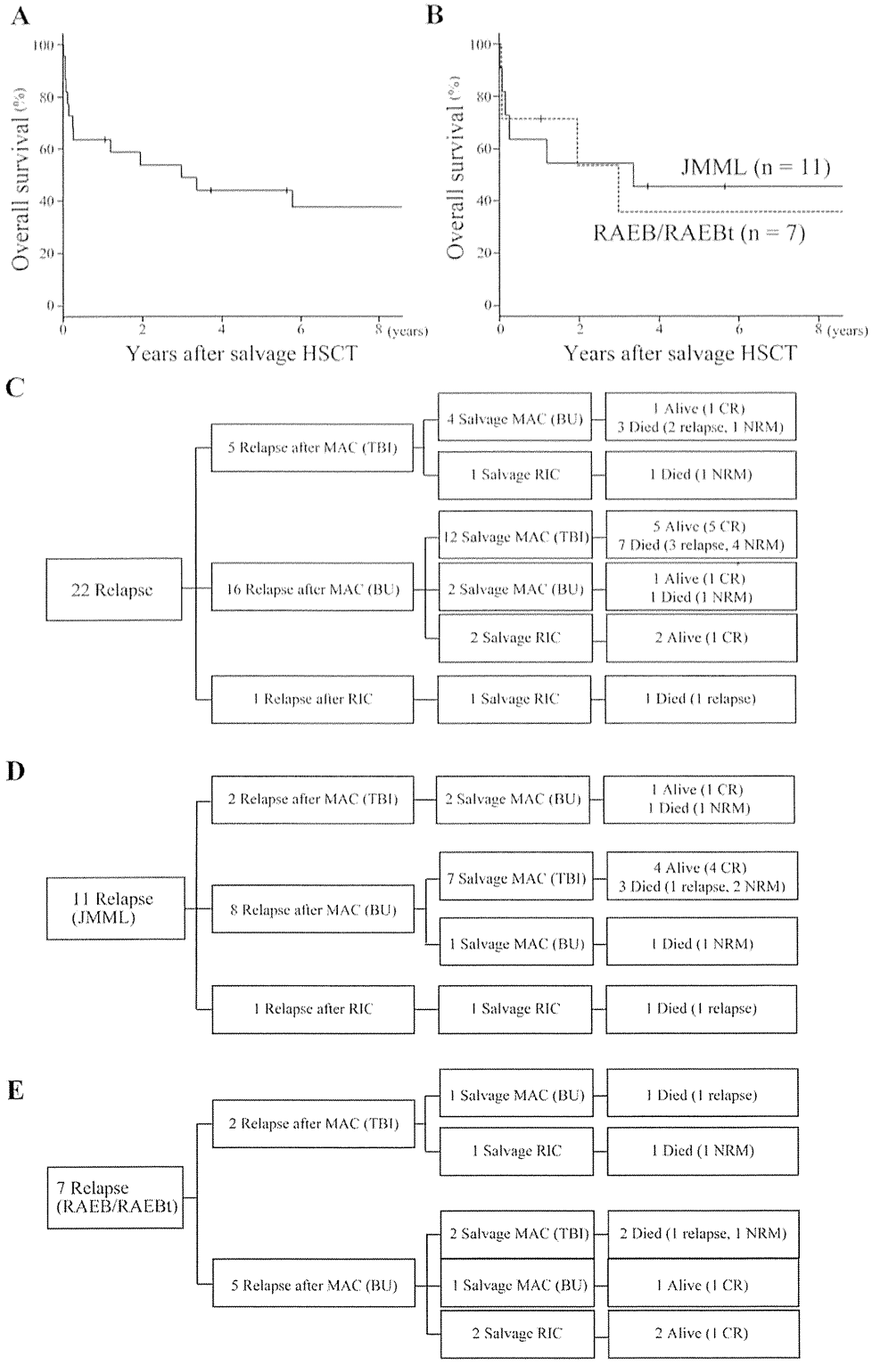

Fig. 1. Outcome of salvage transplantation for relapse. (**A**) Overall survival probability of 22 relapsed patients after salvage transplantation. (**B**) Overall survival according to disease subtypes. (**C**) Relationship between prior and salvage HSCTs and patient outcomes for all patients, (**D**) for JMML, and for RAEB/RAEBt. BU, busulfan; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; CR, complete remission; NRM, non-relapse mortality; TBI, total body irradiation.

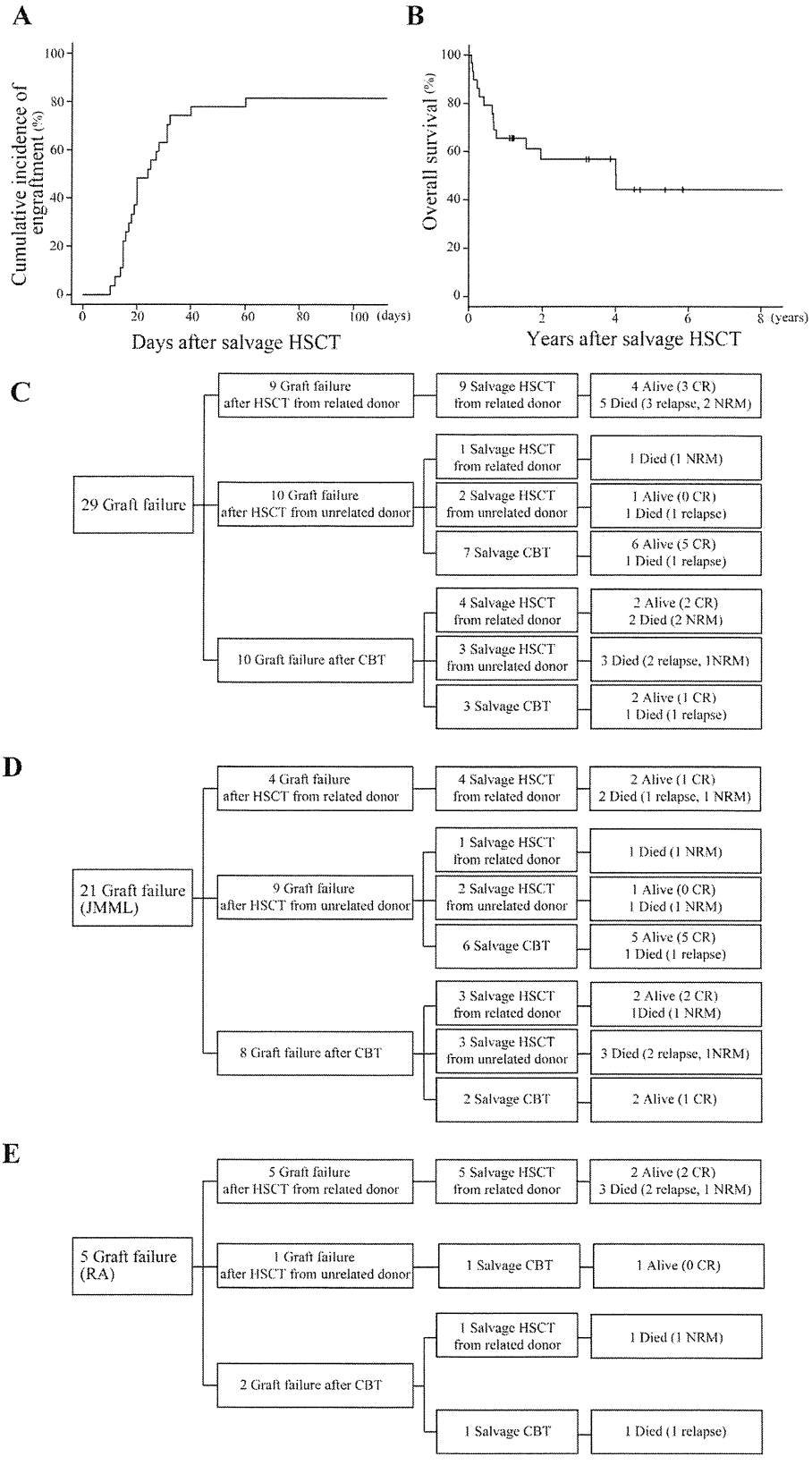

Fig. 2. Outcome of salvage transplantation for graft failure. (**A**) Cumuative incidence of engraftment and (**B**) Overall survival probability of 29 graft failure patients after salvage transplantation. (**C**) Relationship between prior and salvage HSCTs and patient outcomes for all patients, (**D**) for JMML, and for RAEB/RAEBt. HSCT, hematopoietic stem cell transplantation; CBT, cord blood transplantation; CR, complete remission; NRM, non-relapse mortality.

No relationship was observed between complete remission (CR) duration after the first HSCT and the outcome of salvage HSCT. The OS rate of early relapse (180 days or earlier after the prior HSCT) patients was 63.6 ± 14.5%, while that of late relapse (later than 180 days after the prior HSCT) was 40.0 ± 17.4% ($P = 0.38$).

Salvage HSCT for Graft Failure

Of the 29 patients with graft failure that received salvage HSCT for graft failure, 24 achieved engraftment, and the cumulative incidence of engraftment was 81.5 ± 8.0% on day 100 (Fig. 2A). Fourteen of the 29 patients died, including eight deaths after relapse; therefore, the OS probability of salvage HSCT for graft failure was estimated to be 56.8 ± 9.6% at 3 years (Fig. 2B).

The stem cell source of the two HSCTs and outcomes are shown in Figure 2C. Cord blood was selected for 10 graft failures, nine of whom achieved engraftment in a median of 28 days. Salvage HSCT from related donors was performed on 14 patients, and 11 patients achieved engraftment in a median of 15 days after salvage HSCT. Four of the five patients who received HSCT from two or three antigen mismatched related donors achieved engraftment.

Graft failure with donor dominant chimerism occurred in one patient following a previous bone marrow transplantation from a matched related donor using fludarabine and cyclophosphamide as conditioning agents. Salvage peripheral blood stem cell transplantation from the same donor without any conditioning agent resulted in engraftment 31 days after salvage transplantation.

Various conditioning regimens were used for salvage transplantation. Eleven of the 29 patients with graft failure received TBI-containing salvage HSCT with various irradiation doses (four patients received 2–4 Gy, seven patients 10–12 Gy), and all of whom achieved engraftment. However, five of 18 patients that received salvage HSCT without TBI did not achieve engraftment, whereas 13 of 14 patients who received fludarabine as a conditioning agent in salvage HSCT did.

DISCUSSION

By analyzing JSHCT registry data, we showed that HSCT for relapse or graft failure in patients with pediatric MDS/MPN could provide similar outcomes to those after the first HSCT. Furthermore, salvage HSCT was associated with a high incidence of NRM in these patients.

A previous study on relapsed JMML patients who received salvage HSCT demonstrated that 10 of 24 (43%) patients were alive and in remission at a median follow-up of 3.3 years [5]. Consistent with these findings, approximately half of the relapsed patients in the cohort reported here were successfully treated with salvage HSCT, and this was significantly better than that for salvage HSCT to treat relapses in other pediatric hematological malignancies, which was shown to be approximately 30% [15,16].

We could not identify a definite prognostic factor of salvage HSCT for relapsed MDS/MPN due to the small sample size; however, the short CR duration was not associated with the poor outcome of patients with pediatric MDS/MPN, which is related to the outcome of patients with pediatric acute lymphoblastic leukemia [15]. The reason is unclear, but one possible explanation is that intensive chemotherapy usually is required for acute leukemia relapse at earlier post-transplant period, and it can lead to increasing treatment related toxicity, while MDS patients often remain stable without any intensive therapy.

Of note, a larger number of patients died due to NRM (n = 8) than relapse (n = 6). Previous studies reported a higher risk of NRM in patients with pediatric MDS/MPN with the first HSCT than in those with other hematological malignancies [3,8,9], and these findings suggest that children with MDS may have undetected underlying diseases that are inducing higher sensitivity to the preparative agents of HSCT [3].

Graft failure is an important complication associated with allogeneic HSCT. Although MDS/MPN is not a risk factor for graft failure, it is often difficult to distinguish graft failure from relapse in patients with MDS/MPN, a hematopoietic stem cell disorder. The incidence of graft failure was previously reported to be approximately 2–3% following HSCT in patients with pediatric MDS/MPN [2,3]; however, this may increase if a reduced intensity conditioning is used to reduce the incidence of NRM [17]. Our results showed that the engraftment rate achieved by salvage HSCT was higher than that of other diseases [18], and could result in an OS probability of more than 50%, which is similar to the outcome achieved following the first HSCT for patients with pediatric MDS/MPN.

The results of the present study have provided useful and new information into the role of salvage HSCT in patients with pediatric MDS/MPN; however, there were some limitations due to the retrospective nature of this study using registry data. For example, our analysis included various variants of pediatric MDS, or did not include patients who had died before HSCT or were too ill to undergo salvage HSCT. Another limitation to our study was the small number of patients analyzed, and a definitive prognostic factor in salvage HSCT could not be established. Although further evidence is required to confirm our result, second HSCT should be considered as a valuable option for children with MDS/MPN who relapse or experience graft failure.

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Clinical Transplantation

Mycophenolate mofetil use after unrelated hematopoietic stem cell transplantation for prophylaxis and treatment of graft-vs.-host disease in adult patients in Japan

Iida M, Fukuda T, Uchida N, Murata M, Aotsuka N, Minagawa K, Oohashi K, Fukushima K, Kondo T, Eto T, Miyamoto T, Morishima Y, Nagamura T, Atsuta Y, Suzuki R. Mycophenolate mofetil use after unrelated hematopoietic stem cell transplantation for prophylaxis and treatment of graft-vs.-host disease in adult patients in Japan.

Abstract: Our previous study of 301 patients who received hematopoietic stem cell transplantation (HSCT) from related donors demonstrated the efficacy of mycophenolate mofetil (MMF) for prophylaxis and treatment of graft-vs.-host disease (GVHD). In this study, we investigated the safety and efficacy of MMF in 716 adult patients who received unrelated HSCT. The incidences of Grade II–IV and III–IV acute GVHD in the prophylactic administration group were 38.3% and 14.3%, respectively. These rates were not statistically significant when evaluating the MMF dosage and graft source. The incidences of limited and extensive chronic GVHD were 16.6% and 11.1%, respectively. In the therapeutic administration group, 69.1% of the subjective symptoms for both acute and chronic GVHD improved. With respect to the adverse events, 75 infections and 50 cases of diarrhea were observed, and the frequency of these events increased with increasing MMF dose. The overall survival rate was 36.4% after a median follow-up period of three yr. This study shows that MMF is safe and effective for the prevention and treatment of GVHD in patients who have received HSCT from unrelated donors.

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Key words: graft-vs.-host disease – mycophenolate mofetil – unrelated allogeneic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective therapy for a variety of hematological disorders. However, one of the limitations of allogeneic HSCT is donor availability; only 30% of patients can undergo transplantation with stem cells from an HLA-matched related donor (1–3). An HLA-matched unrelated donor (MUD) or umbilical cord blood (UCB) is an alternative for a patient lacking a related donor (4–7); however, unrelated HSCT is associated with a higher risk of graft-vs.-host disease (GVHD), which is a major complication of this procedure.

Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase, which impairs the proliferation of activated lymphocytes; MMF has been used as an immunosuppressant in HSCT (8–15). We previously surveyed MMF usage in more than 300 adult patients who received related HSCT in Japan and found that MMF is safe and effective for the prevention and treatment of GVHD (16). In this study, we conducted another survey of MMF use after HSCT from a MUD or a UCB donor in Japan.

Patients and methods

Study design

The basic study design was the same as in our previous study (16). The data on MMF use after allogeneic HSCT from unrelated donors were retrospectively collected using the questionnaire that we used for related donors. The items in the questionnaire included the purpose of treatment (prevention of GVHD or treatment of acute/chronic GVHD), the MMF dosage and dosing period, the presence or absence of subjective symptoms of GVHD, the GVHD grade and stage (before and after treatment), whether there was a decrease or increase in concomitant immunosuppressants, the drug effectiveness, adverse events (AEs), and the outcomes of HSCT. The basic information for each transplantation was extracted from the Transplant Registry Unified Management Program (TRUMP) system, which is a registry of patient outcomes in Japan (17). The number of HLA mismatches was defined as the numbers of mismatched HLA-A, HLA–B, and HLA-DRBI based on low resolution typing in the TRUMP dataset. Several demographic data were not available because they were not entered into the TRUMP system. The effects of MMF, including the rating of subjective symptoms (none, disappearance, improvement, no change or ingravescence) and the use of steroids (none, discontinuation, dose reduction, no change or dose increment), were assessed by the attending physicians at each hospital based on international standards (18). AEs were evaluated using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE, ver. 3). This study was approved by the ethics committees of the Japan Society of Hematopoietic Cell Transplantation and the Nagoya University School of Medicine.

Statistics

Correlations between the two subgroups were examined using the chi-square test and Fisher's exact test. p-Values < 0.05 in two-sided tests were considered statistically significant. The data were

analyzed using STATA version 10 statistical software (STATA Corp, College Station, TX, USA).

Results

Patient background data

From 1999 to 2011, MMF was administered to 716 adult patients. The patient background data are summarized in Table 1. The patient ages at the time of transplantation ranged from 16 to 74 yr (median 51 yr), and the number of male patients was greater than the number of female patients (445 [62.2%] vs. 271 [37.8%], respectively). Unrelated peripheral blood stem cell (PBSC) transplantation had not commonly been conducted in Japan until 2011; therefore, a one-to-one ratio of bone marrow (BM) to cord blood (CB) was approximately achieved (340 vs. 359, respectively). With respect to the donor type, 289 patients (40.4%) received transplants from HLA-matched donors and 400 patients (55.9%) received transplants from HLA-mismatched donors. The HLA data were missing for 27 patients (3.8%). Of the HLA-mismatched donors, 153 (38.3%) were mismatched at one antigen, 242 (60.5%) at two antigens and five (1.2%) at three antigens. The rate of HLA-mismatched transplantation in the BM group was 20.9%, whereas the rate was 95.9% in the CB group. The distribution of diseases in this survey indicated that 95.1% of all of the diseases were hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), myelodysplastic/myeloproliferative syndrome (MDS), malignant lymphoma (ML), and multiple myeloma (MM). The aim of MMF use was GVHD prevention in 440 patients, acute GVHD treatment in 230 patients and chronic GVHD treatment in 84 patients; several of the aims overlapped. In the prevention group (n = 440), CB accounted for 73.2%. The pre-conditioning regimen was myeloablative (MAST) in 290 patients and non-myeloablative (RIST) in 407 patients. In the MAST group, BM accounted for 74.1% of the transplantations, whereas CB accounted for 67.3% of the transplantations in the RIST group.

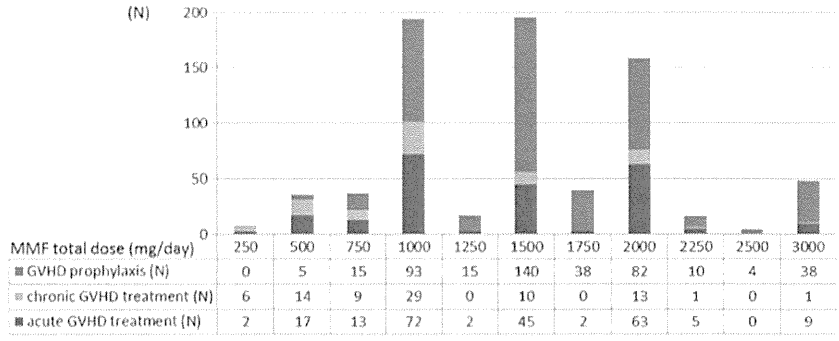
Table 1. Patient characteristics

Variables	Number
Patient number	716
Median age (range)	51 (16–74)
Male/female	445/271
Disease	
Acute myeloid leukemia	315
Acute lymphoblastic leukemia	102
Chronic myelogenous leukemia	28
Myelodysplastic/myeloproliferative syndrome	87
Malignant lymphoma	133
Multiple myeloma	16
Aplastic anemia	18
Other diseases	17
Purpose of mycophenolate mofetil[a]	
Graft-vs.-host disease (GVHD) prophylaxis	440
aGVHD treatment	230
cGVHD treatment	84
Graft source	
Bone marrow (BM)	351
Peripheral blood stem cell	3
Cord blood (CB)	362
Donor type[b]	
Matched (UBM/UPB/CB)	289 (272/3/14)
Mismatched (UBM/UPB/CB)	400 (72/0/328)
1 antigen mismatch (UBM/UPB/CB)	153 (68/0/85)
2 antigens mismatch (UBM/UPB/CB)	242 (4/0/238)
3 antigens mismatch (UBM/UPB/CB)	5 (0/0/5)
Conditioning regimen[b]	
Myeloablative	290
Non-myeloablative	407

[a]Some of these three were overlapped.
[b]There were some blanks in the donor type and conditioning regimen due to lack of patient entry to the Transplant Registry Unified Management Program system.

MMF administration

The daily MMF dosage varied from 250 to 3000 mg. According to the total dosage by purpose, the most common dosage in the prevention group was 1500 mg MMF per day (N = 140), whereas the most common dosage was 1000 mg/d in the acute and chronic GVHD treatment group (N = 72 and 29, respectively; Fig. 1). The number of doses per day ranged from one to eight. The most common dosages and frequencies of MMF administration were 500 mg two times per day, followed by 1000 mg two times per day and 750 mg two times per day, which were given to 156 patients (21.8%), 115 patients (16.0%), and 112 patients (15.6%), respectively. The dosing period varied from <11 d to more than 4000 d. The reasons for early termination of MMF therapy were four early deaths and three adverse events (Quincke's edema, vertigo, and poor oral intake). The average dosing periods in each group were 32, 60, and 221 d in the prophylactic, acute GVHD treatment, and chronic GVHD treatment groups, respectively. In the prophylactic group, most patients (429 patients, 97.5%) were given MMF concurrently with the following immunosuppressants: cyclosporine in 178 patients, tacrolimus in 152 patients, short-term methotrexate plus tacrolimus in 44 patients, and tacrolimus plus steroid in 31 patients. Only 11 patients (2.5%) received MMF alone.



MMF total dose (mg/day)	250	500	750	1000	1250	1500	1750	2000	2250	2500	3000
GVHD prophylaxis (N)	0	5	15	93	15	140	38	82	10	4	38
chronic GVHD treatment (N)	6	14	9	29	0	10	0	13	1	0	1
acute GVHD treatment (N)	2	17	13	72	2	45	2	63	5	0	9

Fig. 1. Mycophenolate mofetil (MMF) daily dose (mg/d) by purpose. MMF was given from 250 to 3000 mg/d. The most common dosages of MMF administration by purpose were 1500 and 1000 mg/d given for prophylaxis (N = 140) and treatment of acute (N = 72)/chronic (N = 29) graft-vs.-host disease, respectively.

Adverse events

All of the AEs that may have been caused by MMF administration are listed in Table 2. The most frequent AE was infection (75 cases, accounting for 30.7% of all cases). The four most common infections were sepsis (19 cases), pneumonia (17 cases), CMV infections (seven cases), and adenovirus infection (four cases). For human herpes virus type 6 (HHV-6) infection, one case of gastritis and four cases of encephalitis/encephalopathy were observed with CB transplantation. Diarrhea was the second most common AE (50 cases, 20.5%); however, excluding one case, the cases were graded as 1–3. In addition, gastrointestinal adverse events, such as nausea, vomiting, stomatitis, and constipation, were less serious. Regarding the therapeutic responses to AEs of grade 3 and 4, the recovery rates for infections and gastrointestinal system-related AEs were relatively favorable (79.8% and 89.2–100%, respectively), whereas the extent of recovery from hematological AEs (thrombocytopenia and neutropenia) were inferior (31.6% and 60.8%, respectively). Overall, 37 patients died of complications that were potentially associated with MMF use, and 73.0% (27) of these cases were attributed to infections (13 cases of pneumonia, five cases of sepsis, two cases of fungal infection, two cases of adeno virus infections, two cases of brain abscess, one case of CMV-related infection, one case of methicillin-resistant *Staphylococcus aureus*/multidrug-resistant *Pseudomonas aeruginosa* infection, and one case of intestinal bleeding due to CMV colitis).

Efficacy of MMF

Among the 440 patients who received MMF for GVHD prophylaxis, the incidence of grade II–IV

Table 2. Adverse events whose relationships to mycophenolate mofetil were not necessarily denied by the NCI-CTCAE (ver. 3) grade

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5[a]		Total	
Adverse events	N	%	N	%	N	%	N	%	N	%	N	%
Infection	0	0.0	7	1.0	31	4.3	10	1.4	27	3.8	75	10.5
Diarrhea	6	0.8	11	1.5	32	4.7	1	0.1	0	0.0	50	7.0
Neutropenia	0	0.0	4	0.6	10	1.4	9	1.3	0	0.0	23	3.2
Thrombocytopenia	0	0.0	4	0.6	8	1.1	11	1.5	0	0.0	23	3.2
Nausea	2	0.3	8	1.1	7	1.0	0	0.0	0	0.0	17	2.4
Gastrointestinal bleeding	1	0.1	1	0.1	4	0.6	1	0.1	0	0.1	7	1.0
Myelosuppression	0	0.0	5	0.7	2	0.3	1	0.1	0	0.0	8	1.1
Vomiting	2	0.3	3	0.4	1	0.1	0	0.0	0	0.0	6	0.8
Stomatitis	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	2	0.3
Constipation	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
Others[b]	4	0.6	6	0.8	8	1.1	4	0.6	10	1.4	32	4.5

[a]Details about Grade 5: pneumonia (13), sepsis (5), fungal infection (2), adenovirus infection (2), brain abscess (2), CMV infection (1), multiple organ failure (2), organ failure (lung) (2), gastrointestinal bleeding due to CMV enteritis, MRSA/MDRP infection, organ failure (central nervous system), EBV-related lymphoproliferative disease, hemophagocytic syndrome, ileus, thrombotic microangiopathy.
[b]Others: grade 1: hypogammaglobulinemia, Quincke's edema, renal tubular acidosis, poor oral intake; grade 2: renal damage, vertigo, heartburn, tongue fur, abdominal pain, drug eruption; grade 3: hypoalbuminemia (2), rhabdomyolysis, thrombotic microangiopathy (2), vertigo, pure red cell aplasia, ileus; grade 4: interstitial pneumonia (2), thrombotic microangiopathy, graft failure.

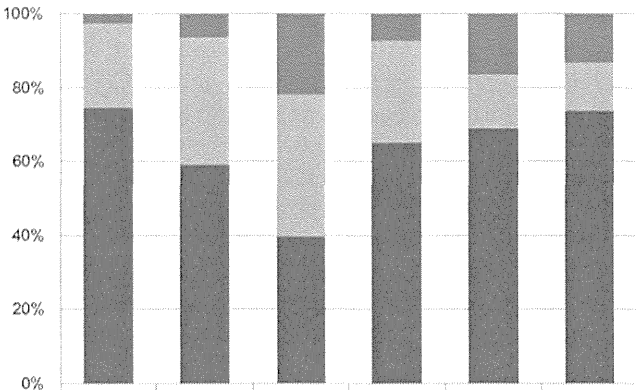
acute GVHD was 38.3% (164/428), and the incidence of grade III–IV was 14.3% (61/428). The incidence of grade II–IV acute GVHD decreased with increasing MMF dosage (~1000, ~2000, and 2001 mg/d~); however, the incidence of grade III–IV acute GVHD remained the same regardless of the dosage. Assessing the incidence of acute GVHD according to the graft source, the rates of grade II–IV and III–IV acute GVHD in the BM group were lower than that in the CB group (33.6% vs. 38.2% and 12.9% vs. 14.0%, respectively; Table 3). No significant differences were found in the incidence of grade II–IV/III–IV acute GVHD between HLA-matched and mismatched transplant patients, excluding grade III–IV gut GVHD (0/94 [0%] vs. 13/295 [4.4%], p = 0.04). With respect to the chronic GVHD incidence, 16.6% (60/361) and 11.1% (40/361) of patients experienced limited and extensive chronic GVHD. The MMF dose was not associated with the incidence of limited and extensive chronic GVHD. In the evaluation according to the graft source, 20.2% (21/104) of patients in the BM group and 14.5% (37/255) of patients in the CB group developed limited chronic GVHD and 15.4% (16/104) of patients in the BM group and 9.4% (24/255) of patients in the CB group developed extensive chronic GVHD (Table 3). There were no significant differences between the HLA-matched and mismatched groups in the development of chronic GVHD (25/93 [37.6%] vs. 61/249 [24.5%], p = 0.31). When we compared the incidence of acute and chronic GVHD with the disease and source, the incidence of grade II to IV acute GVHD in the BM and CB cases were 31% vs. 39% in AML, respectively, and 60% vs. 39% in ALL, respectively. For chronic GVHD, the incidences for BM and CB cases were 18% vs. 21% in AML and 53% vs. 18% in ALL, respectively.

Table 3. Incidence of graft-versus-host disease (GVHD) with prophylactic mycophenolate mofetil use

	a GVHD		c GVHD	
	II–IV (%)	III–IV (%)	Limited (%)	Extensive (%)
Total	38.3	14.3	16.6	11.1
Dosage (mg/d)				
~1000	38.5	16.0	13.3	7.8
1001~2000	39.7	13.5	15.0	11.9
2001~	30.8	15.4	31.1	13.3
Graft source				
Bone marrow	33.6	12.9	20.2	15.4
Cord blood	38.2	14.0	14.5	9.4
Peripheral blood	100.0	50.0	100.0	0
Conditioning regimen				
Myeloablative	38.3	13.1	25.8	11.2
Non-myeloablative	38.1	14.3	14.0	11.6

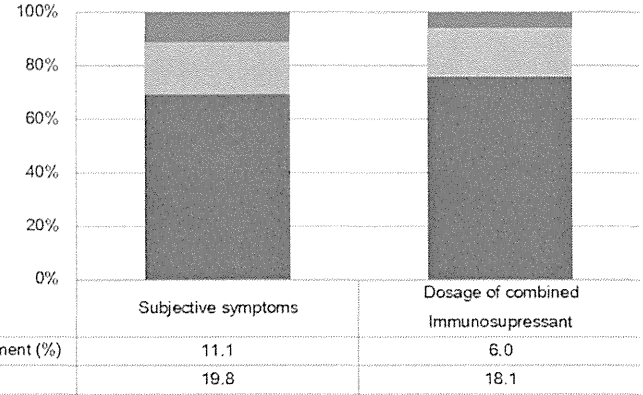
In the acute GVHD treatment group, the disappearance or improvement of subjective symptoms occurred in 69.1% of patients, and 73.7% of the patients in this group reduced or discontinued the combined immunosuppressants (Fig. 2). Especially in the HLA-matched group, the improvement rate in the subjective symptoms was significantly higher than that in the HLA-mismatched group (92/132 [69.7%] vs. 47/85 [55.3%], p = 0.03). The comparison of the effects of MMF according to the target organ indicated that MMF was more effective for skin GVHD than for gut and liver GVHD (143/192 [74.5%], 72/122 [59.0%] and 27/68 [39.7%], respectively; Fig. 2). In the chronic GVHD treatment group, 56/81 (69.1%) of the cases had improved subjective symptoms and 63/83 (75.9%) of the cases reduced or discontinued the dosage of combined immunosuppressants (Fig. 3). In addition, there were no significant differences between the HLA-matched and mismatched patients in each of these observed items (p = 0.44~0.77, data not shown). To assess the efficacy of MMF for GVHD treatment, we divided all of the patients into the following three subgroups according to the MMF dosage: <1000 mg/d, <2000 mg/d, and more than 2001 mg/d (Table 4). The efficacy rates for every acute and chronic GVHD survey item, including improvement in the grade and subjective symptoms and a reduction in the dose of combined immunosuppressants, were higher in the more than 2001 mg/d dosage group than in the <1000 mg/d and <2000 mg/d groups; however, there were no differences in the dose efficacy observed among the three dosage groups (p = 0.13–0.99 for acute GVHD items and p = 0.56–0.99 for chronic GVHD items).

We collected data from a large number of patients who underwent CB transplantation with prophylactic use of MMF (N = 322); 90.4% of these patients were HLA mismatched. The median daily dosage and dosing days in this group were 1500 mg and 32 d, respectively. One hundred and seventy-six (54.7%) and 114 (35.4%) patients were given MMF with cyclosporine and tacrolimus, respectively. The rates of grades II–IV and III–IV acute GVHD were 38.2% and 14.0%, respectively, and the rates of limited and extensive chronic GVHD were 14.5% and 9.4%, respectively (Table 3). Three out of five cases of HHV-6 encephalitis/encephalopathy in this group developed grade II–IV acute GVHD (2 grade III cases and 1 grade IV).



	Skin	Gut	Liver	Grade	Subjective symptoms	Dosage of combined Immuno supressant
Ingravescence / Increment (%)	2.6	6.6	22.1	7.4	16.4	13.2
No Change (%)	22.9	34.4	38.2	27.5	14.5	13.2
Disappearance· Improvement/ Reduction· Discontinuation (%)	74.5	59.0	39.7	65.1	69.1	73.7

Fig. 2. Response to acute graft-vs.-host disease (GVHD) in the treatment group. In the acute GVHD treatment group, the disappearance or the improvement of subjective symptoms occurred in 69.1% of patients and 73.7% of the patients in this group could reduce or discontinue the combined immunosuppressants.



	Subjective symptoms	Dosage of combined Immunosupressant
Ingravescence / Increment (%)	11.1	6.0
No Change (%)	19.8	18.1
Disappearance· Improvement/ Reduction· Discontinuation (%)	69.1	75.9

Fig. 3. Response to chronic graft-vs.-host disease (GVHD) in the treatment group. In the chronic GVHD treatment group, 56/81 (69.1%) of cases improved subjective symptoms and 63/83 (75.9%) of cases reduced or discontinued the dosage of combined immunosuppressants.

Transplantation outcomes

In the GVHD prevention group, engraftment was observed in 360 of 423 patients (85.1%). The engraftment rates according to the graft source were 94.0% and 77.3% for the BM and CB groups, respectively. Of the total 716 patients, 168 (23.5%) relapsed and 425 (59.4%) died after transplantation. The overall survival rates were 40.6% and 36.4% after a median follow-up of period of two and three yr, respectively. The main causes of death were disease recurrence, bacterial infection and acute or chronic GVHD. In the prophylactic group, disease recurrence was the most common cause of death (43%), which was followed by bacterial infection (11%) and acute GVHD (6%). Four out of five cases of HHV-6 encephalitis/encephalopathy died of other infections (3) and relapse (1) instead of acute GVHD.

In the acute GVHD treatment group, the causes of death were acute GVHD (22%), disease recurrence (18%) and bacterial infection (11%). In the chronic GVHD treatment group, the most common cause of death was bacterial infection (22%), which was followed by chronic GVHD and disease recurrence (16%, respectively).

Discussion

Over the past few years, several types of allogeneic HSCT have become available, including CB, non-myeloablative, and haplo-identical transplantation. As the number of new strategies increases, methods for controlling GVHD must be developed

Table 4. Response rate of acute and chronic graft-versus-host disease (GVHD) during therapeutic mycophenolate mofetil use by daily dosage

	Dosage (mg/d)					
	~1000		1001~2000		2001~	
	N	%	N	%	N	%
Acute GVHD						
Grade						
Improvement	66	63.5	71	63.4	12	85.7
No change/ ingravescence	38	36.5	41	36.6	2	14.3
Subjective symptoms						
Disappearance/ improvement	70	72.2	70	64.2	12	85.7
No change/ ingravescence	27	27.8	39	35.8	2	14.3
Dosage of combined immunosuppressant						
Reduction/ discontinuation	75	73.5	82	73.2	11	78.6
No change/ increment	27	26.5	30	26.8	3	21.4
Chronic GVHD						
Subjective symptoms						
Disappearance/ improvement	38	67.9	16	69.6	2	100.0
No change/ ingravescence	18	32.1	7	30.4	0	0.0
Dosage of combined immunosuppressant						
Reduction/ discontinuation	45	77.6	16	69.6	2	100.0
No change/ increment	13	22.4	7	30.4	0	0.0

because GVHD remains one of the greatest post-transplantation complications. MMF is one of the most effective drugs available and is used under various conditions for HSCT (8–10, 12–14, 19–23). As we previously reported, MMF is an important therapeutic agent for the treatment and prophylaxis of acute and chronic GVHD after related HSCT in Japan (16). In this study, we evaluated more than 700 patients who received MMF after unrelated HSCT in Japan. There were few differences in the method of MMF administration for unrelated and related HSCT. The most frequent daily dosage was 1000 mg (dosage/frequency of 500 mg twice a day) in both groups, which was followed by 750 mg (250 mg three times per day) and 2000 mg (1000 mg twice a day) in the related donor group and followed by 1500 mg (750 mg twice a day or 500 mg three times per day) and 2000 mg (1000 mg twice a day) in the unrelated donor group. The most common MMF dosing period was 10–30 d in the related group and 30–60 d in the unrelated group. The MMF dosages and dose regimens in Japan were relatively lower/shorter than those in other countries because of the low incidence of GVHD, the risk for infection due to excess immunosuppressive states, and the fact that MMF is not approved for the treatment and prevention of GVHD.

Murata et al. (24) revealed that the response rate of grade II–IV acute GVHD to systemic corticosteroid therapy in Japanese patients was very high (~64%), especially for CB transplantation. However, if systemic corticosteroid therapy is ineffective, Japanese patients cannot achieve a satisfactory survival rate, and the authors concluded that the establishment of second-line treatment for corticosteroid refractory acute GVHD is required for Japanese patient. Kanda et al. (25) reported that in Japan, the incidences of grade II to IV acute GVHD among unrelated HSCT patients were 41% in the unrelated BM group and 45% in the CB group with conventional GVHD prophylaxis, such as cyclosporine or tacrolimus. In the same report, the incidences of chronic GVHD at two yr were 34%, 40%, and 30% in the matched unrelated BM, mismatched-unrelated BM and CB groups, respectively. Atsuta et al. conducted a disease-specific comparison of Japanese unrelated BM and CB patients with acute leukemia (AML and ALL) using the same GVHD prophylaxis regimen as Kanda et al. The incidences of grade II to IV acute GVHD were lower for CB cases than for BM cases (32% vs. 35% in AML, 28% vs. 42% in ALL) and were the same as for chronic GVHD (8% vs. 20% in AML, 10% vs. 17% in ALL; 26). Considering the results in Table 3, the incidence of grade II to IV acute GVHD and chronic GVHD in this study seems to be better than with conventional prophylaxis; however, the results were too varied to directly compare the use of conventional prophylaxis and our results from MMF administration for each risk factor, such as the disease and source.

MMF has been increasingly used after HSCT worldwide. Among recent reports, Minagawa et al. (11) summarized more than 100 representative reports from studies of MMF use as GVHD prophylaxis in HSCT. Additionally, Wolff et al. (22) conducted a survey in 72 allo-HSCT centers in Germany, Austria, and Switzerland and reported that MMF was used more frequently as a first- and second-line treatment for acute GVHD. There have been an increasing number of reports on the effectiveness of MMF. Xhaard et al. (23) found that the overall response to second-line therapy with MMF for the treatment of steroid-resistant acute GVHD is greater than that with inolimomab

and etanercept. Rodriguez et al. and Basara et al. retrospectively studied the effectiveness of MMF for chronic GVHD treatment compared to historical controls (14, 20). Alousi et al. (19) conducted a randomized phase 2 trial using four drugs (MMF, etanercept, denileukin, and pentostatin plus corticosteroids) for acute GVHD treatment and reported that the use of MMF plus corticosteroids was significantly better than other agents according to the treatment response and long-term survival. Furthermore, Furlong et al. (21), in a prospective trial of refractory acute and chronic GVHD treatment, concluded that MMF is effective at treating GVHD. In contrast, Martin et al. (27) failed to show the efficacy of adding MMF to a prednisolone regimen for the first-line therapy of chronic GVHD in a randomized study. They concluded that adding MMF to immunosuppressive regimens has no effect on controlling chronic GVHD, and the risk of the overall mortality and malignancy recurrence in the MMF group may be higher than in the control group. Retrospective data can be very helpful; however, we should consider the flaws of retrospective data, including the diversity of the background and investigator's biases.

We found it interesting that many patients who received CB as their graft source also underwent prophylactic MMF treatment in Japan. Uchida et al. (28) reported 29 CB transplantation cases with MMF from Japan, and they concluded that the MMF and tacrolimus combination is well tolerated. Styczynski et al. (29) also reported on 29 CB transplantation cases (20 of which received MMF), and the incidences of acute and chronic GVHD were relatively low. Most previous studies have demonstrated that the incidence of acute and chronic GVHD after CB transplantation is ~40% for HLA-mismatched CB grafts (6, 30–33). The incidences of acute and chronic GVHD in our survey were as low as 40%, and the results of our large cohort encourage us to conclude that MMF compares favorably with other immunosuppressants.

HHV-6 reactivation and HHV-6 encephalitis occur more frequently in patients with CB transplantation (34), and Zerr et al. (35) reported that HHV-6 reactivation is associated with an increased risk of grade II–IV acute GVHD and non-relapse mortality. Five cases of HHV-6 encephalitis/encephalopathy were observed with CB transplantation in this study. Among these five cases, 60% developed grade III–IV acute GVHD and 80% died. Because the treatment for HHV-6 encephalitis/encephalopathy has not been established, determining the role of immunosuppressants such as MMF, as well as antibiotics, will become more important.

Regarding other adverse events, no cases of severe mucositis were observed in this study, which is in agreement with previous studies (13, 36). Additionally, severe nephrotoxicity, which is the most common type of toxicity due to cyclosporine and tacrolimus administration (37), did not occur.

Martin et al. (38) reviewed reports on the treatment of acute GVHD that were published from 1990 to 2011, and they summarized 11 first- and second-line systemic treatments, including MMF. They concluded that none of the comparative data demonstrated the superior efficacy of any particular agent and that patients should be treated according to various conditions, such as previous treatments, drug toxicity and drug interactions. Each physician should fully understand the advantages and disadvantages of MMF and immunosuppressants and determine which agent is the most appropriate for each patient/situation. Additionally, Martin et al. reported on the risks of viral infections such as CMV, Epstein-Barr virus and adenovirus caused by long-term immunosuppression. The data from our study on adverse events are in agreement with their findings. Physicians should be more cautious about considering the conditions of each patient when prescribing MMF.

This study has several limitations. One is the possibility of selection bias of the patients. Because this study is retrospective and based on data from questionnaire, a disproportionately refractory and higher risk population may have been included. The physicians who participated in this study may unconsciously have selected patients from a higher risk population, and they might have added MMF in a desperate attempt to control GVHD. Moreover, MMF was used more frequently in patients who participated in another clinical trial or was more often prescribed at the discretion of other physician. The third limitation is that TRUMP does not include information on MMF, and we were missing some data. Fourth, we could not analyze items that were not included in the questionnaire, such as whether MMF was given for first-line or salvage treatment and how many previous treatment regimens had been given to the patients. However, this survey of more than 700 cases of unrelated HSCT is the largest to date and thoroughly demonstrates the effectiveness and safety of MMF, and we found that MMF is effectively and safely used in a large number of HSCT patients in Japan. This is the first step to establishing the value of MMF in Japanese HSCT. We understand the importance of randomized studies,

as Martin et al. (27) emphasized in their report. Future well-designed, prospective phase 2 studies will be needed to confirm our results.

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Authors' contributions

MI, RS, and TF designed the study and wrote the paper. NU, MM, NA, KM, KO, KF, TK, TE, and TM submitted the data. MI, RS, and YA performed the statistical analysis. YM and TN reviewed and compiled the data as well as reviewed the results.

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SPECIAL REPORT

Challenges and opportunities for HSCT outcome registries: perspective from international HSCT registries experts

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Patient registries, frequently referred to as outcome registries, are 'organized systems' that use observational study methods to collect uniform data. Registries are used to evaluate specified outcomes for a population defined by a particular disease, condition or exposure that serves one or more predetermined scientific, clinical or policy purposes. Outcome registries were established very early in the development of hematopoietic SCT (HSCT). Currently, myriads of national and international HSCT registries collect information about HSCT activities and outcomes. These registries have contributed significantly to determining trends, patterns, treatment practices and outcomes. There are many different HSCT registries, each with different aims and goals; some are led by professional organizations, others by government authorities, health care providers or third parties. Some registries simply assess activity and others study outcomes. These registries are complementary and are gradually developing interoperability with each other to expand future collaborative research activities. A key development in the last few years was the incorporation of recommendations into the World Health Organization guiding principles on cell, tissue and organ transplantation. The data collection and analysis should be an integral part of therapy and an obligation rather than a choice for transplant programs. This article examines challenges in ensuring data quality and functions of outcome registries, using HSCT registries as an example. It applies to all HSCT-related data, but is predominantly focused on HSCT registries of professional organizations.

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INTRODUCTION

There is a growing recognition of the value of observational data as a research tool in assessing utilization and patterns of medical care as well as facilitating outcome analysis to fill evidence gaps regarding safety and effectiveness. Patient registries, typically referred to as outcome registries, are the 'organized systems' that utilize observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a particular disease, condition or exposure. This outcome data and analysis can in turn, serves as the basis for future scientific and clinical trials or policy purposes.[1] Registries are classified according to how their populations are defined and their purpose. Populations may be defined by disease or conditions, exposures such as treatments, procedures or adverse events or groups defined by boundaries such as geography, socio-economic status and other arbitrary measures. The most common purposes of registries are to describe the natural history of disease or exposure, determine effectiveness, measure safety and toxicity and assess quality in a systematic approach.

Outcome registries were established very early in the development of hematopoietic SCT (HSCT), a treatment of choice for myriads of hematological malignancies and other life-threatening diseases. As outcome registries are observational, the basic source document is usually the patient's medical record from which pertinent information is abstracted for use in the registry. HSCT registries provide a tool for understanding the trends and patterns of HSCT in a defined population. They can serve as a local, national, regional or international resource or a combination, thereof. These registries are a major source of clinical information and can have an important role in monitoring and influencing HSCT activities and guidelines. They facilitate research into HSCT outcomes by addressing questions difficult to answer by clinical trials[2] or complementing clinical trial findings.[3] Registries also form the basis for prevention/intervention program development, delivery and effectiveness. They can help in designing the optimal schema for prospective and retrospective studies and for comparative analyses of diverse HSCT strategies or for HSCT versus non-HSCT therapies. If data collection is sufficiently comprehensive, outcome findings from patient registries can be widely generalizable.

By introducing data feedback and reporting loops, registries can be made synergistic with continuous quality improvement processes and can lead to patient care optimization with minimization of complications. Registries provide insight into the patient population, demographics, changing patterns of disease interventions and rates of complications. Providing baseline data,

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trend analysis and outcome measurements is the primary objective of these registries. These can be a foundation for improving the overall health and quality of life of HSCT patients. Outcome measurement evaluates the patient's improvement and the treatment's effectiveness.

The value of HSCT registries is enhanced when they are based on established international ethical and quality standards for the design, collection, analysis, reporting, monitoring and auditing of outcome data for donors and recipients. Easy accessibility of data from such registries to the participating physicians and safeguards for credible and accurate data are essential ingredients of a quality registry. The registry should also provide assurance for the integrity and confidentiality of the data.

Regional HSCT registries can promote HSCT in the region, identify loco-regional trends and practices, standards and interventions and may also be helpful in benchmarking HSCT outcomes. A study from the United Kingdom and Ireland recently compared their data with data in the large multinational outcome registry maintained by the European Group for Blood and Marrow Transplantation (EBMT), and demonstrated the potential for using national registries to benchmark transplant outcome using the EBMT registry as reference.[4] The Center for International Blood and Marrow Transplantation (CIBMTR) annually assesses 1-year survival after allogeneic HSCTs in each US transplant center and makes these results available to participating transplant programs, and the public.[5,6] Globalization of patient and donor registration for HSCT is a realistic goal and can contribute to the improvement of patient care, outcomes and donor safety.[7,8] Registry data have provided important insights into international differences in indications for HSCT, and access to HSCT.[9,10] Data from outcome registries may be useful to evaluate differences in outcomes across regional or international settings to identify modifiable practices and inform program improvement.

Observational studies, databases and registries offer many advantages and valuable information (Table 1), if designed, maintained and analyzed properly. The availability of detailed clinical information from registries, combined with powerful statistical analysis, provides timely and accurate information on the safety and effectiveness of HSCT in hematological malignancies and large number of inherited and acquired hematologic disorders.

Transplant registries face a myriad of challenges (Table 2) that are summarized below in terms of trained personnel, regulations, data collection, data standards, communication, quality management, data utilization and publications.

Qualified personnel

Qualified and adequately trained personnel with HSCT background and skills, operating as a functional team to manage registries are essential to their value. Developing and maintaining these skill sets can be a continuous challenge. Expertise that may be critical to the operation of the registry include: subject matter experts with clinical and scientific expertise; project management; experts in biostatistics and epidemiology; data architects, database administrators and programmers and security experts; personnel experienced with human subjects protection privacy regulations and expertise in quality assurance procedures. Understanding the basic concepts of HSCT by all personnel, regardless of their role in the registry, allows tailoring of the registry to the particular uniqueness of the therapeutic modality and substantially increase their value.

Working collaboratively, these groups of experts can effectively manage the registry activities from data acquisition through dissemination of data, reports and publications. They must marshal resources to effectively administer the registry, and skillfully allocate those resources to optimize the balance between data collection, burden upon those providing data, and utilization of data for reports and publications of highest impact for the field.

Table 1. Strengths of HSCT registry-based research

- If comprehensive, excellent source of demographic and activity data—dynamic measure of patterns of care.
- Useful for planning intervention trials—hypothesis generation, calculating effect size and potential recruitment.
- 'Real world' therapeutic effectiveness and safety data (as opposed to efficacy)—compare disease management by program, region and country.
- Heterogeneity of standard practice across participating sites facilitates research into 'best practices'.
- Heterogeneity among study subjects.
- Detection of rare consequences is satisfied by large numbers of patients followed for long periods of time—a unique advantage.
- Low risk to participating subjects (observational rather than interventional) can promote broad participation.
- Flexibility: serves as a platform for extending observation or intervention to particular groups of subjects—sub-studies.
- Relatively low cost to develop and maintain on a per-patient basis.
- Useful as a comparative arm in comparative effectiveness research.
- Provide meaningful data for decision-making where a clinical trial is not feasible or practical.
- Estimates of impact of treatment are more realistic.

Regulations—managing ethical, privacy and legal considerations

Development and maintenance of outcome registries requires particular attention to human subjects' protection, privacy considerations and legal considerations in the collection, ownership and exchange of data for registry purposes, including public health and research. An appropriate security infrastructure is essential to protect these interests. The framework for these considerations is made more challenging when the operation of the registry involves international sharing. The bylaws, data transfer agreements, accreditation for standardization by the Joint Accreditation Committee of the International Society of Cellular Therapy Europe and the EBMT/Foundation for the Accreditation of Cellular Therapy and others are pivotal in streamlining regulatory trepidations. However, wide ranging human subject protection regulations in different countries, wide variations in ethical committees' composition and deliberations, multifarious consent issues and lack of a Central Institution Review Board all pose challenges, particularly for international registries.

Human subjects' protection must be addressed from an ethical and legal perspective for any outcome registry. However, because outcome registries are observational in nature, they are often considered 'low-risk' with regard to potential for harm to human subjects. Consent for use of data for research obtained from research subjects by outcome registries, must be addressed by the registry, however, registry functions for public health or government program purposes may not require specific consent for research.[11]

Safeguarding patients' privacy and data confidentiality are of utmost importance. Privacy concerns with regard to identifiable patient information can be addressed by registries by collection of de-identified data and collection of identifiable data for 'internal use' with linked identifiers. The legal framework to collect identifiable health information varies by country and purpose of the registry. Registry data collected in the context of a public health reporting obligation, such as the outcome registry requirements of the US CW Bill Young Cell Transplantation Program, are subject to different privacy considerations as a public health authority.[11]

Table 2. Challenges facing HSCT registry-based research

Qualified personnel
Trained and qualified personnel
Familiarity with staging, grading and toxicity criteria
Effective communication/documentation
Work load, proportionality and time management
Regulations
Bylaws, data transfer agreements
Accreditation for standardization (JACIE/FACT)
IRB regulations, wide variation in ethical committees deliberations
Informed consent issues
Central Institution Review Board
Privacy and confidentiality
Data management
Linking data sources for efficiency
Case report forms
Redundancy
Harmonized form (consider instead uniform use of standardized data elements and definitions)
Accuracy and integrity of data
Data quality/comparability/standardization
Data monitoring safety committees/boards
Quality and performance improvement/audits
Cross-training of data managers
Acquiring long-term follow-up data
Electronic medical record
Training and in-service
Standardized registry software
Uniformity, standardization
Communication and cultural issues
Language barriers
Cultural, social and economical heterogeneity
Cultural sensitivities/QOL instruments
Quality management
Homogeneity and uniformity of the registries
Accreditation standards: JACIE/FACT
Variation in labs/toxicity criteria/PS
Annual review of registry: new variables, biomarkers and staging/grading
Data utilization and publications
Overlapping registries/databases
Integration/interfacing/interoperability
Access to data
Authorship guidelines
Obtaining and sustaining funding
Value of the registry on long term requires sustainable funding sources
Information represents substantial value that can be used to develop resources

Abbreviations: FACT = Foundation for the Accreditation of Cellular Therapy; JACIE = Joint Accreditation Committee of the International Society of Cellular Therapy Europe and the EBMT; PS = performance status; QOL = quality of life.

In HSCT, most outcome registries have chosen to obtain identifiable information with linked identifiers to expand the opportunity to connect the registry data to other important data sources. For instance, approximately half of the HSCT performed annually around the world use an allogeneic donor acquired through a donor registry or cord blood bank. As many donor registries and cord blood banks have regulatory obligations to report on outcomes of the products used for these transplants, the ability to connect patient outcomes with the donor product at the level of a donor or bank 'registry' is of high importance, and provides justification for collection of identifiable information. Between 25 and 30% of all allogeneic HSCT involve recipients and donors from different countries, the challenges of connecting these data while respecting the boundaries of international regulations are substantial, but represent an important opportunity for international HSCT registries. In HSCT, projects coordinated by the Worldwide Marrow Donor Association seek to overcome these challenges.

Several outcome registries collect international recipient outcome data, and collaborate to share the data to expand study size and evaluate regional differences. Use of limited identifiable information is important to avoid inclusion of overlapping patients from different registries in the analyses. Collection of limited identifiable information allows the outcome registry data to be linked to other important sources of data, such as disease incidence data, mortality databases and payer databases to leverage the research and quality improvement uses of HSCT data. Research applications of identifiable information often require authorization from the participating subject, which is usually collected at the time of consent for research.

The use of unique patient identifiers can be confusing and may lead to duplication. The major international registries including Center for International Blood and Marrow Transplantation, EBMT and the Asia-Pacific Blood and Marrow Transplant Group each have their own unique patient identification system that is compliant with relevant rules for protection of privacy. The Eastern Mediterranean Blood and Marrow Transplantation Group is currently in the process of assigning a Unique Patient Identification Number (UPIN) based on country code, city code and hospital code. In the context of the worldwide network for Blood and Marrow Transplantation, a framework for sharing registry data while avoiding overlap through use of limited identifiable information is being discussed. Although the World Health Organization has stipulated that data collection and data analysis should be considered mandatory components of cell and tissue transplantation programs such as HSCT, competent authorities are challenged to implement solutions that address ethical, legal and privacy considerations.

Data management

Usefulness of an outcome registry is directly related to the scope and quality of the data collected. The scope of the data collected by the outcome registry is framed by the purpose and objectives, but is affected by many other factors. Geographic location and setting of data collection for the target population help to define the scope of a registry. The number of observations necessary to achieve the objectives will affect the size of the registry, as will the complexity of the data elements and outcomes deemed essential to be collected by the registry organizers. The duration of data collection is an important consideration to achieve registry objectives, but must be balanced by the ability to reliably collect the data.

Balancing the costs of registry management with the burden of data collection and the value of the information generated will frame the scope of the registry. Registries should define a core data set of essential data elements and patient outcomes that will address the critical questions anticipated by the purpose and objectives for which it was created. The core data set should be defined by clinical, epidemiological and biostatistical experts; balance the burden of data collection with the value; and be re-evaluated periodically to be current with the field or changing objectives of the registry. In HSCT, an internationally accepted core data set has been established through initial collaboration of experts from the two largest outcome registries (Center for International Blood and Marrow Transplantation and EBMT),

working with accreditation bodies. The data contained in the core data set are now recognized internationally as a model for HSCT registries, and the worldwide network for Blood and Marrow Transplantation has endorsed the use of standard data elements contained in this core data set for any program beginning to establish an HSCT registry. Case report forms need to be periodically revised, to make them up-to-date, especially in relation to new diagnostic and prognostic markers as well as treatment modalities. Redundancy in data collection can also be a challenge as different centers report to several international registries.

Accuracy, integrity and completeness of data are the most important elements in the quality and value of any registry. Low data quality can be due to inadequate collection of data at individual reporting sites, inattentive abstracting of information from clinical data sources, poor definition and specificity of data elements, inadequate understanding of complex data elements by those providing the data and lack of incentive and collaboration among reporting centers. Comparability of data is essential for interpretation and this in turn, depends on standardization of the methodology and the diagnostic criteria applied. These threats to data quality must be addressed by the outcome registry. Effective quality control using regular internal and external audits and monitoring site visits can help to achieve these foremost goals. Quality and performance improvement can be augmented by continuous updating of the case report forms, advanced survey forms, data collection and follow-up mechanisms. Long-term follow-up of registry participants represents a particular challenge. In a specialty model registry, such as HSCT, recipients are typically not followed long term by the transplant center that performed the procedure. However, the data collected at time points beyond 1 year is difficult for non-HSCT providers to interpret, especially as they are usually not engaged in the purpose and value of the registry. The burden of providing long-term follow-up is substantial for the HSCT centers, even while the unique value of an outcome registry for late effects is readily acknowledged. With growing numbers of HSCT recipients having an interest in long-term complications, and access to the internet, HSCT registries are beginning to explore direct-to-patient communication as a means to maintain long-term follow-up. Cross-training of the data managers to have a broader understanding of the multidisciplinary approach in the HSCT can be very helpful to overcome this challenge. Continuous education and advanced training of the data professionals/registrars at the participating centers in the registry can enhance quality and compliance with reporting standards.

Transplant registries, with effective data management, are intended for creation of a database that would identify and describe the quantity and quality of transplants and outcomes. Registries outcomes encompass time trends in stage, treatment patterns and survival outcomes. Treatment improvement will transpire if survival outcome derived from registries can serve as a guide for the quality of care in the future.

Most data collection for HSCT outcome registries is conducted using electronic applications. Good quality information systems are needed for effective data collection to support the registry. They must be user friendly, cost effective to maintain, reliable with minimal downtime, validated and compatible with standard operating systems. Web-based data entry applications, with robust data validation tools are needed to streamline observational registries, enhance electronic data capturing efforts and to provide tools for centers to receive back and analyze their own data for quality and performance improvement projects and research.

Communication and cultural issues

Language barriers among different countries participating in a regional or international registry can be a challenge. There can be several languages, dialects and norms stemming from a historic background of different countries taking part in the registry. There can be enormous cultural, social and economical heterogeneity. Cultural sensitivities can be another challenge, especially when trying to incorporate collection of patient reported information, such as quality of life data. Occasionally, there are limitations in using certain quality of life tools for socio-cultural reasons and conservatism in general. Quality of life forms need to be culturally sensitive and validated, specifically for those regions.

Performance/quality management

Outcome registries can be a key component of HSCT centers' quality management/performance improvement programs. The current accreditation bodies for HSCT in the United States and Europe, Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee of the International Society of Cellular Therapy Europe and the EBMT, require that HSCT programs collect and use the standard core data set defined by the field to analyze and understand their program quality.[12] Accreditation helps in implementing basic unified standards and uniformity for good clinical practice across the board among all participating centers for accuracy, integrity, reliability and transparency of the registry data. A future objective for HSCT registries is to exploit this synergy of data collection and accreditation to achieve better integration of outcome registry reporting and centres' use of the reported data for their own performance improvement objectives. Outcome registries can also provide a quality context or benchmark for HSCT centers to use when evaluating the performance of their program. Registries can also facilitate research into quality management that informs improvements in transplant practices and individual center outcomes. Different transplant centers use different lab units/standards, toxicity criteria (Bearman *et al.*,[13] Common Terminology Criteria for Adverse Events and World Health Organization), GVHD definitions (National Institutes of Health,[14] others) and performance status (Karnofsky Performance Status, Eastern Cooperative Oncology Group/Zubrod and so on), to name a few. Poor data quality leads to inconsistency and fragmentation of the data. The registry case report forms and database need to be periodically reviewed by the audit committee and the Principal Investigator/Working Committee Chairs in order to incorporate the new variables, biomarkers, staging (American Joint Committee on Cancer (AJCC) 7.0 versus 8.0), grading and so on. High-quality registry requires strong methodology and operational excellence. Levels of rigor that enhance validity and usefulness for guiding decisions are research quality (scientific process) and evidence quality (data/findings).

Data utilization and publications

Findings from observational research have led to significant improvement in the field of HSCT and better clinical trial planning.[15] Collaboration and sharing of data for maximum utilization and optimizing patient outcome is the key to an effective registry.[16–18] Many centers report data to a myriad of overlapping registries and databases. Integration, interfacing and interoperability are the key ingredients for optimum outcomes and use of these registries. Centers submitting data need to have full access to their own center's data in a registry. There is a need to develop harmonized registry forms encompassing existing forms (for example, Minimum Essential Data (MED-A) and Pre-Transplant Essential Data (Pre-TED)) for standardization, uniformity, validity and homogeneity. Strict adherence to well-outlined authorship guidelines needs to be followed and unanimously approved by the participating centers based on number of transplants, contribution and the centre's participation.

An ideal registry will enhance the understanding of transplant outcomes by addressing questions such as transplant results in

specific patient groups, analysis of prognostic factors, evaluation of new transplant regimens, comparison of transplant with non-transplant therapy, defining inter-center variability in practice and outcome, characterizing rare late effects and developing innovative analytical approaches.[19,20] Linking with other epidemiological data can provide insights into the availability and economics of HSCT. Linking clinical data with immunological and genetic information can provide important insights into transplant biology.

HSCT registry can have a significant role in designing the randomized control clinical trials. Registry data can be very helpful in focusing prospective transplantation trials in areas not well studied and understood, especially the role of geographical variations, genetic differences, genotypic and phenotypic variations and biology of disease by providing preliminary data. It can help in developing and improving the use and efficacy of innovative and novel therapeutic strategies. It can also be utilized in the estimation of outcomes and accrual patterns, sample size calculations and implementation plans. Information about the most commonly used supportive care measures can be used to adapt protocols to standard practices and thus, increase their acceptability in the transplant community. Comparison of clinical trials outcomes with observational outcomes can give an insight about generalizability and patient selection practices. Source of stem cells is highly influenced by chance for each patient and on many occasions, it will not be possible to apply prospective randomization to answer some of the important clinical questions. Therefore, well-designed retrospective observational studies, using a registry database, can provide important information that is highly applicable to clinical practice in HSCT[21–23] and significantly helpful in clinical trials planning.[24]

Funding and sustainability

Depending on its objectives, an outcome registry may take several years to develop sufficient numbers of subjects to provide meaningful information. Particular strengths of registries, as elaborated above, are to track and report evolving trends in practice, and collect sufficient numbers of patients to identify and report rare events, such as late effects of interventions. Registry operations to collect complete, high-quality data are resource intense. For these and other reasons, outcome registries are generally intended to operate for long periods of time. To be sustainable over this time horizon, particular attention must be given to long-term funding solutions. Consideration of the intended uses of the registry and those who can derive value from registry information should provide guidance to potential funding sources. These may include government agencies, scientific granting organizations, research collaborators, pharmaceutical manufacturers, accreditation bodies, philanthropic organizations and others. Government regulatory agencies, that may have particular interest in a registry to provide information regarding utilization and outcomes of services it supports, may represent a source of funding. In the context of the contract for the US Stem Cell Therapeutic Outcomes Database, the Center for International Blood and Marrow Transplantation derives substantial funding from the Department of Health and Human Services to support its outcome registry operations. Data collected for this effort are also used to indirectly support reporting of cord blood information to the Food and Drug Administration. As an outcome registry develops robust information, it can be a rich source of data for research, and grant funding to support research represents an excellent opportunity. Such funding may come through resource grants to support overall registry function, or through funding for individual research project grant support. Pharmaceutical or device manufacturers may have an interest in registry data to better understand utilization of their products, and short-term projects or long-term reporting may represent a source of compensation for the registry. Outcome registries must remain vigilant for new innovation or collaborative opportunities to use or expand the registry to seize new funding opportunities.

Registries at the beginning of their life cycle will need a plan for growth and development that matches registry size and comprehensiveness with the available resources. Early data collection may be relatively simple and focus on complete collection of the most essential data elements necessary for regulatory, government and accreditation, and quality improvement purposes. This foundation can be used to demonstrate early success on which to build confidence and develop additional funding initiatives, including research.

CONCLUSION

There is a growing acknowledgment of a clear need to have a HSCT database on institutional, national, continental and global levels. The standardization of data quality is essential to ascertain scientific credibility and function of international HSCT registries. It will also enhance registries collaboration and function worldwide. It can then serve as a global data and research tool as well as an instrument for health technology assessment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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