -mismatched transplant, the rate was almost comparable (14/25 = 56% vs. 14/29 = 48%, $P = 0.60$). Among 238 evaluable patients who received preemptive CMV therapy, antigenemia was resolved in 183 (77%) and improved in 31 (13%), but was not changed in 17 (7%) and worsened in 7 (3%). No patient developed outbreaks of CMV disease. The effectiveness was higher for those who had not received prior ganciclovir, but the difference was not significant (93/99 = 93% vs. 121/139 = 87%, $P = 0.13$).

Table 2 Response to foscarnet

	Symptoms				Antigenemia			
	Prior GCV		No prior GCV		Prior GCV		No prior GCV	
	N	%	*N*	%	*N*	%	*N*	%
CMV disease								
Disappeared	4	9	1	6	26	65	8	89
Improved/decreased	17	37	11	65	7	18	1	11
No change	18	39	2	12	4	10	0	0
Worsened/increased	7	15	3	18	3	8	0	0
No symptoms/antigenemia	1[a]	–	–	–	7	–	8	–
Unevaluable	1	–	0	–	1	–	0	–
Preemptive								
Disappeared	–	–	105	74	78	80		
Decreased	–	–	17	12	14	14		
No change	–	–	14	10	3	3		
Increased	–	–	5	4	2	2		
No antigenemia	–	–	4[a]	–	–	–		
Unevaluable	–	–	3	–	3	–		

GCV ganciclovir

[a] Symptoms/antigenemia had disappeared after prior GCV

Although the effectiveness in preemptive use was lower in HLA-matched transplant as compared with HLA-mismatched transplant, the difference was not also significant (64/75 = 85% vs. 114/123 = 93%, $P = 0.14$). Among the patients who received prior ganciclovir, the effectiveness was significantly higher in the patients in whom an insufficient effect of ganciclovir was seen compared with those who had suffered an adverse reaction to ganciclovir (64/68 = 94% vs. 57/71 = 80%, $P = 0.02$). The overall effectiveness of treatment and preemptive use was significantly higher in those who had not received prior ganciclovir (91 vs. 76%, $P = 0.001$) because of the low effectiveness in the patients of the CMV disease group who had received prior ganciclovir use. The changing courses of CMV antigenemia are box plotted in Fig. 3a for the patients who received prior ganciclovir and in Fig. 3b for those who did not. After the administration of foscarnet, the CMV antigenemia decreased in both groups ($P < 0.0001$ and $P = 0.01$, respectively).

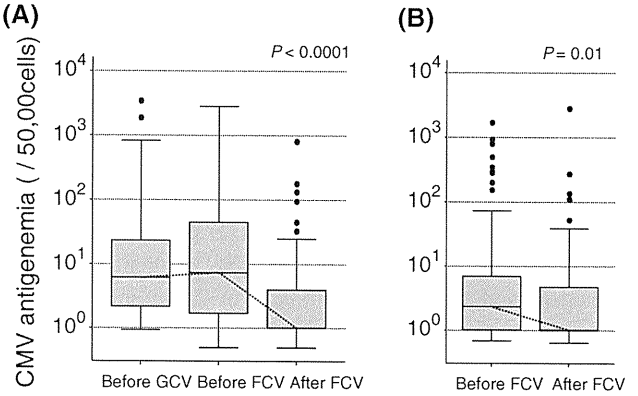

Fig. 3 Change in CMV antigenemia due to foscarnet therapy. The levels of antigenemia before ganciclovir, before foscarnet, and after foscarnet are box plotted. A significant decrease in antigenemia due to foscarnet treatment was observed both (**a**) for patients who had received prior ganciclovir treatment and (**b**) for those who had not

The responses to foscarnet according to the 5 dose categories are summarized in Fig. 4. The symptoms of CMV disease improved in around 50% of patients in every dose category. In the CMV disease patients the response rate of

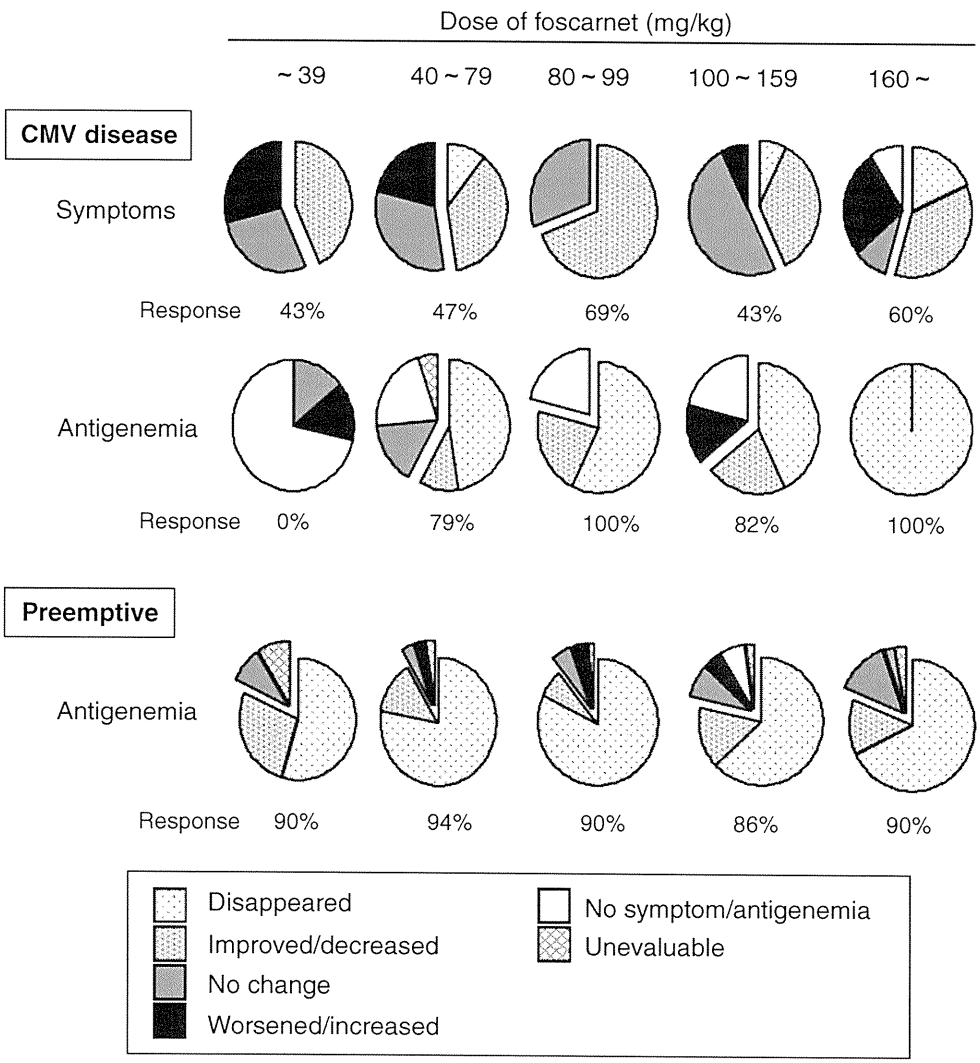

Fig. 4 Response to foscarnet according to 5 dose categories. The number of patients from the CMV disease group was 7 in the <39 mg/kg group, 19 in the 40–79 mg/kg group, 14 in the 80–99 mg/kg group, 14 in the 100–159 mg/kg group, and 11 in the 160 mg/kg or higher group, and those of the preemptive group were 11, 81, 73, 46, and 37, respectively. The response rate was around 50% for symptoms of CMV disease and was generally higher for antigenemia