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Title

Risk factors of human herpesvirus 6 encephalitis/myelitis after allogeneic hematopoietic stem cell transplantation

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Running title

HHV-6 encephalitis/myelitis after HSCT

Abstract

Background. Human herpesvirus 6 (HHV-6) encephalitis/myelitis is now a well-known complication after allogeneic stem cell transplantation (allo-HSCT), particularly after cord blood transplantation (CBT). In this study, we evaluated the risk factors of HHV-6 encephalitis/myelitis.

Methods. We evaluated 253 patients who received allo-HSCT from 2007 to 2015 at our institute. HHV-6 encephalitis/myelitis was defined as HHV-6 DNA detection in the cerebrospinal fluid or peripheral blood by polymerase chain reaction in the presence of typical manifestations without other concurrent condition which led to the manifestations.

Results. HHV-6 encephalitis/myelitis occurred in 11 patients (4.5%, encephalitis; 3.7%, myelitis; 0.8%). Multivariate analysis showed CBT, mycophenolate mofetil (MMF) for graft-versus-host disease (GVHD) prophylaxis, history of allogeneic hematopoietic stem cell transplantation (allo-HSCT), and engraftment syndrome (ES) were significantly associated with incidence of HHV-6 encephalitis/myelitis ($P = 0.025$, $P = 0.017$, $P = 0.017$, and $P = 0.014$, respectively).

Conclusion. Although it has been shown that CBT, ES, and history of allo-HSCT are risk factors for HHV-6 encephalitis/myelitis, our study demonstrated MMF is also a risk factor for the disease.

Key words

Human herpesvirus 6, mycophenolate mofetil, hematopoietic stem cell transplantation

Introduction

Almost all children have infected with human herpesvirus 6 (HHV-6) which causes exanthema subitum and HHV-6 remains latent in host cells lifelong. After allogeneic hematopoietic stem cell transplantation (allo-HSCT), incidence of reactivation of HHV-6 ranges from 35.0% to 72.2% (1-5). HHV-6 encephalitis/myelitis is a devastating complication after allo-HSCT in association with HHV-6 reactivation. HHV-6 encephalitis/myelitis generally occurs in 0.96-11.6% of patients mostly 2-6 weeks after allo-HSCT (2, 6-15). HHV-6 encephalitis/myelitis causes memory dysfunction and seizure (16, 17). These sequelae are often lifelong and lead to deteriorated quality of life.

Several studies indicate an association between umbilical cord blood transplantation (CBT) and HHV-6 encephalitis/myelitis. Incidence of HHV-6 encephalitis/myelitis is 4.9-21.4% after CBT (2, 8, 9, 11, 13). However, the other factors which have impact on HHV-6 encephalitis/myelitis remain elusive. To elucidate the risk factors of HHV-6 encephalitis/myelitis, we retrospectively analyzed patients who received allo-HSCT in our institute.

Patients and methods

Patients

Between 2007 and 2015, 253 adult patients underwent allo-HSCT in our institute and medical records of these patients were reviewed. This study was approved by our Institutional Review Board and was conducted according to the guidelines of the Declaration of Helsinki.

Conditioning regimen

Myeloablative conditioning (MAC) regimens were defined as using total body irradiation (TBI) with fractionated doses of >8 Gy, busulfan doses >9 mg/kg, or melphalan doses >140 mg/m². Reduced-intensity conditioning (RIC) regimens were

defined as a combination of fludrabine and alkylating agent (busulfan doses ≤ 9 mg/kg or melphalan doses ≤ 140 mg/m²) with or without TBI doses ≤ 4 Gy (18, 19).

Graft-versus-host disease (GVHD) prophylaxis

GVHD prophylactic regimens include tacrolimus (TAC), cyclosporine (CsA), methotrexate (MTX), mycophenolate mofetil (MMF), anti-thymocyte globulin (ATG), and posttransplantation cyclophosphamide (PTCY). CsA was given aiming for therapeutic trough levels between 150 and 300 ng/mL in divided dose q12h or between 250 and 400 ng/mL in continuous infusion. TAC was given aiming for therapeutic levels between 10 and 15 ng/mL in continuous infusion. MMF was administered at a dose of 30mg/kg/day and MTX was administered at a dose of 15 or 10 mg/m² on day 1, and 10 or 7 mg/m² on day 3 and 6 after transplantation. PTCY was used in the setting of allo-HSCT from HLA haploidentical donor (20).

HHV-6 encephalitis/myelitis

HHV-6 encephalitis was defined as presence of short-term memory dysfunction, disturbance of consciousness, or seizure in a patient with HHV-6 DNA detected in the cerebro spinal fluid (CSF) (or serum if CSF was unavailable) after exclusion of other causes. HHV-6 myelitis was defined as presence of dysesthesia, lancinating pain, and

pruritus of extremities and trunk, or dysautonomia such as bladder and rectal disturbance or tachycardia with HHV-6 DNA detected in the CSF (or serum if CSF was unavailable) after exclusion of other causes. These criteria were based on the previous report and all cases which we studied met this definition (8, 10, 16, 21-23).

Statistical analysis

We compared characteristics of the patients by Fisher's exact test and t-test for categorical and continuous variables, respectively. To clarify risk factors for HHV-6 encephalitis/myelitis, we examined categorical variables, including age, sex, underlying disease, disease status at transplant, conditioning regimen, stem cell source, a history of prior allo-HSCT, engraftment syndrome (ES), use of steroid at engraftment, HLA matching between the donor and recipient, and GVHD prophylaxis using Gray test for univariate analysis. As most of HHV-6 encephalitis/myelitis occurs within 100 days after allo-HSCT (9, 11, 12, 17, 22, 24, 25), we examined cumulative incidence rate of HHV-6 encephalitis/myelitis at 100 days after allo-HSCT. The variables were included in a multivariate analysis if they had P -values < 0.05 in a univariate analysis and Fine-Gray regression for proportional hazards modeling was used for a multivariate analysis. However, one of the correlated variables whose P -values were < 0.05 in a univariate analysis was excluded from a multivariate analysis. Phi coefficient was

obtained to examine the correlation of the variables. To reveal influence of HHV-6 encephalitis/myelitis on overall survival (OS), we calculated survival curves by the Kaplan-Meier method and log-rank test was used for the comparison of survival curves. A landmark analysis of patients who developed HHV-6 encephalitis/myelitis within 42 days after transplantation (n = 10) were performed to evaluate an impact of HHV-6 encephalitis/myelitis on OS. This is because HHV-6 encephalitis/myelitis occurs frequently between 2-6 weeks after transplantation (6, 7, 15). *P*-values < 0.05 were considered as a statistical significance. The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated with a predetermined reference risk of 1.0. All statistical analyses were performed with EZR (Saitama medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (26).

Results

Patients' characteristics

Patients' characteristics are listed in Table 1. A median age of the patients was 48 years old. Primary diseases included acute myeloid leukemia (AML, n = 77), acute lymphoblastic leukemia (ALL, n = 45), chronic myelogenous leukemia (CML, n = 8),

myelodysplastic syndrome (MDS, n = 35), malignant lymphoma (ML, n = 56), multiple myeloma (MM, n = 6), adult T-cell leukemia/lymphoma (ATLL, n = 12), aplastic anemia (AA, n = 9), and others (n = 5).

Clinical features of patients with HHV-6 encephalitis/myelitis are shown in Table

2. There were 2 patients with HHV-6 myelitis characterized by generalized pruritus, discomfort, and pain resembling calcineurin inhibitor induced pain syndrome (27). All of the 9 patients with HHV-6 encephalitis showed impaired consciousness and disorientation. Two of the 9 patients also exhibited pruritus. Lumber puncture was carried out in 8 of the 11 patients with HHV-6 encephalitis/myelitis. HHV-6 DNA was positive in all 8 patients and in 6 patients quantitative data were available with a median of 2.6×10^4 copies/mL of HHV-6 DNA, ranging from 5.3×10^2 to 6.1×10^4 . HHV-6 DNA was also positive in peripheral blood of 4 of the 11 patients with a median of 4.8×10^4 copies/mL of HHV-6 DNA, ranging from 1.2×10^3 to 5.8×10^5 . Magnetic resonance imaging (MRI) demonstrated hyperintensities in the vicinity of the hippocampus in 5 of the 11 patients.

Risk factors

A total of 11 (4.5%) of 253 patients developed HHV-6 encephalitis/myelitis, including 9 (3.7%) encephalitis and 2 (0.8%) myelitis at 14-55 days (median, 21 days) after allo-HSCT. The results of univariate analysis are shown in Table 3. Incidence of HHV-6 encephalitis/myelitis was higher after CBT than after PBSCT or BMT (11.3% vs. 2%, $P < 0.001$). That was higher in patients with a history of prior allo-HSCT than those without it (13.2% vs. 1.7%, $P < 0.001$). ES is also a risk for HHV-6 encephalitis/myelitis; HHV-6 encephalitis/myelitis developed in 6 (11.7%) of 52 patients with ES and in 5 (2.6%) of 194 patients without ES. Interestingly, GVHD prophylaxis using MMF in combination with calcineurin inhibitors showed significantly higher incidence of HHV-6 encephalitis/myelitis than other GVHD prophylaxis (16.7% vs. 3.2%, $P = 0.002$). The number of variables was too much in contrast with the number of cases to perform multivariate analysis. To enhance reliability of analysis, we calculated phi coefficient between 2 of the 7 significant variables in univariate analysis. All combinations were examined and one of the correlated variables was excluded from multivariate analysis. As a result, non-use of MTX for GVHD prophylaxis, HLA mismatch, and steroid use at engraftment were excluded from multivariate analysis because they had correlation with use of MMF, CBT, and ES, respectively (phi

coefficient 0.702, 0.548, and 0.641, respectively). Factors whose phi coefficient over 0.4 are considered as having correlation.

Among these factors above, CBT (Hazard ratio [HR] 6.182; $P = 0.017$), prior allo-HSCT (HR 4.942; $P = 0.017$), use of MMF as GVHD prophylaxis (HR 4.163; $P = 0.025$), and ES (HR 7.179; $P = 0.014$) remained as independent risk factors of HHV-6 encephalitis/myelitis in multivariate analysis (Table 3).

Outcome

All patients were treated with ganciclovir (GCV) or foscavir (FCV), which eliminated HHV-6 DNA in the CSF or serum, but memory dysfunctions were not recovered in 2 patients.

No patient died of HHV-6 encephalitis/myelitis and 7 patients died of the other causes, including relapse of the diseases in 5 patients, infection in a patients, and acute GVHD in a patient (Table 2). OS rate at 1 year after transplantation in patients with and without HHV-6 encephalitis/myelitis was 40.0% and 71.3%, respectively (Figure 1). Development of HHV-6 encephalitis/myelitis trended to be associated with poor prognosis ($P = 0.052$).

Discussion

CBT is an obvious risk factor for HHV-6 encephalitis/myelitis (28). We also demonstrated that CBT was a significant risk of HHV-6 encephalitis/myelitis in this study. This may be associated with the absence of primed HHV-6-specific memory T cells and the immunologic immaturity of CBT (13, 29-31). Yoshihara et al. reported that donor lymphocyte infusion was effective in a patient with HHV-6 encephalitis, suggesting a role of HHV-6-specific T cells in preventing HHV-6 reactivation (32).

We showed a novel finding that MMF was a significant risk of HHV-6 encephalitis/myelitis. Mori et al. previously suggested the association of MMF and HHV-6 encephalitis/myelitis although the association was not statistically significant (16). MMF is rapidly hydrolyzed after absorption to mycophenolic acid which reversibly inhibits inosine monophosphate dehydrogenase, leading to decreased B- and T-cell proliferation. MMF also leads to immunosuppression through other mechanisms as well, including the induction of apoptosis of activated T cells and the inhibition of adhesion molecule expression and lymphocyte recruitment (33). Such effects of MMF may injure anti-HHV-6 immune responses although there are conflicting results of association of MMF with virus reactivation (34, 35). Concerning virus reactivation after allo-HSCT, previous studies showed that MMF was significantly associated with the reactivation of CMV or BK virus (36-40).

Previous report has found that HHV-6 encephalitis/myelitis occurred more frequently in recipients who underwent twice or more HSCTs, especially CBTs (16). Our study also demonstrated that patients who had history of prior allo-HSCT developed HHV-6 encephalitis/myelitis more frequently than patients who received allo-HSCT for the first time. When this analysis was restricted to a second or more-time CBT, the incidence of HHV-6 encephalitis/myelitis increased to 36.5% (5 of 14 patients). It was reported that it took a long time to restore the ability of the immune system, especially CD4 positive T cells, and there was the association of CD4 positive T cell counts and infection rates (41, 42), indicating that history of prior allo-HSCT has association with immune depression at second or more-time allo-HSCT leading to development of HHV-6 encephalitis/myelitis.

In this study, ES was also a risk factor of developing HHV-6 encephalitis/myelitis. It was reported that interleukin 6 was elevated preceding HHV-6 encephalitis/myelitis and inflammatory condition is considered to be associated with development of HHV-6 encephalitis/myelitis (43-45).

Previous report showed that MRI in 7 days after development of HHV-6 encephalitis can not always show typical abnormal signal intensity, such hyperintensities in the bilateral hippocampus (23), although another report indicated

effectiveness of diffusion-weighted MRI imaging in early period of HHV-6 encephalitis (46). In our study, MRI which was carried out in 5 days after development of HHV-6 encephalitis/myelitis did not detect any abnormalities in 6 of 11 HHV-6 encephalitis/myelitis patients. MRI itself may not have an influence on decision of early treatment of HHV-6 encephalitis/myelitis and it may be reasonable to consider MRI as diagnosis supporting device.

Incidence of HHV-6 encephalitis/myelitis in our study was similar to the results in previous studies (2, 8, 9, 11-13). FCV is currently used to treat HHV-6 encephalitis/myelitis, however, the outcome have been reported to be still dismal with inferior survival and significant sequelae. In this study, 2 patients developed HHV-6 encephalitis/myelitis during GCV therapy against cytomegalovirus reactivation. To reduce morbidity and mortality of HHV-6 encephalitis/myelitis, prophylactic or preemptive administration of anti-viral agents, such as FCV and GCV, may be beneficial. However, dynamic kinetics of HHV-6 load after transplantation have been pointed out, and the timing and doses of effective preemptive or prophylactic anti-HHV-6 agents administration have not been established so far (47-49). OS rate at 1 year after development of HHV-6 encephalitis/myelitis in the patients (n=8) treated with FCV was better than in the patients (n=3) treated with GCV (50.0% vs. 0%, $P = 0.0065$,

log-rank test). Although it was reported that the efficiency of FCV against HHV-6 in vitro was higher than that of GCV (50), to reveal the impact of GCV or FCV on clinical outcome, prospective studies under standardized conditions are required.

Differentiation of HHV-6 infection and chromosomally integrated HHV-6 is important (51, 52). We confirmed that HHV-6 viral loads in all patients declined after treatment. Therefore, we could rule out the possibility of chromosomal integration and we consider all patients were definitely diagnosed with HHV-6 encephalitis/myelitis.

There are some limitations in this study. The first limitation is the small number of cases studied. However, considering predisposition of HHV-6 encephalitis/myelitis after allo-HSCT and the previous reports in which 23 cases were at most reported (median, 9 cases) (2, 8-13, 25), the number of cases (n=11) studied does not seem to be too small. Secondly, we did not differentiate HHV-6A from HHV-6B in this study although HHV-6 encephalitis/myelitis after allo-HSCT is considered to be associated with reactivation of HHV-6B in most cases (53, 54). Prospective studies under standardized conditions are needed to better understand physiopathology of HHV-6 encephalitis/myelitis and to establish optimum prophylaxis and treatment.

Conclusion

In summary, HHV-6 encephalitis is not a rare complication of allo-HSCT especially in the setting of CBT, MMF use for GVHD prophylaxis, prior allo-HSCT, and ES. Optimum prophylaxis and preemptive therapy against HHV-6 encephalitis/myelitis have remained elusive. At the present moment, the understanding of risk factors of HHV-6 encephalitis/myelitis is important for its early diagnosis and treatment. We believe that our identification of a new possible risk factor, MMF, is useful for medical examination and treatment of HHV-6 encephalitis/myelitis, although further prospective studies validating our findings are mandatory.

Author contribution

T. Endo, Critical revision of article; M. Onozawa, Critical revision of article; D. Hashimoto, Critical revision of article; J. Sugita, Data analysis/interpretation; K. Kahata, Critical revision of article; T. Matsukawa, Data analysis/interpretation; S. Hashino, Data analysis/interpretation; T. Kondo, Data analysis/interpretation; K. Fujimoto, Data analysis/interpretation; H. Goto, Data analysis/interpretation; T. Teshima, Approval of article.

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Table 1. Patient characteristics

Characteristics	Total	HHV-6 encephalitis/myelitis		P-value
		Yes (n = 11)	No (n = 242)	
Age, median (range)	48 (17-66)	33 (24-63)	48 (17-66)	0.113
Sex				0.759
Male	137	5	132	
Female	116	6	110	
Underlying disease				0.531
AML	77	4	73	
ALL	45	3	42	
CML	8	0	8	
MDS	35	2	33	
ML	56	1	55	
MM	6	0	6	
ATLL	12	0	12	
AA	9	0	9	
Others	5	1	4	
Disease status before allo-HSCT				0.365
CR	127	4	123	
non CR	126	7	119	
Conditioning regimen				0.751
MAC	92	3	89	
RIC	161	8	153	
Donors and stem cell type				0.003
Related PB	50	2	48	
Related BM	21	0	21	
Unrelated BM	134	2	132	
Unrelated CB	48	7	41	
Prior allo-HSCT				<0.001
Yes	62	3	59	
No	191	8	183	
ES				0.013
Yes	52	6	46	
No	194	5	189	
unevaluable	7	0	7	
Steroid use at engraftment				0.004
Yes	60	7	53	
No	193	4	189	
HLA matching				<0.001
Match	151	1	150	
Mismatch	102	10	92	
GVHD prophylaxis				
TAC based/CsA based	253	10/1	182/60	0.468
sMTX	207	3	204	<0.001
MMF	25	4	21	0.015
PTCY	10	0	10	1
ATG	19	2	17	0.196

Bold value is significant.

Fisher's exact test and t-test was used for categorical and continuous variables respectively to calculate the *P*-values.

Abbreviation. HHV-6, human herpesvirus-6; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; ML, malignant lymphoma; ATL, adult T-cell leukemia/lymphoma; AA, aplastic anemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ES, engraftment syndrome; CR, complete response; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; PB, peripheral blood; BM, bone marrow; CB, cord blood; HLA, human leukocyte antigen; GVHD, graft-versus host disease; TAC, tacrolimus; CsA, cyclosporine; sMTX, short-term

methotrexate; MMF, mycophenolate mofetil; PTCY, posttransplantation cyclophosphamide; ATG, anti-thymocyte globulin.

Table 2. Characteristics of patients with human herpesvirus-6 encephalitis/myelitis

Patient	Age	Sex	Encephalitis/ myelitis	Prior HSCT	Conditioning regimen	Stem cell type	GVHD prophylaxis	ES	Use of steroid at engraftment	Onset (Day)	Clinical manifestation	HHV-6 viral load in CSF/serum (copies/mL)	HHV-6 viral load in CSF/serum after treatment (copies/mL)	MRI (days after the onset of HHV-6 encephalitis/myelitis)	Antiviral treatment	CMV antigenemia	Sequela	Outcome	Survival time after development of HHV-6 encephalitis/myelitis (days)
1	37	M	encephalitis	Yes	RIC	UCB	TAC+ mPSL	No	Yes	35	Impaired consciousness	Positive / -	<1x10 ² / -	DWI, FLAIR, T2 (day2): hyperintensities in the bilateral hippocampus	GCV	Positive		Dead by relapsed AML	22
2	63	F	encephalitis	Yes	RIC	URBM	TAC + sMTX	Yes	Yes	24	Impaired consciousness	Positive / -	<1x10 ² / -	No abnormalities (day1)	GCV	Negative		Dead by relapsed ML	57
3	48	F	encephalitis	No	MAC	UCB	TAC + sMTX	No	No	21	Impaired consciousness Memory dysfunction	3x10 ³ / -	<1x10 ² / -	DWI, FLAIR, T2 (day0): hyperintensities in the bilateral temporal lobe	FCV	Negative	Memory dysfunction	Alive	2503
4	30	M	encephalitis	No	MAC	URBM	TAC + sMTX	Yes	Yes	55	Pruritus Depression	- / 9x10 ⁴	- / <1x10 ²	No abnormalities (day4)	FCV	Negative		Dead by infection	169
5	33	M	myelitis	Yes	RIC	UCB	TAC + MMF	No	No	15	Paralysis	- / 1.2x10 ³	- / <1x10 ²	No abnormalities (day5)	FCV	Positive		Dead by acute GVHD	33
6	24	F	encephalitis	Yes	RIC	UCB	TAC	Yes	No	21	Impaired consciousness Headache	8.5x10 ² / -	<1x10 ² / -	No abnormalities (day0)	FCV	Negative		Alive	1013
7	60	F	encephalitis	No	MAC	UCB	TAC + MMF	Yes	No	28	Impaired consciousness Pruritus	4.8x10 ⁴ / 5.1x10 ³	<1x10 ² / -	FLAIR (day0): hyperintensities in the bilateral basal nuclei	FCV	Positive		Alive	700
8	31	M	encephalitis	Yes	RIC	UCB	TAC + MMF	Yes	Yes	14	Impaired consciousness	- / 5.8x10 ⁵	<1x10 ² / -	FLAIR (day0): hyperintensities in the bilateral hippocampus	FCV	Negative	Memory dysfunction	Dead by relapsed MDS	262
9	54	F	encephalitis	Yes	RIC	UCB	CsA + MMF	Yes	Yes	15	Impaired consciousness	6.1x10 ⁴ / -	<1x10 ² / -	DWI, FLAIR, T2 (day0): hyperintensities in the bilateral temporal lobe	GCV	Positive		Dead by relapsed AML	152
10	30	F	myelitis	Yes	RIC	RPBSC	TAC + PSL	No	Yes	15	Paralysis Pain	5.4x10 ⁴ / -	<1x10 ² / -	No abnormalities (day0)	FCV	Negative		Alive	601
11	24	M	encephalitis	Yes	RIC	RPBSC	TAC + mPSL + ATG	No	Yes	15	Impaired consciousness	5.3x10 ² / -	<1x10 ² / -	No abnormalities (day0)	FCV	Negative		Dead by relapsed ALL	207

Abbreviations. M, male; F, female; HHV-6, human herpesvirus-6; CMV, cytomegalovirus; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; ML, malignant lymphoma; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; RPBSC, related peripheral blood stem cell; URBM, unrelated bone marrow; UCB, umbilical cord blood; HLA, human leukocyte antigen; GVHD, graft-versus host disease; TAC, tacrolimus; mPSL, methylprednisolone; sMTX, short-term methotrexate; MMF, mycophenolate mofetil; CsA, cyclosporine; PSL, prednisolone; ATG, anti-thymocyte globulin; ES, engraftment syndrome; CSF, cerebro spinal fluid; N.D., no data; MRI, magnetic resonance imaging; DWI, diffusion-weighted MRI imaging; FLAIR, fluid attenuated inversion recovery; GCV, ganciclovir; FCV, foscavir; CMV, cytomegalovirus.

Table 3. Proportional Hazards Modeling of Risk of HHV-6 encephalitis/myelitis after Allogeneic Hematopoietic Stem Cell Transplantation

Characteristics		Cumulative incidence (%)	Univariate analysis P-Value	Multivariate analysis (stepwise) Hazard ratio (95% Confidence interval)	P-Value
Age	<55	5.4	0.329		
	≥55	2.6			
Sex	Male	5.3	0.571		
	Female	3.8			
Underlying disease	Benign	0.0	0.463		
	malignant	4.7			
Disease status before allo-HSCT	non CR	6.1	0.277		
	CR	3.2			
Conditioning regimen	MAC	3.5	0.512		
	RIC	5.1			
Stem cell type	non UCB	2.0	<0.001	6.182 (1.387-27.550)	0.017
	UCB	11.3			
donor	Related	2.8	0.436		
	Unrelated	5.2			
HLA	Match	0.7	<0.001		
	Mismatch	10.6			
Prior allo-HSCT	Prior allo-HSCT –	1.7	<0.001	4.942 (1.335-18.300)	0.017
	Prior allo-HSCT +	13.2			
GVHD prophylaxis	TAC based	5.4	0.253		
	CsA based	1.7			
	MMF –	3.2	0.002	4.163 (1.200-14.450)	0.025
	MMF +	16.7			
	MTX –	18.4	<0.001		
	MTX +	1.5			
	ATG –	4.0	0.182		
	ATG +	10.5			
	PTCY –	4.7	0.487		
	PTCY +	0			
ES	ES –	2.6	0.006	7.179 (1.487-34.65)	0.014
	ES +	11.7			
Use of steroid at engraftment	Steroid –	2.1	0.001		
	Steroid +	12.3			

Bold value is significant.

Abbreviation. allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; UCB, umbilical cord blood; HLA, human leukocyte antigen; GVHD, graft-versus host disease; TAC, tacrolimus; CsA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; PTCY, posttransplantation cyclophosphamide; ATG, anti-thymocyte globulin; ES, engraftment syndrome.

