Table 1 Patient characteristics in the three data sources

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

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

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

Transition probabilities (TPs) and utilities

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

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

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

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

Table 2 Transition probabilities of the whole population

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

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

Table 3 Transition probabilities of subgroups

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

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

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

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

Sensitivity analyses

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

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

Results

Baseline analysis

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

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

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

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

Sensitivity analysis

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

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

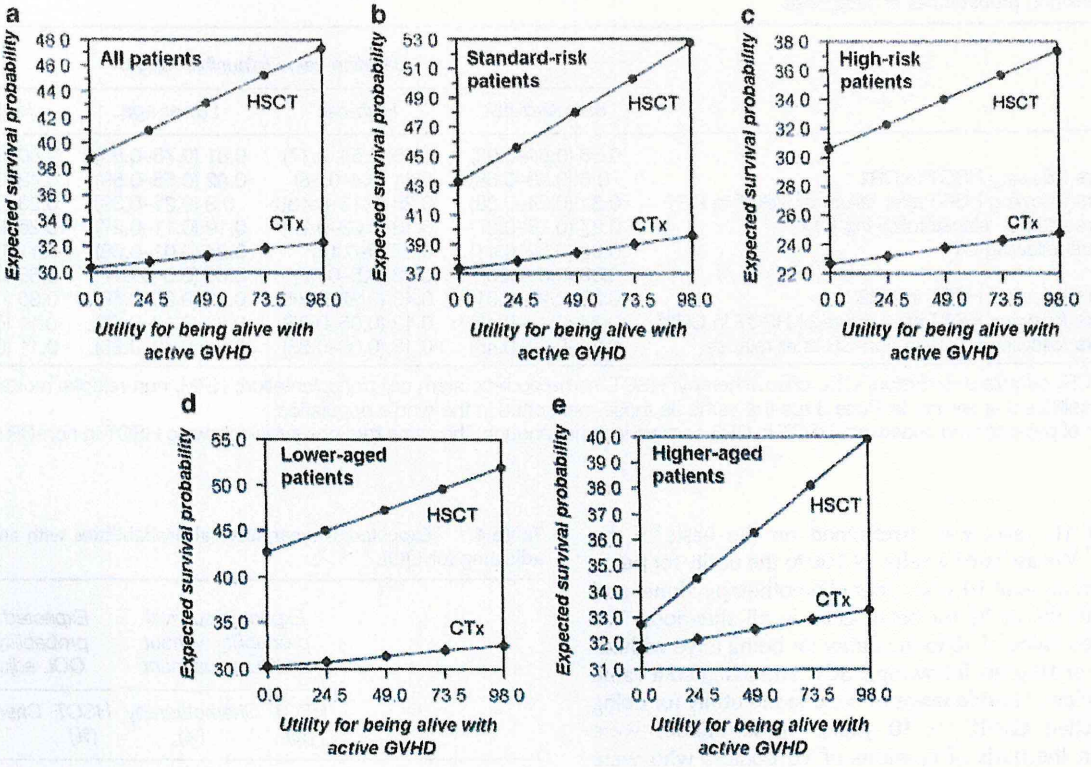

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently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

Subgroup analyses

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

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

Discussion

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

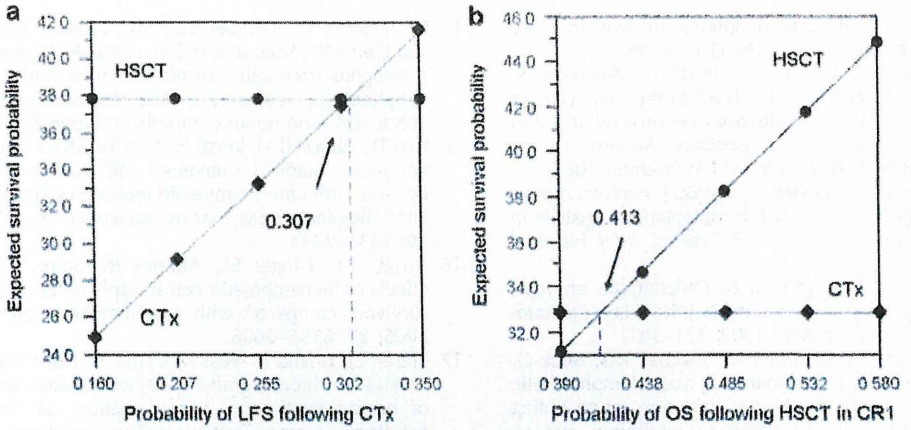

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy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

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

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

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

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

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

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

Conflict of interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

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

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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

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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

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

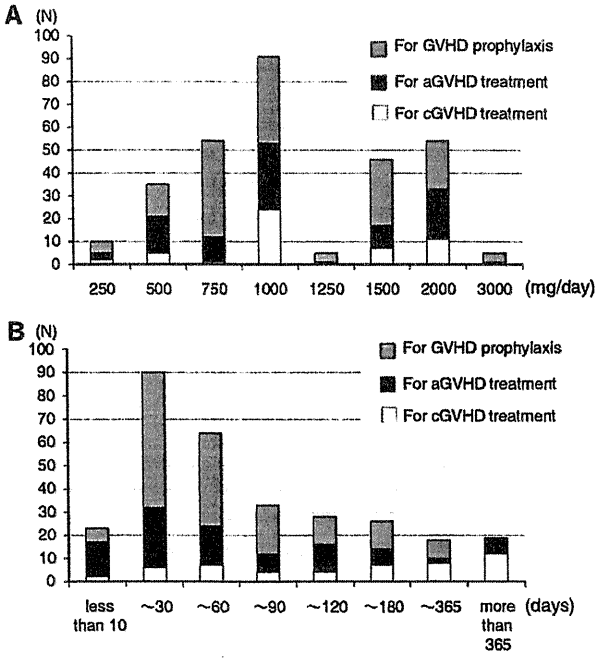

Fig. 1 a Initial dose of MMF. MMF was given at a variety of doses ranging from 250 mg per day to 3,000 mg per day. The most common dose was 500 mg twice a day ($N = 67$ among 91 patients taking 1,000 mg per day). b Dosing period of MMF. MMF was given for a variety of dosing periods (median 45 days)

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

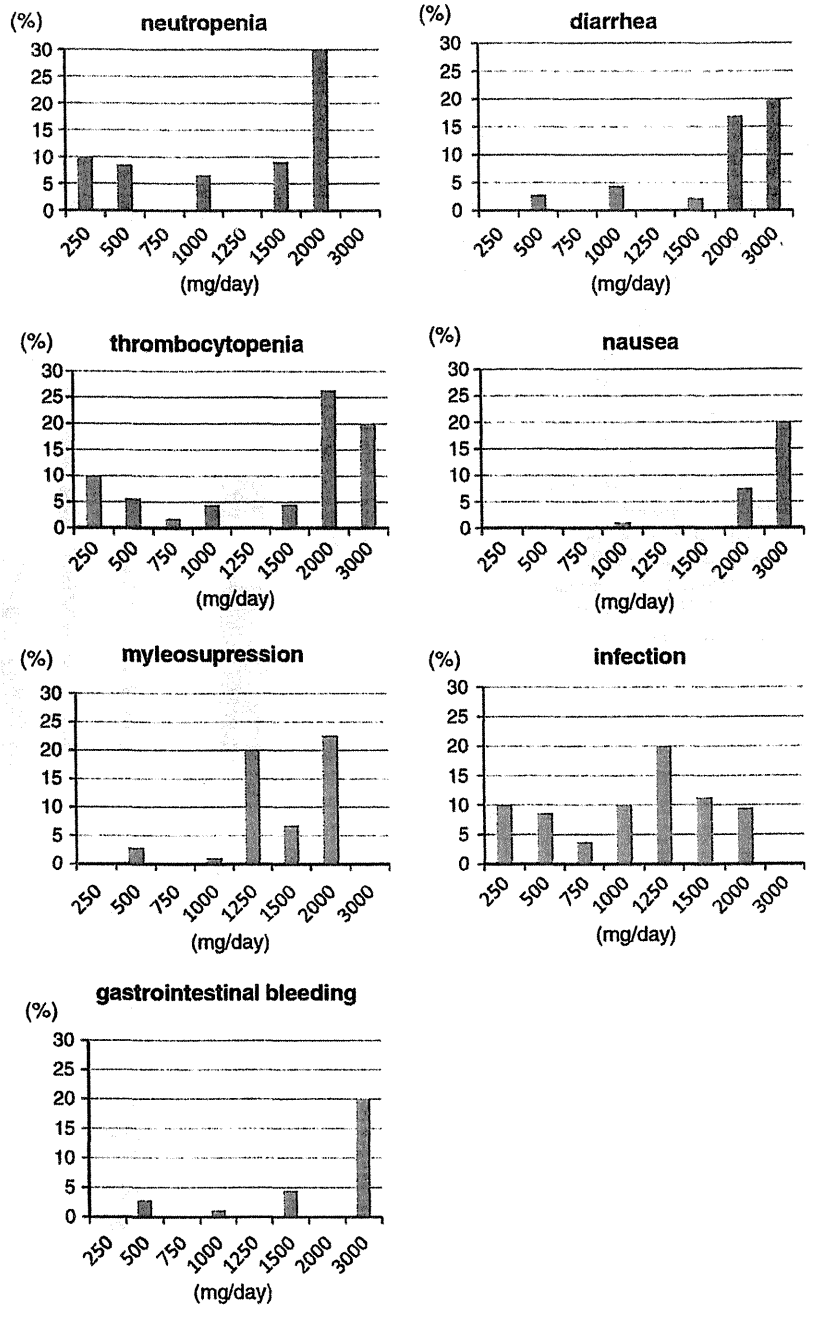

Fig. 2 Frequency of adverse events (grades 3–5) separated by total daily dose. High doses of MMF resulted in higher rates of hematological and gastrointestinal adverse events. Infections developed at all doses of MMF

(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.