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Prophylactic and therapeutic treatment of graft-versus-host disease in Japan

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Abstract Allogeneic hematopoietic stem cell transplantation in Japan is very different from that in Western countries in terms of the homogeneous genetic background, the preference for bone marrow to peripheral blood stem cells, use of a single unit in cord blood transplantation, and frequent use of non-myeloablative preconditioning due to a large number of elderly patients. Therefore, conclusions obtained from well-designed prospective and/or comparative studies of treatment of graft-versus-host disease (GVHD) performed in the United States or Europe may not fit Japanese transplant patients. This article reviews the studies of prophylactic and therapeutic treatment of acute and chronic GVHD that have been conducted in Japan. A randomized study demonstrated a lower incidence of acute GVHD in tacrolimus-based prophylaxis than in cyclosporine A-based prophylaxis. Retrospective and non-randomized prospective studies suggest that cyclosporine A-based and tacrolimus-based GVHD prophylaxis regimens are well researched and nearly optimized for Japanese patients, including infusion methods and target blood concentration. However, most other studies were performed in a single institute including a small number of patients, resulting in biased conclusions. There is no conclusive report on steroid-refractory acute and chronic GVHD. This review provides a baseline for starting prospective studies to create new evidence for GVHD treatment from Japan.

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Introduction

Despite prophylaxis with immunosuppressive agents, many patients suffer from graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). There has been considerable research on prophylactic and therapeutic treatment of GVHD, but optimization has not been accomplished. In particular, HSCT is very different in Japan than in Western countries, in that, in Japan: most transplant physicians prefer bone marrow transplantation (BMT) to peripheral blood stem cell transplantation (PBSCT), especially in unrelated donor transplantation; cord blood transplantation (CBT) with a single cord unit is performed with the greatest number in the world; non-myeloablative preconditioning is frequently used because of a large number of elderly patients; and the genetic background is homogeneous. In fact, large-scale international studies have demonstrated a significantly lower incidence and severity of acute GVHD after BMT or PBSCT in Japanese patient–donor pairs than in Caucasian pairs [1, 2]. Non-comparable large studies suggested a lower incidence of chronic GVHD in the Japanese population than in the Caucasian population [3–5], although this is controversial [1]. Therefore, conclusions obtained from well-designed prospective and/or comparative studies performed in the United States or Europe may not apply to Japanese HSCT patients.

Contrary to my expectations, the search of the PubMed database using the terms “GVHD”, “prophylaxis” or “treatment”, and “Japan”, excluding “review”, identified more than 30 reports a year in recent years. This article reviews the studies on the prophylaxis and treatment of acute and

chronic GVHD that have been conducted in Japan. Articles regarding the pathogenesis of GVHD, the effects of human leukocyte antigen (HLA) and non-HLA gene polymorphisms on GVHD, and the prediction of GVHD by biomarkers are excluded, because excellent review articles have been published in this journal [6–9]. Valuable research outcomes have been reported from Japan as well as other countries.

GVHD prophylaxis regimens for BMT and PBSCT

Cyclosporine A (CsA)-based regimens

The standard regimen for GVHD prophylaxis in BMT from HLA-matched sibling donors is a combination of CsA and short-term methotrexate (sMTX), which was established in 1986 [10, 11].

Studies on CsA-based regimens reported from Japan are summarized in Table 1. Morishima et al. [12] reported a lower incidence of acute GVHD with CsA and sMTX than with CsA alone or MTX alone in Japanese leukemia patients after BMT from HLA-matched sibling donors in 1989. They subsequently confirmed the efficacy of a combination of CsA and sMTX in unrelated donor BMT [13]. Kanda et al. [14] analyzed the data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and reported a cumulative incidence of grade II–IV acute GVHD of 24 % in 1843 patients after HLA-matched sibling donor BMT with CsA and sMTX. A retrospective study of patients after HLA-matched sibling BMT suggested no benefit of the combination of CsA and methylprednisolone (mPSL) instead of CsA and sMTX [15].

Ogawa et al. [16] retrospectively compared the incidences of acute GVHD in adult patients between continuous infusion (CI) and twice-daily infusion (TDI) of CsA. The incidence of grade II–IV acute GVHD was significantly higher in the CI group than in the TDI group, and multivariate analysis identified CI as a risk factor for grade II–IV acute GVHD. Another retrospective comparative study in pediatric patients conducted by Umeda et al. [17] showed a significantly higher incidence of severe hypertension in the CI group than in the TDI group, with no difference in the incidences of acute GVHD between the two groups.

Based on the observation that the blood concentration of continuously infused CsA during the third week after transplantation affected the incidence of grade II–IV acute GVHD [18], Kanda and his colleagues [19, 20] evaluated the safety and efficacy of CI of CsA with a high target blood concentration (450–550 ng/mL). They concluded that CI of CsA at 450–550 ng/mL was feasible and effective prophylaxis for acute GVHD.

In contrast, to test the hypothesis that a reduction in the CsA dosage would reduce the risk of relapse and toxicity of immunosuppressive agents, Kohno et al. [21] conducted a prospective phase 2 study to evaluate low-dose (1.5 mg/kg/day) continuous CsA with sMTX for GVHD prophylaxis in HLA-matched sibling donor BMT. Grade II–III acute GVHD was marginally more common ($P = 0.065$) in the low-dose CsA group than in the historical control CsA group (3.0 mg/kg/day), but this did not increase mortality.

In TDI of CsA, the blood concentration of CsA at 3 or 5 h after the start of infusion, as well as trough concentration, was suggested to be a good marker for the development of grade II–IV acute GVHD [22, 23]. The feasibility of once-daily 4-h infusion of CsA was retrospectively studied in HLA-matched unrelated donor BMT [24]. Administration of cyclophosphamide as pretransplant conditioning may affect the blood concentration of CsA for 2 weeks after transplantation [25].

Tacrolimus (Tac)-based regimens

Two phase 3, randomized, multicenter studies from the United States demonstrated a reduced incidence of acute GVHD among patients receiving Tac and sMTX relative to patients receiving CsA and sMTX, although survival was not different [26, 27]. Currently, a combination of Tac and sMTX is frequently used, particularly in transplantation from unrelated donor BMT and PBSCT.

Studies for Tac-based regimens performed in Japan are summarized in Table 1. Hiraoka et al. [28] conducted a phase 3 study comparing Tac with CsA as GVHD prophylaxis in BMT from related and unrelated donors. The cumulative incidence of grade II–IV acute GVHD was significantly lower in the Tac-based regimen than in the CsA-based regimen, but there was no difference in survival rates between the two groups, presumably due to the lack of a graft-versus-leukemia effect. The incidence of chronic GVHD was similar in the two groups.

Nishida et al. [29] conducted a phase 2 study to evaluate Tac and sMTX for GVHD prophylaxis in patients receiving BMT from an HLA-A, B, or DRB1 genotypically mismatched unrelated donor. The results suggested the efficacy of the Tac and sMTX regimen in HLA genotypically mismatched unrelated donor BMT.

Yanada et al. [30] performed a large-scale retrospective study to compare Tac-based and CsA-based regimens. The use of Tac significantly reduced the risk of grade II–IV and III–IV acute GVHD in unrelated donor BMT, but not in HLA-matched sibling BMT or PBSCT. On the other hand, Tac significantly reduced the risk of chronic GVHD in sibling donor BMT/PBSCT, but not in unrelated donor BMT.

Table 1 Summary of studies on GVHD prophylaxis regimens mainly for BMT and PBSCT in Japan

References	Regimen	No. of patients	Design	Donor	Stem cell source	Grade II–IV acute GVHD		Grade III–IV acute GVHD		Chronic GVHD	
						Incidence (%)	HR or RR	Incidence (%)	HR or RR	Incidence (%)	HR or RR
CsA-based											
Morishima [12]	Twice-daily CsA + sMTX	39	Retro	MSD	BM	5	1	0		43	
	Twice-daily CsA	37				27	5.6	0		45	
	MTX	44				30	6.18	16		50	
Gondo [15]	CsA + sMTX	14	Retro	MSD	BM	0		0		61	
	CsA + mPSL	11				45		36		39	
Morishima [13]	CsA + sMTX	51[a]	Retro	MUD, mmUD	BM	32		17		72	
Kanda [14]	CsA + sMTX	1843	Retro	MSD	BM	24		7		47	
Ogawa [16]	Continuous CsA + sMTX	71	Retro	MRD, MUD, mmRD, mmUD	BM, PB	56	2.59 (1.46–4.60)				
	Twice-daily CsA + sMTX	58				27	1				
Kohno [21]	Continuous CsA (1.5)[b] + sMTX	21	Phase 2	MSD	BM	48				51	
	Continuous CsA (3.0)[b] + sMTX	22	Retro			23				54	
Kanda [18]	Continuous CsA + sMTX	171	Retro	MSD	BM, PB	30		10			
Nawa [24]	Once-daily CsA + sMTX	19	Retro	MUD	BM	37		0			
Izumi [22]	Twice-daily CsA + sMTX	73	Retro	MRD, MUD, mmRD, mmUD	BM	25					
Oshima [19]	Continuous CsA (500)[c] + sMTX	33	Pro	MRD, MUD, mmRD, mmUD	BM, PB	27	0.43 (0.19–0.96)	3		47	
	Continuous CsA (300)[c] + sMTX	33	Retro			52	1	18		73	
Machishima [20]	Continuous CsA (500)[c] + sMTX	69	Retro	MRD, MUD, mmRD, mmUD	BM, PB	35	0.81 (0.41–1.59)	10	0.28 (0.09–0.83)		
	Continuous CsA (300)[c] + sMTX	29				41	1	24	1		
Umeda [17]	Continuous CsA ± Other	34	Retro	MRD, MUD, mmRD, mmUD	BM, PB, CB	27		3		32	
	Twice-daily CsA ± Other	36				26		0		17	

Table 1 continued

References	Regimen	No. of patients	Design	Donor	Stem cell source	Grade II–IV acute GVHD		Grade III–IV acute GVHD		Chronic GVHD	
						Incidence (%)	HR or RR	Incidence (%)	HR or RR	Incidence (%)	HR or RR
Tac-based											
Hiraoka [28]	Tac ± other	66	Phase 3	MSD, MUD, mmRD	BM	18		10		47	
	CsA ± other	65				48		21		48	
Ogawa [35]	Tac + sMTX + mPSL	20	Pilot	MUD, mmUD	BM	0		0		67[f]	
Yanada [30]	Tac ± other	51	Retro	MSD	BM, PB	33	Not significant		Not significant	12	1
	CsA ± other	1884				38				33	3.69 (1.18–11.53)
	Tac ± other	191	Retro	MUD, mmUD	BM	36	1		1	38	Not significant
	CsA ± other	586				58	2.20 (1.60–3.04)		2.10 (1.32–3.34)	35	
Nishida [29]	Tac + sMTX	55	Phase 2	mmUD	BM			24		72	
Yagasaki [36]	Tac ± other	47	Retro	MUD, mmUD	BM	29				13	
	CsA ± other	47				33				36	
Watanabe [32]	Tac (>7)[d] ± other	51	Retro	MRD, MUD, mmRD, mmUD	BM, PB, CB	34	1	17			
	Tac (≤7)[d] ± other	46				66	3.47 (1.13–4.15)	49			
Mori [33]	Tac + sMTX	60	Retro	MUD	BM	52		18			
Nasu [37]	Tac ± sMTX	35	Retro	MRD, MUD, mmRD, mmUD	BM, PB, CB	34		14		28[f]	
	CsA ± sMTX	76				33		14		24[f]	
MTX alone											
Koga [43]	MTX	30	Retro	MSD	BM	30				19	
Watanabe [44]	MTX	94	Retro	MSD	BM	20		11		32	
MMF											
Mizumoto [49]	Tac + sMTX + MMF	21	Retro	MUD, mmUD	BM	33		5		55	
Nishikawa [50]	CsA or Tac + MMF (d30)[e]	25	Retro	MRD, MUD, mmRD, mmUD	BM, PB, CB	42					
	CsA or Tac + MMF (d50–94)[e]	16				13					
Iida [52]	MMF ± other	157	Retro	MRD, mmRD	BM, PB	30		20		45	

Table 1 continued

References	Regimen	No. of patients	Design	Donor	Stem cell source	Grade II–IV acute GVHD		Grade III–IV acute GVHD		Chronic GVHD	
						Incidence (%)	HR or RR	Incidence (%)	HR or RR	Incidence (%)	HR or RR
Wakahashi [51]	Tac + MMF	36	Retro	MUD, mmUD	BM, CB	29				13	
Iida [53]	MMF ± other	440	Retro	MUD, mmUD	BM, PB, CB	38		14		28	
In vivo purge											
Azuma [59]	ATG-containing conditioning + CsA + sMTX	10	Retro	MSD	BM	0		0		10	
Kojima [60]	ATG-containing conditioning + CsA or Tac + sMTX	15	Retro	MUD, mmUD	BM	33		13		13	
Kojima [61]	ATG-containing conditioning	82	Retro	MUD, mmUD	BM	29		20	1	30	
	Non-ATG-containing conditioning	72							4.21 (1.36–13.1)		
Nakai [64]	ATG-containing RIC + CsA	20	Retro	MRD	PB	10	0.16			30	
	Non-ATG-containing RIC + CsA	19				63	1			63	
	Non-ATG-containing MAC + CsA + sMTX	33				33				64	
Teshima [65]	ATG-containing RIC	49	Retro	MRD, mmRD	BM, PB		0.55 (0.29–1.02)				0.42 (0.20–0.85)
	Non-ATG-containing RIC	292					1				1
Tanosaki [66]	ATG-containing RIC	15	Phase 1	MSD	PB	60		33		46	
	Non-ATG-containing RIC	14	Phase 1	MSD	PB	57		21		83	
Hatanaka [68]	ATG-containing conditioning	86	Retro	MUD, mmUD	BM	20		8		19	
Fuji [67]	ATG-containing RIC	33	Retro	MUD, mmUD	BM	15	0.17 (0.06–0.44)	0		33	0.45 (0.23–0.88)
	Non-ATG-containing RIC with TBI 2 Gy	40				61	1	8		57	1
	Non-ATG-containing RIC with TBI 4 Gy	30				50		30		50	
Kanda [63]	Alemtuzumab-containing RIC + CsA + sMTX	15	Pro	MRD, MUD, mmRD, mmUD	PB	0		0		13	

Table 1 continued

References	Regimen	No. of patients	Design	Donor	Stem cell source	Grade II–IV acute GVHD		Grade III–IV acute GVHD		Chronic GVHD	
						Incidence (%)	HR or RR	Incidence (%)	HR or RR	Incidence (%)	HR or RR
Ex vivo purge											
Sao [69]	$CD6^+$ cells negative selection	10	Phase 1/2	mmRD, mmUD	BM	11		0		14	

Blank represents no data

GVHD graft-versus-host disease, *HR* hazard ratio, *RR* relative risk, *CsA* cyclosporine A, *Tac* tacrolimus, *sMTX* short-term methotrexate, *MTX* methotrexate, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone, *ATG* antithymocyte globulin, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning, *Retro* retrospective study, *Pro* prospective study, *MSD* HLA-matched sibling donor, *MUD* HLA-matched unrelated donor, *mmUD* HLA-mismatched unrelated donor, *MRD* HLA-matched related donor, *mmRD* HLA-mismatched related donor, *BM* bone marrow, *PB* peripheral blood stem cells, *CB* cord blood

[a] One patient received Tac + sMTX

[b] CsA was given at an initial dosage of 1.5 mg/kg (1.5 group) or 3.0 mg/kg (3.0 group) per day

[c] The dose of CsA was adjusted to maintain the blood CsA concentration at 450–550 ng/mL (500 group) or 150–300 ng/mL (300 group) during the first 3 weeks after transplantation

[d] The dose of Tac was adjusted to maintain the blood Tac concentration at >7 ng/mL (>7 group) or ≤7 ng/mL (≤7 group) during the first 2 weeks after transplantation

[e] MMF was stopped at day 30 (d30 group) or day 50–94 (median day 65) (d50–94 group)

[f] Incidence of extensive chronic GVHD

Finally, Tac instead of CsA was beneficial for the survival of patients receiving unrelated donor BMT, but not sibling donor BMT/PBSCT.

In a retrospective study of a large number of adult patients, Tac-based prophylaxis was identified as a favorable factor for acute GVHD and, interestingly, total body irradiation in pretransplant conditioning was identified as a risk factor [31].

A retrospective study of pediatric patients suggested that blood concentrations of continuously infused Tac of >7 ng/mL were significantly associated with a lower incidence of acute GVHD and a higher survival rate compared with Tac of ≤7 ng/mL [32]. Another group reported that the mean blood concentration of Tac during the third week after transplantation was significantly associated with the grades of acute GVHD [33]. The conversion from intravenous to oral Tac should be performed under close medical supervision [34]. The addition of mPSL to Tac and sMTX strongly suppressed acute GVHD in unrelated donor BMT but not chronic GVHD [35]. It has been suggested that calcineurin inhibitors are involved in the development of intestinal thrombotic microangiopathy, a life-threatening complication after allogeneic transplantation, in humans and rats [38–40]. The blood concentration of Tac was not necessarily high in patients who developed Tac-related encephalopathy [41]. Genetic polymorphisms of *cytochrome P450* may affect the serum concentration of calcineurin inhibitors in transplant patients [42].

MTX alone

Two retrospective studies suggested the feasibility of MTX alone as GVHD prophylaxis in pediatric patients who received BMT from HLA-matched sibling donors [43, 44] (Table 1). The efficacy of folic acid in preventing the toxicity of MTX is controversial [45, 46].

Mycophenolate mofetil (MMF)

Two prospective randomized studies from the United States concluded that MMF provided no advantage over MTX when used with CsA or Tac in terms of the reduction of acute or chronic GVHD and the increase in the survival rate [47, 48]. However, the use of MMF instead of MTX has the advantage of lower incidence and severity of oropharyngeal mucositis.

No prospective study of MMF has been done in Japan (Table 1). Three retrospective studies [49–51] suggested the safety and efficacy of MMF together with Tac or CsA as GVHD prophylaxis. Wakahashi et al. [51] reported that the blood concentration of MMF at 2 h after the start of infusion could be a surrogate marker of the area under the curve and helpful for predicting acute GVHD development.

Nationwide studies conducted by Iida et al. [52, 53] found 157 patients after related donor transplantation and 440 patients after unrelated donor transplantation who had received MMF as GVHD prophylaxis, suggesting that MMF is now widely used in Japan.

In vivo purge

The benefit of anti-thymocyte globulin (ATG) for the prevention of acute and chronic GVHD has been proven in randomized studies [54–57]. A meta-analysis of six randomized, controlled trials demonstrated that the incidences of grade II–IV and grade III–IV acute GVHD and extensive chronic GVHD were significantly lower in patients who received ATG [58]. However, this effect did not lead to a significant improvement of non-relapse mortality and overall survival. They concluded that careful consideration of the use of ATG based on the patient's condition and the risk factors of the transplantation setting was required.

ATG-containing conditioning is often used in BMT or PBSCT for severe aplastic anemia (SAA) in Japan. Azuma et al. [59] retrospectively studied 10 pediatric patients with SAA after HLA-matched sibling BMT using preconditioning with Lymphoglobulin (Pasteur-Merieux, Lyon, France) 15 mg/kg for 4 days, followed by CsA and sMTX (Table 1). All patients achieved engraftment without acute GVHD. Only one patient developed limited chronic GVHD. Kojima et al. [60] retrospectively studied 15 pediatric patients with SAA after unrelated donor BMT using preconditioning with Thymoglobulin (Pasteur-Merieux) 2.5 mg/kg for 4 days, followed by CsA and sMTX. Subsequently, Kojima et al. [61] analyzed the results of 154 patients with SAA after unrelated donor BMT. Non-ATG-containing conditioning was a risk factor for a higher incidence of grade III–IV acute GVHD and lower overall survival. Terasako et al. [62] retrospectively compared the effects of Thymoglobulin and ATG-Fresenius (Fresenius Biotech, Munich, Germany) on immune recovery and cytomegalovirus infection in posttransplant patients with SAA and suggested that Thymoglobulin had a stronger immunosuppressive activity than ATG-Fresenius with a dose ratio of 1:2.5. Kanda et al. [63] evaluated the efficacy of in vivo T cell purge with alemtuzumab as in vivo T cell depletion in a prospective study of 15 patients with SAA.

For malignant diseases, one prospective and three retrospective comparative studies [64–67] demonstrated a significantly or marginally lower incidence of acute and/or chronic GVHD in an ATG-containing regimen than in a non-ATG-containing regimen. However, all studies failed to show the advantage of the use of ATG with regard to overall survival. Interestingly, ATG was combined with reduced intensity conditioning (RIC) in all studies in Japan [64–67]. Hatanaka et al. [68] conducted a national survey and found that, in most cases (92 %), ATG was combined with RIC.

Ex vivo purge

Sao et al. [69] performed a prospective study to assess the safety and efficacy of partial T cell depletion using anti-CD6 monoclonal antibody-conjugated magnetic beads in 10 leukemia patients who received BMT from HLA-mismatched related or unrelated donors. Studies for transplantation of purified CD34-positive cells are summarized in the "GVHD prophylaxis regimens for HLA-haploidentical donor transplantation" section.

GVHD prophylaxis regimens for CBT

Most institutions in the United States and Europe use the combination of CsA or Tac with MMF or steroid as GVHD prophylaxis for CBT [70–74]. Their strategy is characterized by the addition of ATG to pretransplant conditioning, but no comparative study has evaluated the merit of ATG administration prior to CBT. A recent comparison of GVHD after CBT in pediatric patients revealed no differences in the risks of acute GVHD between Japanese and Caucasian populations [5].

GVHD prophylaxis regimens used for CBT in Japan are summarized in Table 2. Takahashi and his colleagues [75–80] at the Institute of Medical Science, the University of Tokyo, reported promising results of CBT for adult patients with hematological malignancies using a combination of once-daily CsA and sMTX as GVHD prophylaxis. Incidences of grade II–IV acute GVHD, grade III–IV acute GVHD, and extensive chronic GVHD were 50–65, 6–41, and 18–34 %, respectively.

Miyakoshi et al. [81] at Toranomon Hospital reported the feasibility of CBT with RIC using CsA alone as GVHD prophylaxis for adult patients. They subsequently reported the merit of the use of Tac instead of CsA to suppress post-CBT immune reactions, including pre-engraftment immune reaction and acute GVHD [82, 83]. After demonstrating the feasibility of RIC CBT with CsA or Tac alone for patients aged 55 years and higher [84], Uchida et al. [85] added MMF to Tac as GVHD prophylaxis in RIC CBT for elderly patients. They reported a significantly higher engraftment rate (90 vs. 69 %) and a lower incidence of pre-engraftment immune reaction (16 vs. 52 %) in the Tac and MMF group, but the incidences of acute and chronic GVHD were comparable between the two groups. A certain plasma level of MMF may be necessary to effectively prevent acute GVHD after CBT [86].

Mori et al. [87] and Yamada et al. [88] retrospectively analyzed the feasibility of CBT with a combination of Tac and sMTX for adult patients. Narimatsu et al. [89]

Table 2 Summary of GVHD prophylaxis regimens for CBT in Japan

References	Regimen	No. of patients	Design	Grade II–IV acute GVHD		Grade III–IV acute GVHD		Chronic GVHD	
				Incidence (%)	HR or RR	Incidence (%)	HR or RR	Incidence (%)	HR or RR
Takahashi [75]	Once-daily CsA + sMTX	68[a]	Retro	50		6		78	
Ooi [76]	Once-daily CsA + sMTX	18[b]	Retro	65		6		83	
Miyakoshi [81]	Continuous CsA	30	Retro	27		23		23	
Kishi [82]	Continuous CsA	57	Retro	66		45			
Takahashi [77]	Once-daily CsA + sMTX	100	Retro	52		7		74	
Miyakoshi [83]	Tac	34	Retro	45				27	
Mori [87]	Tac + sMTX	18	Retro	44		0		54	
Narimatsu [89]	Tac or CsA + sMTX	40	Retro	17	0.55 (0.31–0.98)[d]				
	Tac or CsA	37[c]		28	1[d]				
Uchida [84]	Tac	33	Retro	61		43		40	
	Continuous CsA	37							
Ooi [78]	Once-daily CsA + sMTX	77	Retro	82		25		84	
Yamada [88]	Tac + sMTX	25	Retro	40		5		68	
Uchida [85]	Tac + MMF	29	Retro	67		41		15	
	Tac	29		50		40		36	
Sato [80]	Once-daily CsA + sMTX	33	Retro	67		41		76	
Kato [90]	Tac or CsA + sMTX	149	Retro	40	1	14	1	16	1
	Tac or CsA	41		54	1.74 (1.06–2.83)	37	3.02 (1.55–5.91)	23	1.78 (0.83–3.82)
	Tac or CsA + prednisolone	47		64	1.61 (1.03–2.50)	28	1.89 (0.93–3.83)	29	2.44 (1.24–4.82)

Blank represents no data

GVHD graft-versus-host disease, *HR* hazard ratio, *RR* relative risk, *CsA* cyclosporine A, *sMTX* short-term methotrexate, *Tac* tacrolimus, *MMF* mycophenolate mofetil, *Retro* retrospective study, *Pro* prospective study

[a] Three patients received once-daily CsA only

[b] Two patients received once-daily CsA only

[c] Two patients received Tac + methylprednisolone

[d] Hazard ratios for posttransplant immune reactions including pre-engraftment immune reactions, engraftment syndrome, and grade II–IV acute GVHD

retrospectively studied the effect of the addition of sMTX to a calcineurin inhibitor on the outcome of post-CBT patients. sMTX significantly decreased the incidence of post-CBT immune reactions, including pre-engraftment immune reaction, engraftment syndrome, and grade II–IV acute GVHD. The overall survival rate was significantly higher in patients with sMTX than in those without sMTX. Kato et al. [90] analyzed the clinical outcomes of CBT for 270 pediatric patients with acute lymphoblastic leukemia in Japan. Multivariate analysis revealed that the addition of MTX to calcineurin inhibitor was associated with decreased incidences of grade II–IV and grade III–IV acute GVHD and chronic GVHD, compared with calcineurin inhibitor alone or calcineurin inhibitor and prednisolone (PSL).

According to a recent retrospective study by Kanda et al. [91], the GVHD prophylaxis regimens used for CBT in Japan from 2006 to 2009 were CsA and MTX (37 %), Tac and MTX (25 %), Tac alone (14 %), CsA alone (8 %), Tac and MMF (5 %), CsA and MMF (3 %), CsA and PSL (3 %), and others, and 99 % of the patients received neither ATG nor alemtuzumab.

GVHD prophylaxis regimens for HLA-haploidentical donor transplantation

Infusion of large numbers of highly purified CD34 positive cells (median, 13.8 × 10^6/kg) after ATG-containing

preconditioning provided a high engraftment rate and a low incidence of acute and chronic GVHD in patients who received HLA-haploidentical donor transplantation without posttransplant GVHD prophylaxis [92]. The Peking group reported the feasibility of transplantation using granulocyte colony-stimulating factor-mobilized bone marrow and peripheral blood stem cells from the same haploidentical donor with myeloablative conditioning consisting of cytosine arabinoside, busulfan, cyclophosphamide, semustine, and ATG, followed by GVHD prophylaxis consisting of CsA, sMTX, and MMF [93]. The Johns Hopkins group developed unmanipulated haploidentical bone marrow transplantation with high-dose posttransplantation cyclophosphamide as sole GVHD prophylaxis [94].

Table 3 shows a summary of pretransplant conditioning and GVHD prophylaxis regimens used for HLA-haploidentical donor transplantation in Japan. Infusion of purified CD34-positive cells from bone marrow [95] or peripheral blood mononuclear cells [96, 97] after ATG-containing preconditioning has been studied in Japan as well, with a low incidence of acute GVHD.

Based on the hypothesis that feto-maternal immunological tolerance exists between the mother and fetus, studies of HLA-haploidentical transplantation from the mother, siblings or offspring that were mismatched for noninherited maternal antigens (NIMA) were performed in a small number of cases [98–100]. Ichinohe et al. [101] analyzed the data of the JSHCT and demonstrated that incidences of grade II–IV acute GVHD and extensive chronic GVHD were 56 and 57 %, respectively, in patients who received HLA-haploidentical transplantation from NIMA-mismatched family members.

Ogawa and his colleagues do not restrict donors to NIMA-mismatched family members. Nonetheless, they demonstrated high engraftment rates and low incidences of acute GVHD after HLA-haploidentical donor transplantation with the RIC regimen including ATG and GVHD prophylaxis consisting of Tac and mPSL [102] or with the MAC regimen not including ATG and GVHD prophylaxis consisting of Tac, MTX, mPSL, and MMF [103]. Ikegame et al. [104] reported the feasibility of HLA-haploidentical transplantation using non-ATG-containing preconditioning followed by standard GVHD prophylaxis consisting of CsA and sMTX or MMF for HLA-homozygous patients from heterozygous donors. They analyzed the kinetics of serum soluble interleukin-2 receptor levels in 77 patients who had received HLA-haploidentical donor transplantation and demonstrated that a high soluble interleukin-2 receptor level (>810 U/mL) on day 7 was significantly associated with a higher incidence of grade II–III acute GVHD [105].

A combination of ATG-containing preconditioning and Tac-containing GVHD prophylaxis is used in other institutions [107, 108]. Kanda et al. [63, 109] prospectively evaluated the safety and efficacy of alemtuzumab in PBSCT from HLA-haploidentical donor with continuous CsA and sMTX. Sawada et al. [110] reported the feasibility of HLA-haploidentical BMT and PBSCT with posttransplantation cyclophosphamide for pediatric patients.

Summary of GVHD prophylaxis regimens in Japan

Taken together, a randomized study demonstrated a lower incidence of acute GVHD with a Tac-based regimen than with a CsA-based regimen. Retrospective and non-randomized prospective studies suggest that CsA-based and Tac-based GVHD prophylaxis regimens are well researched and nearly optimized for Japanese patients, including infusion methods and target blood concentration. MMF, which is not currently covered by health insurance in Japan, is used only in a small proportion of transplant institutions, and its benefit has not been proven by a comparative study. ATG is used in transplantation for SAA and HLA-haploidentical transplantation, as well as in transplantation for malignant diseases with RIC. It is noted that a large retrospective study from the Center for International Blood and Marrow Transplant Research confirmed that ATG recipients after RIC had an increased risk of malignancy relapse, more non-relapse mortality, and lower overall survival [111]. For CBT, it is not known whether Tac is better than CsA, whether MMF is better than MTX, and whether ATG is unnecessary. Japan has an obligation to optimize GVHD prophylaxis regimen in single-unit CBT. GVHD prophylaxis in HLA-haploidentical donor transplantation should be discussed in combination with optimization of the preconditioning regimen.

Initial therapy of acute GVHD

A standard initial therapy for grade II or higher acute GVHD is systemic administration of mPSL at 2 mg/kg/day or PSL at 2–2.5 mg/kg/day [112]. A randomized study comparing mPSL at 10 mg/kg/day for 5 days with subsequent tapering and mPSL at 2 mg/kg/day demonstrated no advantage of an initial dose higher than 2 mg/kg/day (2.5 mg/kg/day PSL-equivalent steroid dose) [113]. A retrospective study comparing a PSL-equivalent steroid dose of 1 and 2 mg/kg/day demonstrated no disadvantage of low-dose PSL at 1 mg/kg/day for patients with mild grade II acute GVHD [114]. Comparative studies evaluating a combination of PSL and other immunosuppressants, including antibodies against interleukin-2, ATG, etanercept, and infliximab [115–120], did not demonstrate an advantage of the addition of these immunosuppressants to PSL. Oral beclomethasone dipropionate (BDP) allowed PSL to

Table 3 Summary of pretransplant conditioning and GVHD prophylaxis regimens for HLA-haploidentical donor transplantation in Japan

References	Pretransplant conditioning/GVHD prophylaxis regimen	No. of patients	Design	Donor	Stem cell source	Incidence of grade II–IV acute GVHD (%)	Incidence of grade III–IV acute GVHD (%)	Incidence of chronic GVHD (%)
Yabe [95]	MAC + ATG/CD34$^+$ cells positive selection + twice-daily CsA + PSL	3	Retro	Parent	BM	0	0	47
Kawano [96]	MAC ± ATG/CD34$^+$ cells positive selection + Tac or CsA ± other	13[a]	Phase 1	Parent, sibling	PB	22	11	0
Matsuda [97]	MAC + ATG/CD34$^+$ cells positive selection + no immunosuppressant	5	Retro	Parent, sibling	PB	0	0	40
Shimazaki [98]	MAC/Tac + sMTX	5	Pilot	Mother, NIMA-mm sibling, NIMA-mm offspring	PB	60	20	50
Obama [99]	RIC/Tac + sMTX	4	Retro	NIMA-mm sibling, NIMA-mm offspring	PB	75	25	
Yabe [100]	MAC + ATG/Tac + sMTX ± other	6[b]	Retro	Mother	BM	17	0	83
Ichinohe [101]	MAC or RIC ± ATG/Tac ± other	35	Retro	Mother, NIMA-mm sibling, NIMA-mm offspring	BM, PB	56	24	83
Kanda [109]	MAC or RIC ± alemtuzumab/continuous CsA + sMTX	12	Pro	Sibling, child, uncle, cousin	PB	18	9	25
Ogawa [102]	RIC + ATG/Tac + mPSL	26	Retro	Sibling, child	PB	20	0	45
Yoshihara [106]	MAC or RIC ± ATG/Tac or CsA ± other	72[c]	Retro	Parent, sibling	BM, PB	55	33	73
	MAC or RIC ± ATG/Tac + sMTX ± other	11[c]		Mother, sibling	BM, PB	11	0	63
Ogawa [103]	MAC/Tac + sMTX + mPSL + MMF	30	Retro	Mother, sibling, child, cousin	BM, PB	37	10	
Kurokawa [107]	RIC + ATG/Tac	39	Retro	Parent, sibling, child	BM, PB	38	8	33
	RIC + ATG/Tac + mPSL	27						
Mochizuki [108]	MAC or RIC + ATG/Tac + sMTX + PSL	21	Retro	Parent, sibling	BM, PB	47	5	51
Ikegame [104]	MAC or RIC/CsA + sMTX or MMF	9[d]	Retro	Sibling, daughter	BM, PB	43	0	43
Kanda [63]	MAC or RIC ± alemtuzumab/continuous CsA + sMTX	14	Pro	Related	PB	14	0	14

Blank represents no data

GVHD graft-versus-host disease, MAC myeloablative preconditioning, ATG antithymocyte globulin, *CsA* cyclosporine A, *PSL* prednisone, *Tac* tacrolimus, *sMTX* short-term methotrexate, RIC reduced intensity preconditioning, mPSL methylprednisolone, *MMF* mycophenolate mofetil, *Retro* retrospective study, *Pro* prospective study, *NIMA-mm* noninherited maternal antigens-mismatched, *BM* bone marrow, *PB* peripheral blood stem cells

[a] One patient received methylprednisolone only, and one patient received no GVHD prophylaxis after transplantation

[b] One patient with severe combined immunodeficiency received no pretransplant conditioning

[c] Seventy-two patients with malignant disease and 11 patients with non-malignant disease were analyzed in this study

[d] One patient received CsA only, and one patient received ATG-containing pretransplant conditioning

be rapidly tapered, with fewer recurrences of gastrointestinal GVHD [121].

There are only a few studies on the initial therapy of acute GVHD from Japan (Table 4). A nationwide study revealed that the response rate of grade II–IV acute GVHD to systemic PSL or mPSL in Japanese patients was approximately 64 % [122], which is comparable to that in Caucasian patients [123, 124]. Patients without improvement from initial therapy with systemic corticosteroid had a 2.5-times higher non-relapse mortality and a 0.6-times lower overall survival rate [122]. A higher probability of improvement was obtained in patients after CBT (vs. HLA-matched related BMT).

Takashima et al. [125] evaluated a treatment strategy for mild gastrointestinal GVHD using oral BDP 1.3 mg every 8 h for patients after CBT or a combination of oral BDP and PSL 1 mg/kg/day for patients after BMT and PBSCT. Mild gastrointestinal GVHD was defined as stage 1 gastrointestinal GVHD with stage 0–2 skin manifestations and no liver involvement. Treatment success was achieved in 100 and 64 % of patients after CBT and BMT/PBSCT, respectively. Common adverse events were CMV antigenemia and enteritis.

Second-line therapy of acute GVHD

There are many prospective and retrospective studies evaluating agents for second-line therapy of acute GVHD, including ATG, alemtuzumab, MMF, infliximab, etanercept, MTX, daclizumab, sirolimus, mesenchymal stem cells (MSC), and extracorporeal photopheresis (ECP). However, a consensus in the United States and Europe concluded that, in terms of response rate and survival rate, previous reports do not support the choice of any specific agent for secondary therapy of acute GVHD [112]. They also commented that there is no evidence that any specific agent should be avoided for secondary therapy of acute GVHD. Their recommendation was selected based on the effects of any previous treatment and taking into account potential toxicity and interactions with other agents, convenience, expense, the familiarity of the physician with the agent, and the prior experience of the physician.

No comparative study of second-line therapy of acute GVHD has been conducted in Japan (Table 4). Kanamaru et al. [126] performed a phase 2 study of Tac for patients with PSL- or other immunosuppressant-resistant acute GVHD. Ohashi et al. [127] reported the results of administration of equine ATG (Lymphoglobulin: Aventis Behring, Tokyo, Japan) for patients with steroid-resistant acute GVHD and suggested that low-dose ATG may obtain more favorable outcomes than standard-dose ATG in terms of infection or Epstein–Barr virus-associated posttransplantation lymphoproliferative disorder. Nishimoto et al. [128] also evaluated low-dose Thymoglobulin (Genzyme, Cambridge, MA, USA) and reported a good response in most patients with reduction of opportunistic infections. The nationwide survey of ATG as second-line therapy for acute GVHD is ongoing. Takami et al. [129] evaluated the outcomes of patients who were treated with MMF at a dosage of 1500 mg/day in a prospective study. Onishi et al. [130] retrospectively analyzed the outcome of patients who received MMF at an initial dose of 500–3000 (median 1500) mg/day. Both studies suggested that MMF may be effective for steroid-refractory acute GVHD, and that the most common adverse event was infection. Iida et al. conducted a nationwide survey to analyze the outcomes of patients who had received MMF as GVHD therapy after related [52] or unrelated [53] donor transplantation. Inagaki et al. [131, 132] suggested the efficacy of low-dose MTX at a dose of 10 mg/m^2 weekly for pediatric patients in two retrospective studies. They concluded that low-dose MTX therapy has a low risk of opportunistic infection, is low toxicity, is easy to administer, and is inexpensive. Muroi et al. [133] reported the results of a phase 1/2 study evaluating the safety and efficacy of unrelated bone marrow-derived MSC in patients with steroid-refractory grade II–III acute GVHD. In an application for approval from the Ministry of Health, Labour and Welfare, the preliminary results of an additional prospective study for MSC have also been presented [134]. Pilot studies have been performed to assess the feasibility of colostrum obtained from random donors [135], betamethasone enemas [136], infliximab [137], and narrow-band ultraviolet B phototherapy [138].

In summary, there is no comparative study on therapy for steroid-refractory acute GVHD in Japan, even a retrospective study. If systemic steroid therapy is ineffective, Japanese patients, as well as Western populations, cannot achieve a satisfactory survival rate [122]. We have to pay attention to acute GVHD, especially in elderly patients, because the hazard ratio for non-relapse mortality in patients 50 years or older is twice as great as that of 20-year-old patients [139].

Initial therapy of chronic GVHD

A standard initial therapy of chronic GVHD is prednisone at 1.0 mg/kg/day, which should be tapered within 2 weeks after the first evidence of improvement in the manifestations of chronic GVHD [140]. Six randomized phase 3 studies have been performed [141–146], and only one indicated benefit. Koc et al. [144] suggested that addition of a calcineurin inhibitor to prednisone could reduce the amount of steroid treatment needed to control chronic GVHD and decrease the incidence of avascular necrosis.

There is no report on the initial systemic therapy of chronic GVHD from Japan (Table 4).

Table 4 Summary of studies on GVHD treatment in Japan

References	Agent	No. of patients	Design	Comment
Initial therapy of acute GVHD				
Murata [122]	PSL or mPSL	3436	Retro	Improved response: MRD-BM 74 %, MRD-PB 65 %, MUD-BM 60 %, CB 73 %, significantly higher response rate in CB
Takashima [125]	Oral BDP alone	4	Phase 2	For CB, complete response 75 %, partial response 25 %, CMV antigenemia 50 %, CMV enteritis 25 %
	PSL + oral BDP	11	Phase 2	For BM and PB, complete response 64 %, partial response 0 %, CMV antigenemia 64 %, CMV enteritis 18 %
Second-line therapy of acute GVHD				
Kanamaru [126]	Tac	13	Phase 2	Marked response[a] 38 %, good response[a] 15 %, renal toxicity 53 %, trough level at 15–25 ng/mL was recommended
Inoue [135]	Colostrum	9	Pilot	Colostrum from random donors at 20 mL daily for 5 consecutive days, improve response 75 %
Wada [136]	Betamethasone enema	8	Pilot	Improved response 75 %, no severe toxicity, one was intolerable
Ohashi [127]	ATG	7	Pilot	For 3 patients, 15 mg/kg for 5 days, improved response 33 %, all died of infection or EBV-PTLD For 4 patients, 7.5–15 mg/kg for 1–2 days, improved response 50 %, none died of infection or EBV-PTLD
Yamane [137]	Infliximab	3	Pilot	5 mg/kg weekly for 3 weeks, partial response 33 %, minor response 33 %
Takami [129]	MMF	6	Pro	Initial dose at 1500 mg/day, complete response 67 %, CMV antigenemia or pneumonia 67 %
Inagaki [131]	MTX	10	Retro	5–10 mg/m^2 weekly, complete response 50 %, partial response 20 %, neutropenia and/or thrombocytopenia 11 %
Onishi [130]	MMF	15	Retro	Initial dose at 1500 mg/day, complete response 80 %, CMV antigenemia 73 %
Iida [52]	MMF	94[b]	Retro	For related donor transplant, most common dosage 1000 mg/day, disappearance or improvement of subjective symptoms 59 %
Muroi [133]	MSC	14	Phase 1/2	2×10^6 cells/kg twice a week for 4 weeks, complete response 57 %, partial response 36 %
Iida [53]	MMF	230[b]	Retro	For unrelated donor transplant, most common dosage 1000 mg/day, disappearance or improvement of subjective symptoms 69 %
Inagaki [132]	MTX	35	Retro	10 mg/m^2 weekly, complete response 37 %, partial response 9 %, fatal infection 9 %
Iyama [138]	NB-UVB	11	Pilot	For steroid-refractory skin acute GVHD without gut or liver involvement, complete response 72 %, partial response 18 %
Nishimoto [128]	ATG	11	Retro	Initial dose at 1 mg/kg, total dose at 3 mg/kg, complete response 9 %, partial response 55 %
Initial therapy of chronic GVHD				
No report				
Second-line therapy of chronic GVHD				
Kanamaru [126]	Tac	26	Phase 2	Marked response[a] 8 %, good response[a] 38 %, renal toxicity 53 %, trough level at 15–25 ng/mL is recommended
Takami [129]	MMF	5	Pro	Initial dose at 1500 mg/day, complete response 40 %, CMV antigenemia or pneumonia 67 %
Okamoto [149]	Rituximab	3	Pilot	375 mg/m^2 weekly for 4 weeks for scleroderma, improved response 100 %, one died of sepsis
Inagaki [131]	MTX	17	Retro	5–10 mg/m^2 weekly, complete response 24 %, partial response 35 %, neutropenia and/or thrombocytopenia 11 %
Teshima [150]	Rituximab	7	Phase 2	375 mg/m^2 weekly for 4 weeks for extensive chronic GVHD, partial response 43 %, B cells were quickly eliminated within 2 weeks

Table 4 continued

References	Agent	No. of patients	Design	Comment
Hidaka [151]	Bezafibrate	8	Retro	400 mg b.i.d. for liver chronic GVHD with a poor response to ursodeoxycholic acid and immunosuppressants, complete normalization of hepatobiliary enzymes in 2 patients
Onishi [130]	MMF	11	Retro	Initial dose at 500–1000 mg/day, complete response 45 %
Iida [52]	MMF	50[b]	Retro	For related donor, most common dosage 1000 mg/day, resolution or improvement of subjective symptoms 52 %
Iida [53]	MMF	84[b]	Retro	For unrelated donor, most common dosage 1000 mg/day, improvement of subjective symptoms 69 %
Therapy of BOS				
Yamane [156]	Lung transplantation	7	Retro	Living-donor lobar lung transplantation for 6 patients with bronchiolitis obliterans and 1 patient with lung fibrosis, 5 were alive with 7–100 months follow-up period (median, 38 months)
Therapy of eye chronic GVHD				
Ogawa [159]	Autologous serum	14	Pro	For severe dry eye, 20 % autologous serum in sterile saline
Ogawa [158]	Tranilast	8	Pro	For mild dry eye, compared with 10 patients receiving topical artificial tears, sodium hyaluronic acid and vitamin A
Yaguchi [160]	Lacrimal punctal cauterization	10	Pro	For dry eye with recurrent punctal plug extrusion, punctal thermal cauterization with a high-temperature disposable cautery device

GVHD graft-versus-host disease, *PSL* prednisone, mPSL methylprednisolone, *BDP* beclomethasone dipropionate, *Tac* tacrolimus, *ATG* antithymocyte globulin, *MMF* mycophenolate mofetil, *MTX* methotrexate, *MSC* mesenchymal stem cell, *NB-UVB* Narrowband ultraviolet B phototherapy, *BOS* Bronchiolitis obliterans syndrome, *Retro* retrospective study, *Pro* prospective study, *MRD* HLA-matched related donor, *MUD* HLA-matched unrelated donor, *BM* bone marrow, *PB* peripheral blood stem cells, *CB* cord blood, *CMV* cytomegalovirus, *EBV-PTLD* Epstein–Barr virus-associated posttransplantation lymphoproliferative disorder

[a] Marked response means improvement of two or more points of grade, and good response means improvement of one point of grade

[b] Some patients received MMF as initial therapy of acute or chronic GVHD

Second-line therapy of chronic GVHD

According to a consensus in the United States and Europe [147], treatment modalities for steroid-refractory chronic GVHD are additional steroids, calcineurin inhibitors, immunomodulating modalities (ECP, mTOR-inhibitors, thalidomide, hydroxychloroquine, vitamin A analogs, clofazimine), and cytostatic agents (MMF, MTX, cyclophosphamide, pentostatin). Other treatment options are rituximab, alemtuzumab, etanercept, tyrosine kinase inhibitors, and low-dose interleukin-2 [147, 148]. Even in the United States and Europe, evidence for second-line therapy of chronic GVHD is limited to prospective studies without randomization or retrospective studies.

Studies of second-line therapy for chronic GVHD are summarized in Table 4. Kanamaru et al. [126] performed a phase 2 study of Tac for 26 patients with PSL- or other immunosuppressant-resistant chronic GVHD. Takami et al. and Onishi et al. evaluated the safety and efficacy of MMF for steroid-refractory chronic GVHD in a prospective [129] and a retrospective [130] study, respectively. Iida et al. reported the results of a nationwide survey to determine the safety and efficacy of MMF in patients with chronic GVHD after related [52] or unrelated [53] donor transplantation. Following a report of three cases in which rituximab was possibly effective [149], Teshima et al. [150] reported the results of a phase 2 study of 375 mg/m^2 rituximab therapy for 7 patients. Rituximab allowed a reduction in the steroid dose in 4 patients. They suggested the effectiveness of rituximab therapy for selected patients with steroid-refractory chronic GVHD that is not advanced. Inagaki et al. [131] demonstrated that administration of MTX at a dose of 3–10 mg/m^2 weekly had allowed steroid treatment to be reduced or discontinued in 15 (88 %) of 17 pediatric patients with steroid-refractory or steroid-dependent chronic GVHD. Hidaka et al. [151] reported the efficacy of bezafibrate for liver chronic GVHD with a poor response to ursodeoxycholic acid. A clinical trial for ECP is ongoing in Japan.

Therapy of bronchiolitis obliterans syndrome (BOS)

Bronchiolitis obliterans syndrome is a rare complication, with a cumulative incidence of 2.8 % at 5 years after allogeneic HSCT in Japanese patients [152]. Effective immunosuppressive therapy has not yet been established and, in practice, some therapies including systemic corticosteroids, azithromycin and inhaled steroids, ECP, leukotriene

inhibitors, etc. are being tried [153]. The prognosis is poor, with overall survival at 5 years after BOS diagnosis at 45 % [152]. Higher risk factors for the development of BOS are female recipient, ABO-mismatched donor, busulfan and cyclophosphamide-based myeloablative conditioning, and acute GVHD, whereas CBT was found to be associated with a lower risk [154].

There have been no reports assessing the efficacy of drug treatments of BOS patients from Japan (Table 4). However, successful cases of living-donor lobar lung transplantation (LDLLT) have been reported [155, 156]. Given a severe deficit of cadaveric donor organs, LDLLT is performed for various lung diseases including BOS after HSCT in Japan [157]. Yamane et al. [156] demonstrated that LDLLT for post-HSCT patients with respiratory failure ($n = 7$) was effective, with less rejection episodes compared with control patients without prior HSCT ($n = 41$), but they suggested that LDLLT may have a higher risk for the development of infectious complications.

In summary, there is no comparative study of therapy for steroid-refractory chronic GVHD in Japan, even a retrospective study.

Nonsystemic therapy of chronic GVHD

Interventions including topical corticosteroids, topical Tac, CsA eye drops, and other nonsystemic therapies, as well as supportive care to prevent infections, osteoporosis, metabolic abnormalities, and other problems, are important components of the management of chronic GVHD. However, only a few studies of nonsystemic therapy have been reported from Japan (Table 4).

Chronic eye GVHD

Because the severity of ocular disease often does not correlate with that of systemic disease, systemic immunosuppression is not necessarily an optimal approach for ocular GVHD, except in occasional cases. Ogawa et al. are involved in the establishment of topical treatment for ocular chronic GVHD (Table 4). They reported the safety and efficacy of topical tranilast for mild dry eye [158], autologous serum eye drops for severe dry eye [159], and lacrimal punctal cauterization for dry eye with recurrent punctal plug extrusion [160] in Japanese patients with chronic GVHD affecting the eyes.

Conclusion

This review has documented how many studies on prophylactic and therapeutic treatment of acute and chronic GVHD have been conducted in Japan. We should not play down our own data. However, what was surprising is that most studies were performed in a single institute and included a small number of patients, resulting in biased conclusions. Given the establishment of the "Transplant Registry Unified Management Program" in the JSHCT [161], it is important to actively use not only detailed data in limited institutions, but also large-scale registry data to obtain more reliable results in the future.

Unfortunately, only one phase 3 study has been conducted in Japan [28]. A prospective, randomized study of GVHD treatment is extremely difficult, partly due to the small number of eligible patients in each transplant institute, the need for prompt initiation of therapy, and, maybe in Japan, the thought of leaving the question of GVHD to other countries. This review may provide a baseline for starting prospective studies to create new evidence for GVHD treatment from Japan.

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Conflict of interest The author declares no conflict of interest.

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