Table 2 Characteristics and outcomes in chronic GVHD patients

UPN	*Sex*	*Age*	*Disease*	*Donor*	*HLA disparity*	*Prophylaxis for GVHD*	*At the start of MTX*				*Duration of MTX (months)*	*Overall response*	*At the time of last contact*		
							cGVHD		*PSL (mg/kg)*	*Other agent*			*PSL (mg/kg)*	*MTX or other agent*	*Outcome (no. of days follow-up) and disease status*
							From	*Type*							
187	M	4	WAS	UBM	0	FK506/sMTX	Quie	Lim	1.6	FK506	10	CR	0	—	Alive (2163)
205	F	9	ALL	UBM	0	FK506/sMTX	Quie	Lim	0.5	CsA	27	CR	0.17	MMF	Alive (1922) in CR
241	F	6	ALL	RBM	0	CsA	Prog	Ex	1	FK506	31	CR	0	MTX/FK506	Alive (1307) in CR
322	F	2	JMML	RBM	0	CsA	Quie	Ex	0.7	CsA	3	CR	0.13	MTX/CsA	Alive (183) in CR
169	F	12	HLH	RBM/DLI	0	CsA	Quie	Ex	1	—	5	PR	0	—	Alive (2507) in CR
176	F	10	ALL	RBM	1	CsA/sMTX	Quie	Ex	0.8	—	63	PR	0	MTX	Alive (2390) in CR
188	F	11	ALL	RPB	0	CsA	Prog	Ex	2	CsA	41	PR	0	—	Alive (2150) in CR
201	F	5	ALL	RPB	0	CsA	Quie	Ex	1	CsA	53	PR	0	MTX	Alive (1984) in CR
273	M	16	ALL	UBM	1	FK506/sMTX	Quie	Ex	0.2	—	16	PR	0.13	MTX/CsA	Alive (794) in CR
274	F	6	AML	UBM	2	FK506/sMTX	Quie	Ex	0.55	CsA	11	PR	0.15	MTX/CsA	Alive (774) in CR
223	M	16	ALL	RPB	0	CsA	Quie	Ex	0.52	CsA	18	MR	0.07	MMF	Alive (1583) in CR
284	M	6	ALL	UCB	1	FK506/sMTX	Quie	Ex	0.16	—	8	MR	0.08	MTX	Alive (618) in CR
179	M	9	ALL	RBM	2	FK506/sMTX	Quie	Ex	0.5	FK506	68	NR	0	MTX	Alive (2280) in CR
185	F	10	ALL	UBM	0	FK506/sMTX	Prog	Ex	0.3	—	57	NR	0.1	MTX	Alive (2181) in CR
214	M	15	AML	UBM/ DLI	0	FK506/sMTX	Quie	Ex	0.16	—	30	NR	0.4	MTX	Alive (1760) in CR
260	M	16	ALL	UBM	0	FK506/sMTX	Quie	Ex	2	CsA	0	NR	1.7	CsA	Died (272)
287	F	8	CML	UBM	0	FK506/sMTX	Quie	Ex	0.17	—	14	NR	0.28	MTX/MMF	Alive (523) in CR

Abbreviations: cGVHD = chronic GVHD; CML = chronic myelogenous leukemia; CR = complete response; DLI = donor lymphocyte infusion; F = female; FK506 = tacrolimus; HLH = hemophagocytic lymphohistiocytosis; JMML = juvenile myelomonocytic leukemia; M = male; NR = no response = PR = partial response = MR = mixed response = MMF = mycophenolate mofetil; prog = progressive; PSL = prednisone; Quie = quiescent; RBM = related bone marrow; RPB = related peripheral blood; sMTX = short-term MTX; UBM = unrelated bone marrow; UCB = unrelated cord blood; UPN = unique patient number; WAS = Wiskott–Aldrich syndrome.

of GVHD were histologically confirmed in the diagnosis of either acute or chronic GVHD.

Treatment prior to low-dose MTX

All but one of the 10 patients with aGVHD were treated with calcineurin inhibitor and 2 mg/kg prednisone at the start of the low-dose MTX administration. Eight of these patients received high-dose methylprednisolone (pulse) therapies resulting in poor response prior to the low-dose MTX. In one patient, aGVHD of grade III occurred after DLI and prednisone of 2 mg/kg was administered prior to low-dose MTX.

Ten of seventeen patients with cGVHD received a calcineurin inhibitor in combination with various doses of prednisone and remaining seven patients including two patients post DLI were with prednisone alone at the start of low-dose MTX. No other immunosuppressive agents were used prior to MTX for the treatment of acute or chronic GVHD.

Evaluation of response and toxicity

We evaluated overall response in patients with acute and chronic GVHD treated with low-dose MTX as follows; a complete response (CR) was defined as the resolution of all clinical manifestations of aGVHD. Partial response (PR) was defined as an improvement in at least one involved organ without deterioration in others nor the emergence of other organs. Mixed response (MR) was defined as improvement in at least one organ with deterioration in another organ or the emergence of involvement of other organs. No response (NR) was defined as no improvement or deterioration of all affected organs. The manifestation of each organ in acute and chronic GVHD after low-dose MTX was estimated as resolution, improvement, stable or progression.

The toxicity of low-dose MTX was graded based on the Common Terminology Criteria for Adverse Events version 3.0, according to physical examination of patients and laboratory findings including complete blood counts, liver function tests and renal function tests.

Results

Responses

Responses and outcomes in patients with aGVHD are shown in Table 1. The median number of low-dose MTX administrations was five (range, 1–7). Seven of the ten (70%) patients responded well to low-dose MTX and achieved CR or PR. The dose of prednisone was successfully reduced to equal to or lower than 1 mg/kg in these seven responding patients at the end of the MTX therapy. CR was achieved by three of the four patients with aGVHD grade II with stage 3 cutaneous involvement without any other involved organs, and two of six patients with grade III with skin and the gut involvement (one had skin stage 2, gut stage 2 and the other skin stage 2, gut stage 3). In CR and PR patients, signs of improvement of GVHD-related symptoms appeared within median 4 (range, 2–7) days after low-dose MTX administration without additional agents. No other MR patient was identified. Three NR patients had aGVHD of grade III including gut involvement of equal to or more severe than stage 3 and liver disease of equal to or more severe than stage 2, either with or without skin disease. They all died of infectious complications following the progression of aGVHD.

The responses and outcomes of the patients with cGVHD are shown in Table 2. The median duration of low-dose MTX administration was 18 (range, 0–68) months. CR was achieved in four patients, PR in six, MR in two and NR in five patients, respectively. Two of four CR cases had the limited disease and the other 2 cases had the extensive disease, including cutaneous and oral mucosal involvement. In these four CR patients, three began low-dose MTX soon after the diagnosis of cGVHD and the remaining patient began 25 days after the diagnosis. At the time of the last contact, seven patients discontinued prednisone and three of these patients were free from any other immunosuppressive agent. In all except one patient could the dose of prednisone be reduced to lower than 0.4 mg/kg, but four patients were treated with an additional agent such as CsA or MMF. Although the efficacy of low-dose MTX was not observed in NR patients, in two (UPN 179 and 185) of five NR patients, the dose of prednisone could be reduced to lower than 50% of baseline dose after a long duration of MTX administration. Three patients developed the progressive forms of cGVHD with skin involvement of more than 50% of the body surface area. In two of these three patients, cGVHD positively responded to MTX therapy, thus resulting in CR and PR, respectively and prednisone was therefore eventually discontinued. The other patient did not respond to MTX, however, the dose of prednisone could be reduced to 0.1 mg/kg at the time of last contact, namely, 57 months after the start of MTX administration.

The responses in each of the involved organs are shown in Table 3. In the case of aGVHD, seven (88%) of the eight patients with skin diseases showed favorable response, resulting in resolution or improvement. On the other hand, in the cases with aGVHD of the liver, only one (25%) of four cases responded. In the cases with aGVHD of the gut, responses were observed in three (50%) of six cases. In cGVHD, resolution or improvement was observed in 8 (57%) of 14 cases with the oral mucosa, 6 (55%) of 11 cases with the liver and 5 (42%) of 12 cases with the skin.

Table 3 Response of involved organs

Site	*Acute GVHD*			*Chronic GVHD*				
	Skin	*Liver*	*Gut*	*Skin*	*Oral mucosa*	*Liver*	*GI*	*Eyes*
n	8	4	6	12	14	11	1	2
Resolution	5	0	2	3	7	2	1	1
Improvement	2	1	1	2	1	4	0	1
Stable	1	1	1	5	4	5	0	0
Progression	0	2	2	2	2	0	0	0

Abbreviation: GI = gastrointestine.

Table 4 Toxicity related to low-dose MTX

	Hematological toxicity			Liver toxicity	
	ANC	Hb	PLT	AST	ALT
Grade III	0	0	1	1	1
Grade IV	1	0	2	0	0

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; Hb = hemoglobin; PLT = platelet count.

Toxicity

Severe toxicity greater than grade III was observed in six patients (Table 4). As for any hematological adverse effect, one patient developed grade IV neutropenia and three patients developed grade III to IV thrombocytopenia. Both neutropenia and thrombocytopenia occurred in one patient (UPN 267) soon after the first dose of MTX. She suffered from refractory aGVHD of grade III and her general condition rapidly deteriorated with progressive pancytopenia before MTX.

Two patients had elevated levels of serum transaminase up to grade III toxicity and improved after interruption of MTX. Although the liver enzyme levels elevated in other many patients, the levels were limited to grade I to II. No other adverse effects of grade III or more were observed. All instances of grade I and II toxicity, including the liver and marrow, later resolved without any treatment.

One patient (UPN 263) with aGVHD developed hemorrhagic cystitis with BK virus occurring 6 weeks after the beginning of MTX. Another patient (UPN 260) died of pulmonary aspergillosis. He suffered from cGVHD of the skin, liver and lung for about 3 months. No other infectious complications evidently related to MTX therapy occurred.

Overall, the low-dose MTX therapy was well tolerated and median duration of this therapy for cGVHD was 18 months (range, 0–68).

Survival

Overall, 4 of 10 patients with aGVHD died and the probability of survival was 58.3% (95% CI 26.7–89.9%). Three patients with aGVHD grade III died of infectious complications following severe aGVHD and one died of relapsed underlying disease. One of 17 patients with cGVHD died of invasive pulmonary aspergillosis which overlapped with steroid-refractory cGVHD and the probability of survival was 93.8% (95% CI 81.8–105.8%).

Discussion

Acute GVHD is one of the major causes of morbidity and mortality after allogeneic HSCT. It has been reported that only less than 50% of patients showed complete response to initial treatment with steroid for aGVHD.[24,25] A salvage treatment is often required for patients who fail to respond to steroid therapy but high mortality is reported in these steroid-refractory cases.[4,5] To date, many investigators have demonstrated the poor outcome of patients treated with ATG for steroid-refractory aGVHD.[5,26–28] In these reports, the major causes of death were progressive aGVHD, infectious complication or post transplant lymphoproliferative disorder. Recently, efficacies of monoclonal antibodies to some inflammatory cytokines against aGVHD were reported in many literatures. One of these reports demonstrated that 13 (62%) of 21 patients who received infliximab for steroid-refractory aGVHD experienced complete response.[29] However, high rates of infections were also observed and the overall survival rate was 38%. Others have shown similar associations between the use of monoclonal antibodies and infections in aGVHD patients.[30,31] Similarly, the use of MMF for steroid-refractory aGVHD was reported to have relations to high incidence of infectious complications.[32] Pentostatin for the treatment of 23 patients in steroid-refractory aGVHD as phase I dose escalation study was reported in 2005.[33] Although the response rate in that report was 78%, only five patients were alive. Most patients died of refractory GVHD, relapse of disease, or infectious complications. These results showed that one of the most important factors contributing to the lower survival rate after the salvage therapy was the intensification of immunosuppression leading to the opportunistic infection.

Chronic GVHD is also the major cause of non-relapse mortality in patients surviving more than 2 years after allogeneic transplantation.[3] One prospective cohort study demonstrated that response rates to combination therapy with steroid, CsA and azathioprine were 61, 53 and 50% at 6 months, 1 year and 2 years, respectively and the overall survival rate was 39% at 10 years.[34] In addition, cGVHD is associated with substantial deficits of the quality of life such as decreased physical and functional status, sexual inactivity and frequent infection.[35] The long-term treatment with prednisone, which is one of the agents in the first-line treatments for cGVHD, may enhance this compromised quality of life in patients with cGVHD. As a result, mortality in chronic GVHD is largely attributable to infection.[2,3,34] As the secondary or salvage treatment for cGVHD, a number of trials have been published. Most of them reported a success rate of 25 to 50% using a variety of agents such as MMF, a monoclonal antibody to the inflammatory cytokines and rituximab with possibility of increasing risk of infection.[3,36,37]

Considering the circumstances mentioned above, one of the most important strategies for the treatment of acute and chronic GVHD is to lessen the risk of infection. Because it is considered that low-dose MTX has little impact for immunosuppression leading to the risk of infectious complications, the agent may be beneficial for patients with lower immune function by prior intensive immunosuppressive treatment. In the present study, many patients with acute and chronic GVHD was able to reduce the dose of prednisone after the initiation of low-dose MTX without increasing the risk of opportunistic infection and other complications caused by long-term prednisone treatment. In addition, only 1 of 27 patients demonstrated a relapse of an underlying disease, thus suggesting that low-dose MTX does not increase the risk of relapse.

The results of the present study indicate that low-dose MTX might be ineffective in cases of aGVHD with stage 4

disease of the gut or multiple organ involvement. For these patients, a more immunosuppressive agent might thus be needed. In seven patients with aGVHD who responded to this treatment regimen, an improvement of GVHD-related symptoms appeared within median 4 (range, 2–7) days after the initiation of low-dose MTX without any additional agents. It seems that if a sign of the improvement of aGVHD is observed within a week after the first dose of MTX, then a good response may be expected in aGVHD. Low-dose MTX seemed to be effective for cGVHD of the liver, oral mucosa and skin involvement. Depending on the responding organs, the manifestations of the oral mucosa and skin tended to improve within a few weeks after the initiation of MTX treatment while it might take a long time for the findings of liver function tests to normalize. In fact, most of the observed responses in cGVHD of the liver demonstrated either an improvement or stable disease. Many other medications or complications after HSCT might also influence the resolution process of liver disease. Sixteen of seventeen patients were alive at last follow-up either with or without a small dose of prednisone. Given the long-term usage of prednisone influence to morbidity and mortality, this result suggested that low-dose MTX might have a potential to lessen mortality, thus possibly improving the quality of life of patients with cGVHD. The number of cases investigated in this study was too small to draw any definitive conclusions, and therefore further large-scale analyses are required.

Severe toxicities occurred only in a few patients presenting cytopenias or elevated levels of the serum transaminases. Most of these adverse events developed in advanced aGVHD patients. Because these patients were extremely ill and were on many medications that have myelo- and/or hepatotoxicity, it was difficult to evaluate whether these toxicities were related to MTX alone. There were no episodes of severe infectious complications obviously related to MTX. No other well-described adverse event such as gastrointestinal symptoms, immune-mediated pneumonitis, renal impairment and secondary malignancies were seen even in the patients with long-term follow up. These results suggested that low-dose MTX might therefore be safe and well tolerated for long-term use over a period of several years, even in the post transplant setting.

There are two published reports, which evaluated the feasibility of MTX in the treatment of GVHD. Giaccone *et al.*[15] demonstrated the possible steroid-sparing effect of low-dose MTX for patients with long-standing, severe chronic GVHD. Despite the fact that 12 of 14 patients in this retrospective study had at least one high-risk feature such as scleroderma, fasciitis or thrombocytopenia, the disease could be successfully controlled in 10 patients with prednisone at doses below 1 mg/kg every other day without the addition of other agents. On the other hand, Huang *et al.*[16] reported the result of a clinical study using low-dose MTX to treat patients with acute and chronic GVHD. Most patients in this study were not in the advanced stages of GVHD and the response rate was very high for both acute and chronic GVHD including post DLI GVHD. In addition to the efficacy of low-dose MTX, these two reports showed the safety and tolerability of this agent and our present study supported and confirmed the more long-term use of MTX over a period of several years even for children.

In conclusion, low-dose MTX is less toxic, easy to administer and effective to the steroid-refractory or -dependent GVHD, in addition, reducing the dosage and duration of steroid therapy. Low-dose MTX is worthy of further evaluation as second-line treatment of severe GVHD.

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