HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2014 August 01.

Published in final edited form as:

Bone Marrow Transplant. 2014 February ; 49(2): 236–240. doi:10.1038/bmt.2013.157.

Six Month Freedom from Treatment Failure is an Important Endpoint for Acute Graft-Versus-Host Disease Clinical Trials

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Abstract

We studied the ASBMT 6 month (m) freedom from treatment failure (FFTF) as a predictor of survival for patients with acute graft-versus-host disease (aGVHD) requiring treatment. Adult patients undergoing allogeneic hematopoietic cell transplant (HCT) from February 2007 to March 2009 who were enrolled in a prospective biomarker clinical trial and developed aGVHD requiring systemic corticosteroids by day +100 were included (N=44). Six month FFTF was defined per ASBMT guidelines [absence of death, malignancy relapse/progression, or systemic immunosuppression change within 6 months of starting steroids and before chronic GVHD development]. aGVHD was treated with systemic corticosteroids in 44 patients. Day 28 response after steroid initiation (CR+VGPR+PR) occurred in 38 (87%) patients, but only 28 (64%) HCT recipients met the 6 m FFTF endpoint. Day 28 response predicted 6 m FFTF. Achieving 6 m FFTF was associated with improved 2 year (y) overall survival (OS) [81% vs. 48%, P= 0.03)] and decreased 2 y non-relapse mortality [8% vs. 49% (P= 0.01)]. In multivariate analysis, 6 m FFTF continued to predict improved OS (HR, 0.27; P=0.03). The 6 m FFTF endpoint measures fixed outcomes, predicts long-term therapeutic success, and could be less prone to measurement error than aGVHD clinical response at day 28.

Keywords

acute graft versus host disease; hematopoietic stem cell transplant; clinical trials

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Declaration of commercial interest: None

Conflict of interest

The authors declare no conflict of interest

Supplementary Information:

Supplementary Information is available at BMT's website.

Introduction

Despite prophylactic immunosuppression (IST) and improvements in high-resolution HLA typing, acute graft-versus-host disease (aGVHD) remains the major early complication following allogeneic hematopoietic cell transplantation (HCT). High dose corticosteroids are the established first-line treatment of moderate to severe aGVHD,[1] however, only 50-60% of patients will achieve a complete response to front-line therapy with steroids. [2] Incomplete responses and recurrent aGVHD symptoms are common with steroids, thus indicating a need for improved treatment options. Furthermore, there is no established second-line therapy for steroid-refractory aGVHD. Well-designed clinical trials with validated endpoints for treatment success are needed to rigorously examine new therapies to improve aGVHD outcomes. [3] At present, the optimal endpoints for aGVHD clinical trials have not been established thus interfering with the ability to identify and compare novel regimens for aGVHD treatment.

Emerging data indicates that aGVHD response after 28 days of treatment could be an important early endpoint for assessing therapeutic success in aGVHD clinical trials. [2, 4, 5] Although day 28 response appears to be a valid proximal predictor of more distal outcomes, there are several important limitations associated with this marker. First, day 28 response as determined by rash, persistent anorexia/nausea, quantity of diarrhea, and serum bilirubin concentration can be affected by non-GVHD factors including infections, medications, or organ dysfunction related to conditioning (*i.e.*, hepatic veno-occlusive disease / sinusoidal obstruction syndrome). In addition, grading of aGVHD and determining clinical response to treatment can be associated with inter-observer variation, which could be problematic for multicenter clinical trials. The American Society for Blood and Marrow Transplantation (ASBMT) has proposed the 6 month (m) freedom from treatment failure (FFTF) as a primary endpoint to gauge treatment efficacy in aGVHD clinical trials. The ABSMT 6 m FFTF is not directly determined by clinical response and is instead defined by the absence of death, malignancy relapse/progression, or systemic immunosuppression (IST) change within 6 months of starting initial treatment and prior to chronic GVHD (cGVHD) diagnosis. [1, 6] The association of 6 m FFTF with important clinical characteristics and transplant outcomes is currently unknown. We hypothesize that the ASBMT 6 m FFTF will be associated with the day 28 response and that the 6 m FFTF can predict long term therapeutic success in patients with aGVHD requiring treatment without the associated limitations inherent to the more commonly used day 28 clinical response.

Methods

Patients

From February 2007 to March 2009, 100 adult patients with hematological malignancies received myeloablative or reduced intensity conditioning (RIC) followed by a T cell replete matched related or unrelated donor (URD) HCT at Vanderbilt University Medical Center (VUMC). Seventy-four of these individuals were enrolled in a prospective biomarker clinical trial. [7] Within 100 days of transplant, 45 (61%) HCT recipients developed aGVHD requiring treatment with systemic steroids. One patient was excluded due to malignancy progression prior to steroid treatment. Thus 44 patients were included in the final analysis.

The study protocol was reviewed and approved by the Human Subject Institutional Review Board (IRB) at VUMC. Signed informed consent was obtained.

All patients received GVHD prophylaxis with a calcineurin inhibitor and either methotrexate or mycophenolate mofetil. Patients receiving T cell depletion with thymoglobulin were excluded from the original clinical trial. Only 1 patient received a donor lymphocyte infusion for relapsed malignancy during the study period. aGVHD was diagnosed clinically and was confirmed by biopsy in all patients. Clinical features of aGVHD or cGVHD were assessed weekly for the first 100 days after HCT. Thereafter GVHD status was updated at least monthly during visits in the long-term transplant clinic or at the time of acute hospitalizations. The recorded features included aGVHD or cGVHD incidence, organ involvement, severity, recurrence rates, and response to treatment. The clinical severity of aGVHD was determined by the overall grade (0-4) and the individual organ stage (0-4), as defined by the 1994 consensus conference criteria.[8] cGVHD diagnosis and severity was determined as per 2005 National Institutes of Health (NIH) consensus guidelines. [9]

aGVHD therapy and response

Patients with moderate to severe aGVHD were treated with high dose corticosteroids (1-2 mg/kg/day of intravenous methylprednisolone or oral prednisone) per institutional guidelines for 7-10 days followed by a standard taper of 10% every 5-7 days. Secondary aGVHD therapy was administered to patients per standard of care practice within our institutional guidelines for 1) aGVHD progression after 3 days of high dose corticosteroids, 2) no response after 7 days of corticosteroids, or 3) aGVHD flare while on corticosteroids and after initial response to treatment. Generally, extracorporeal photopheresis (ECP) was used as the standard second-line treatment for aGVHD at our institution. Rituximab or TNF-blockade were added to ECP for severe skin or gut aGVHD, respectively or they were used as primary therapy if ECP was contraindicated (*i.e.*, medically unstable patient, inability to place pheresis catheter due to active bacteremia, etc.).

Patients were followed for 6 months after the start of steroids. aGVHD response to systemic steroids at day 28 after treatment initiation was classified as complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR) as previously defined by the ASBMT joint statement and modified by Macmillan *et. al.* (Supplementary Table 1).[2, 10] Six month treatment failure was defined per recent ASBMT consensus as follows: death from any cause, relapse or progression of malignancy, or change in systemic IST within 180 days of starting steroid therapy and prior to cGVHD diagnosis.[1, 6] During analysis, patients meeting criteria for 6 month treatment failure were counted only once irrespective of the number of failure events they experienced. Triamcinolone cream and psoralen with ultraviolet A therapy (PUVA) were not considered systemic IST and when added to primary therapy were not counted as steroid failure events. cGVHD development was treated as a competing risk for 6 month aGVHD steroid failure.

Statistical analysis

Overall survival (OS) was estimated using the Kaplan-Meier method and cumulative incidence was used to estimate the probability of non-relapse mortality (NRM) and 6 month

treatment failure. OS and NRM were calculated from the initiation of steroid therapy. NRM was defined as death in the absence of disease relapse or progression. Relapse was considered a competing risk for NRM. Time to 6 month treatment failure was defined as the date from steroid initiation to 6 months of follow up or the first of the following events: death, malignancy relapse/progression, or initiation of second-line systemic treatment for aGVHD. Patient data was censored at the time of cGVHD if diagnosis occurred during the first 180 days of steroid treatment for aGVHD. Survival outcomes between groups were compared with a log-rank test for univariate analysis and a Cox proportional hazards regression for multivariate analysis. Nominal variables were described by the percentage or frequency and were compared by the $\chi 2$ or Fisher's exact test. McNemar's test was used to compare the proportion of patients in a group before and after an intervention. *P*-values were 2-tailed and considered significant at $P < 0.05$. Analyses were performed using SPSS version 18 (SPSS Inc, Chicago, IL) and R version 2.7.0 (Free Software Foundation, Boston, MA).

Results

Patients

Response to systemic corticosteroids was assessed in 44 evaluable patients with aGVHD [grade 1 (N= 2), grade 2 (N= 30), grade 3-4 (N=12)]. Two patients with grade 1 aGVHD were treated with systemic steroids for rapid progression of skin rash despite topical therapy with triamcinolone cream. Clinical characteristics of the cohort are outlined in Table 1. The median time to aGVHD and initiation of steroid therapy after HCT was 24 days (range, 7-56) and 28 days (range, 7-91), respectively. Skin only, gut only, and multi-organ aGVHD affected 7 (16%), 19 (43%), and 18 (41%) patients, respectively.

aGVHD Treatment Response

Day 28 response to steroids was CR [N=14 (32%)], VGPR [N= 7 (16%)], PR [N= 17 (39%)], and NR [N= 6 (13%)]. The probability of achieving 6 m FFTF was 61% (95% CI, 0.46-0.76) for the entire cohort. Thus, 38 (87%) patients responded (CR+VGPR+PR) to treatment by day 28 after steroid initiation, but only 28 (64%) patients met the 6 m FFTF endpoint. The causes for treatment failure are described in Figure 1. cGVHD developed in 11 (25%) patients during the first 6 months of treatment but only 1 of these individuals had a failure event censored for cGVHD diagnosis prior to IST change. The most common indication for 6 month treatment failure was the addition of new IST (11 out of 16 treatment failure events), occurring at a median of 37 days (range, 4-160) after starting steroids. Indications for adding second line-therapy were progressive aGVHD after 3 days of high dose steroids (N= 3), no response after 7 days of high dose steroids (N= 1), or aGVHD flare while on steroids and after initial response to treatment (N= 7). Among patients with changes in systemic IST, 7 had initially responded to treatment by day 28 but had recurrent aGVHD symptoms during the steroid taper. Specifically, 3 patients had a flare of aGVHD > 100 days after the start of steroids, requiring second line therapy. The type and number of second-line agents used to treat aGVHD after steroid failure varied and therapies included: ECP (N= 8), TNF-α blockade (N= 4), and rituximab (N= 3). The remaining steroid failure events were not associated with changes in IST and were attributed to 4 patients with malignancy relapse and 1 patient death while in remission (Figure 1).

As expected day 28 NR was significantly associated with treatment failure at 6 months (P= 0.01) (Table 1). In addition, grade 3-4 aGVHD tended to be more common in patients categorized as 6 month treatment failures [7 out of 16 patients (44%)] as compared to HCT recipients with 6 m FFTF [5 out of 28 individuals (18%)] (P= 0.06). No other clinical variables outlined in Table 1 were associated with 6 m FFTF.

Survival

The median follow-up for surviving patients (N= 29) was 3 years (range, 0.5-4 y). Death from relapse and NRM occurred in 8 (18%) and 7 (16%) individuals, respectively. Causes of NRM included: infection (N= 2), bronchiolitis obliterans (N= 2), aGVHD (N= 1), diffuse alveolar hemorrhage (N= 1), and secondary malignancy (N= 1). Transplant outcomes were improved in patients responding to steroids (CR+VGPR+PR) when compared to those with NR at day 28 [2 y OS of 75% (95% CI, 0.58-0.86) vs. 22% (95% CI, 0.01-0.62) P= 0.02 and 2 y NRM of 11% (95% CI, 0.04-0.30) vs. 73% (95% CI, 0.31-0.99) (P= 0.01)]. FFTF at 6 months was associated with superior 2 y OS [81% (95% CI, 0.61-0.92) vs. 48% (95% CI, 0.22-0.70) P= 0.03] and decreased NRM [8% (95% CI, 0.02-0.29) vs. 49% (95% CI, 0.22-0.84) (P= 0.01)] when compared to individuals failing steroids by 6 months (Figure 2). To replicate a therapeutic aGVHD clinical trial, analyses were repeated using only patients with grade 2-4 aGVHD (N= 42). Results were unchanged after excluding the 2 individuals with grade 1 aGVHD with a 2 y OS of 85% (95% CI, 0.71-0.99) vs. 48% (95% CI, 0.22-0.73) (P= 0.03) and 2 y NRM of 8% (95% CI, 0.03-0.19) vs. 49% (95% CI, 0.14-0.84) (P= 0.02) for HCT recipients with FFTF contrasted with those with failure at 6 months, respectively. To minimize heterogeneity, a subset analysis was also performed using only patients with related donors (N= 23). All of these transplants were HLA identical and all patients received mobilized peripheral blood stem cells except 1 individual. Among patients with match related donors, OS at 2 y was 80% (95% CI, 0.60-0.99) for those with FFTF at 6 months and 38% (95% CI, 0.04-0.72) for treatment failures (P= 0.04), similar to the results using the entire cohort.

Prolonged exposure to high dose corticosteroids can have detrimental health outcomes. Therefore we modified the original ASBMT criteria for 6 m FFTF to include 10 additional patients who had an increase in steroid dosage within 6 months of starting initial treatment or who had steroid doses ≥ 0.25 mg/kg 180 days after beginning treatment but this did not improve the predictive power of the endpoint [OS (P=0.17) or NRM (P=0.23)].

Multivariate Analysis

After adjusting for important clinical variables including recipient age, disease risk, conditioning regimen intensity, donor type, and stem cell source, the 6 month FFTF continued to be associated with improved OS (HR, 0.27; 95% CI, 0.08 to 0.85; P= 0.03) and decreased NRM (HR, 0.02; 95% CI, 0.01 to 0.39; P= 0.01) (Table 2).

Discussion

We studied the 6 m FFTF as recently proposed by Martin and colleagues as a potential clinical trial endpoint for determining aGVHD treatment success. [1, 6] The 6 m FFTF was

found to be an important marker of therapeutic efficacy which was associated with both improved OS and decreased NRM in patients receiving T cell replete transplants. The primary implication of this endpoint is that the necessity of changing aGVHD therapy results from suboptimal response to initial treatment which ultimately increases the risk for adverse outcomes. It also takes into account that most deaths related to uncontrolled aGVHD or from infections due to excessive immunosuppression occur within 6 months and that longer follow up may be confounded by recurrent malignancy or cGVHD.[6] The advantage to this endpoint is its inherent reduction of subjectivity by assessing fixed outcomes including: death, relapse, or change in systemic IST within 6 months of steroid initiation and prior to the development of cGVHD.

To investigate whether expanding the 6 m FFTF definition could further enhance the prediction of outcomes, we added the following endpoints: 1) any increase in steroids within 180 days, or 2) a steroid dose ≥ 0.25 mg/kg/day at 180 days after initiation of therapy as additional markers of treatment failure. In our limited sample size, these supplementary endpoints were not statistically significant. However, there may be value in studying this expanded definition of 6 month steroid failure in a larger cohort of patients.

Our study also showed that day 28 response predicted treatment failure at 6 months as defined by the ASBMT criteria. Levine *et. al.* first examined whether response to aGVHD treatment predicted outcomes by analyzing time to response at days 14, 28, and 56 in a phase II trial that consisted of initial therapy with high dose steroids plus a second immunosuppressive agent. While all 3 response time-points showed utility in predicting outcomes, they particularly identified that day 28 CR or PR was most predictive of OS and NRM after 9 months from initiation of treatment. [5] Day 28 response to initial steroid therapy has been further studied by MacMillan *et. al.*[2] and Saliba *et. al.*[4], and their results suggest that the day 28 response is also likely the best early endpoint. Our data is consistent with these studies in that OS and cumulative incidence of NRM at 2 years was significantly improved in steroid responders at day 28 (CR+VGPR+PR) when compared to those with NR.

For aGVHD, day 28 response may be inadequate to fully measure treatment efficacy, specifically in a clinical trial setting. A major limitation of this endpoint is its dependence on accurately measuring clinical response to aGVHD treatment which is subject to inter-observer variation. Furthermore, response to aGVHD treatment is usually based on measuring clinical variables including: body surface area involved by rash, volume of diarrhea, and liver function tests. These parameters can be affected by a variety of other etiologies unrelated to alloreactivity such as medications, and thus confound the aGVHD response assessment. The advantage to the 6 m FFTF is that it assesses fixed endpoints and is therefore less affected by these problems. The composite 6 m FFTF endpoint also evaluates other important clinical outcomes that could be affected by aGVHD therapy including death and relapse which are not directly measured by the day 28 response criteria. It is possible that an extremely effective immunosuppressant which induces high rates of response could be associated with undesirable consequences including increased risk for fatal infections or increased incidence of relapses due to impaired graft-versus-leukemia

effect. Clinical trials will need to account for both the positive and negative outcomes associated with therapy that effectively suppresses aGVHD.

This present study is limited by patient heterogeneity and a small sample size. As with previous aGVHD trials, other parameters such as variability in initial steroid doses, duration of therapy, and steroid tapering schedules are confounding issues that are difficult to account for. On the other hand, this was a prospective clinical trial with weekly blinded assessment of aGVHD parameters. Despite the modest sample size and heterogeneous cohort, we have shown that the 6 m FFTF predicted survival and confirmed previous data regarding day 28 response indicating that these are robust endpoints even in small cohorts. The predominance of gut aGVHD could suggest under-diagnosis of skin aGVHD, however even if cutaneous involvement was underdiagnosed the clinical significance is questionable since it did not meet threshold for treatment with systemic steroids and therefore should not affect the current analysis. In addition, our results pertain only to patients undergoing T cell replete transplants as individuals receiving manipulated grafts or thymoglobulin were excluded.

aGVHD causes significant morbidity and mortality. Despite this, no therapeutic agent has obtained FDA approval for the treatment of aGVHD. This is due in part to lack of standardized endpoints in aGVHD clinical trials. Therefore, establishing accepted markers of effective aGVHD treatment which also serve as surrogates measures of long-term transplant survival is of paramount significance for aGVHD trials. Our data indicates that 6 m FFTF is associated with day 28 response and both are predictive of transplant outcomes. However 6 m FFTF which assesses fixed outcomes is less affected by the limitations and the variability associated with determining clinical response to aGVHD therapy. If validated, the 6 m FFTF could be used as the primary endpoint in future therapeutic aGVHD trials and subsequently facilitate approval of new therapies for aGVHD treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the National Institutes of Health/National Cancer Institute Grant K12 CA090625, the American Cancer Society–Institutional Research Grant (#IRG-58-009-48) and the Sartain-Lanier Family Foundation.

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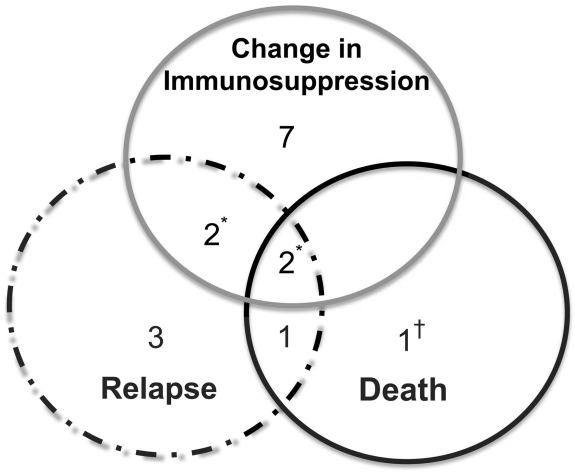

*The addition of immunosuppression preceded relapse.

†Death while in remission was due to aGVHD which occurred after steroid dose escalation.

Figure 1.

Venn diagram showing causes for 6 month treatment failure and their associations with each other in patients with aGVHD treated with systemic corticosteroids (N= 16).

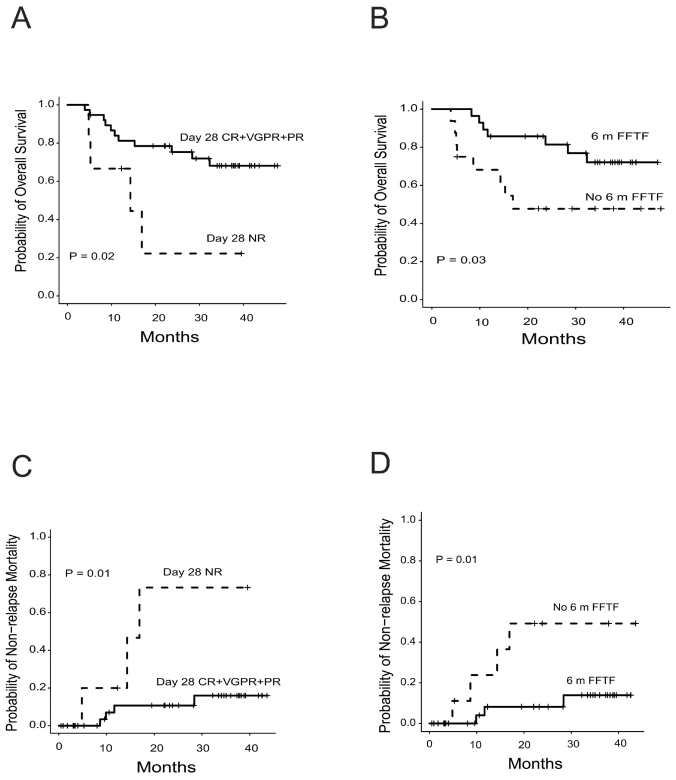

Figure 2. Clinical outcomes stratified by day 28 response and 6 month freedom from treatment failure (6 m FFTF) in patients with aGVHD requiring systemic corticosteroids

Probabilities of overall survival based on day 28 response (A) and 6 m FFTF (B). Cumulative incidence of non-relapse mortality based on day 28 response (C) and 6 m FFTF (D). All graphs were calculated from the start of corticosteroids.

Table 1

Clinical and transplant characteristics of 44 patients with aGVHD requiring systemic corticosteroids, stratified by 6 month treatment failure (percentage)

	6 Month Responders	6 Month Treatment Failures
Number	28	16
Age		
Median	46	42
Range	27-65	21-70
Gender		
Male	12 (43)	6 (38)
Female	16 (57)	10 (62)
Diagnosis		
Acute leukemias, MDS	13 (46)	7 (44)
CML + MPD	3 (11)	0
NHL + HL + MM + CLL	8 (29)	4 (25)
Other	4 (14)	5 (31)
Disease Risk*		
Standard	17 (61)	8 (50)
High	11 (39)	8 (50)
Conditioning Regimen		
Reduced Intensity	9 (32)	5 (31)
Myeloablative	19 (68)	11 (69)
Donor		
Related	15 (54)	8 (50)
Unrelated	13 (46)	8 (50)
Stem Cell Source		
Peripheral Blood	18 (64)	10 (63)
Other	10 (36)	6 (37)
HLA		
Matched	24 (86)	14 (88)
Mismatched	4 (14)	2 (12)
Donor/Recipient Sex		
Female to male	3 (11)	0
Other	25 (89)	16 (100)
$CD34^+$, × 10^6/kg	5.89	5.85
Median	0.04-10.1	0.09-9.81
Range		
aGVHD prophylaxis		
CSA + Methotrexate	17 (61)	9 (56)
CSA + MMF	11 (39)	7 (44)
aGVHD grade		
Grade 1	2 (7)	0

	6 Month Responders	6 Month Treatment Failures
Grade 2	21(75)	9 (56)
Grade 3-4	5(18)	7 (44)
aGVHD organ involvement		
Skin only		
Gut only	4 (14)	3 (19)
Multi-organ	13 (47)	6 (37)
	11 (39)	7 (44)
aGVHD day 28 response		
CR †	12 (43)	2 (12)
VGPR	4 (14)	3 (19)
PR	10 (36)	7 (44)
NR	2 (7)	4 (25)

aGVHD, acute graft-versus-host disease; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; MPD, myeloproliferative disorder; NHL, Non-Hodgkin lymphoma; HL, Hodgkin's Lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; CSA, cyclosporine; MMF, mycophenolate mofetil; CR, complete response; VGPR, very good partial response; PR, partial response; NR, no response

*Standard risk disease is defined by acute leukemia in CR1 or 2, CML in chronic phase 1, MDS without excess blasts. All others were considered high-risk disease

†Two patients met study criteria for 6 month steroid response but were categorized as NR at day 28 due to steroid escalation in 1 patient and the addition of psoralen with ultraviolet A therapy (PUVA) in the other individual

Table 2

Cox proportional hazard regression models for overall survival and non-relapse mortality

	Overall Survival			Non-relapse Mortality		
Prognostic Factor	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
6 m FFTF	0.27	0.08 - 0.85	0.03	0.02	0.01 - 0.39	0.01
Age	1.04	0.97 - 1.11	0.29	0.98	0.89 - 1.08	0.67
High risk disease	1.47	0.45 - 4.74	0.52	2.01	0.38 - 10.75	0.41
Ablative conditioning	1.82	0.28 - 12.07	0.54	17.51	0.58 - 530	0.10
Related donor	7.58	0.90 - 63.75	0.06	12.43	0.54 - 289	0.12
Peripheral blood graft	0.22	0.03 - 1.88	0.17	0.10	0.01 - 2.09	0.14

HR, hazard ratio; CI, confidence interval; 6 m FFTF, 6 month freedom from treatment failure.