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Outcomes and Predictors of Response in Steroid-Refractory Acute Graft-versus-Host Disease

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The prognosis of steroid-refractory acute graft-versus-host disease (aGVHD) is poor, and predictors of response and survival are unclear. In an exploratory analysis of 203 steroid-refractory aGVHD patients with prospectively collected GVHD data who received antithymocyte globulin, etanercept, or mycophenolate mofetil (MMF) as second-line treatment, we determined the predictors of day 28 response, 2-year overall survival, and 2-year nonrelapse mortality (NRM). To minimize the risk of finding false-positive results, we used least absolute shrinkage and selection operator regression, aggressively eliminating variables that are unlikely to be associated with outcome. Day 28 response to second-line therapy was 38% (complete response, 23%), with a 2-year overall survival of 25% and a 2-year NRM of 62%. Factors associated with response were GVHD prophylaxis, organ involvement, and initial aGVHD to steroid-refractory aGVHD interval. Specifically, compared with cyclosporine/MMF as GVHD prophylaxis, the odds ratio (OR) for calcineurin inhibitor/methotrexate was .8 and for cyclosporine/prednisone .6. The OR for aGVHD to steroid-refractory aGVHD interval $\geq$ 14 versus $<$14 days was 1.3. The ORs for skin only involvement and gut or liver only involvement when compared with multiorgan involvement were 1.4 and 1.2, respectively. The only variable associated with worse survival was age, with a hazard ratio (HR) per decade of 1.04 for overall mortality. Similarly, age was the only variable associated with NRM (HR per decade, 1.02). When compared with complete response, no response at day 28 increased the risk of death (HR, 2.4; 95% confidence interval, 1.5 to 3.7). In conclusion, by means of an underused statistical technique in the field of transplantation, we identified predictors of response and survival in steroid-refractory aGVHD. Our results highlight the importance of developing novel treatment strategies because current treatments yield poor outcomes.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation [1]. High-dose steroids are the mainstay of frontline therapy for aGVHD, and the addition of other agents in this setting has not improved outcomes [2,3]. Steroid-refractory aGVHD has a dismal prognosis, and most patients succumb to organ failure or infection after a few months [4–6]. Using our prospectively collected, regularly updated, and strictly curated bone marrow transplantation database at the University of Minnesota, we asked the following questions in patients with steroid-refractory aGVHD: What are the outcomes of steroid-refractory aGVHD? What baseline patient-, disease-, transplant-, and aGVHD-related characteristics are associated with steroid-refractory aGVHD outcomes? Is steroid-refractory aGVHD response to second-line therapy associated with better overall survival (OS)?

METHODS

Data from all first allogeneic hematopoietic cell transplant recipients at the University of Minnesota (1990 to 2016) who developed aGVHD were reviewed. aGVHD was graded by the Minnesota grading system, which uses standard clinical criteria derived from organ staging [7] modified to include upper gastrointestinal aGVHD per the GVHD consensus conference [8–10]. All patients received prednisone 60 mg/m^2/day or methylprednisolone equivalent (divided in 3 doses) for 7 consecutive days, followed by daily prednisone for 7 days as initial therapy for aGVHD. Patients were maintained on therapeutic levels of cyclosporine (CsA), tacrolimus, or sirolimus. Additionally, patients with skin acute GVHD were treated with topical .1% triamcinolone cream or 1% hydrocortisone cream (for facial rash) 3 time daily. If a response to prednisone was observed, patients continued therapy with oral prednisone 60 mg/m^2/day through day 14 and then commenced a taper of steroids over 8 weeks [3,11]. Response to therapy was recorded weekly in the University of Minnesota Bone Marrow Transplant Database. All GVHD data were retrospectively reviewed and adjudicated by 4 authors (M.L.M., D.J.W., S.G.H., and A.R.).

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Progression was defined as worsening GVHD in at least 1 organ within 28 days. Steroid-refractory aGVHD was defined as progression of aGVHD after 3 days of the initial treatment, no improvement after 7 days, or requirement for second-line treatment at any point during or after completion of steroid taper. Continuation and dosage of steroids after the diagnosis of steroid-refractory aGVHD was at the discretion of the treating physicians. We considered steroid-refractory aGVHD responsive to therapy at day 28 ± days if the patient was alive, had improvement in GVHD stage in at least 1 organ, and no worsening in other organs. Ten patients started steroid-refractory aGVHD therapy before day 3 of initial GVHD therapy; another 96 patients received steroid boosts alone, sirolimus alone, tacrolimus alone, or experimental agents. These 106 patients were not included in the final data set. The remaining patients were selected for analysis. These patients received 1 of the 3 most commonly used treatments during the study period: antithymocyte globulin (ATG; equine, 30 mg/kg/day given either in divided b.i.d. doses or once daily for 5 days) [6], etanercept (25 mg twice weekly for 4 weeks), or mycophenolate mofetil (MMF).

The primary objective of this study was to study the clinical predictors of day 28 overall response, 2-year OS, and 2-year nonrelapse mortality (NRM) after second-line therapy without emphasis on any formal comparisons between second-line therapies. Data were prospectively collected but retrospectively reviewed. Response was estimated with simple proportions, survival by Kaplan-Meier curves, and NRM by cumulative incidence, treating relapse as a competing risk. Following the recommendations of the American Statistical Association, we reported confidence intervals (CIs) around our point estimates to show precision without focusing on whether or not the intervals included a specific value such as 1.0 [12]. Because this analysis was exploratory in nature and we had many potential predictors for outcomes, we performed least absolute shrinkage and selection operator (lasso) [13] regression (logistic for day 28 response and Cox for OS and NRM) rather than standard regression. Standard regression in such cases often results in model overfitting and/or spurious findings that may not be replicable in independent cohorts. The goal of lasso regression is to select only a subset (typically small) of covariates in the final model by aggressively eliminating other variables that are unlikely to be associated with the dependent variable. Lasso achieves the subset of the most influential predictors by forcing the sum of the absolute value of the regression coefficients to be less than a fixed value. This process forces the regression coefficient of certain variables to "shrink" to zero, thereby achieving a simple model with only a few likely correlates of the dependent variable among all covariates. Lasso regression is frequently used for the analysis of high-throughput datasets. Lasso was implemented using the R package (R Foundation for Statistical Computing, Vienna, Austria) glmnet. Ten-fold cross-validation was used to estimate the optimal lasso constraint parameter that minimized prediction error (mean squared error for logistic regression and partial likelihood for Cox regression).

We included the following variables in lasso regression: aGVHD grade and Minnesota risk (standard versus high risk) [14,15] at the initial diagnosis of aGVHD and steroid-refractory aGVHD, patient age (per increase by decade), patient gender (male versus female), donor type (matched sibling versus unrelated donor versus umbilical cord blood), underlying disease (acute leukemia versus other malignancies versus nonmalignant disorders), GVHD prophylaxis (CsA plus MMF versus calcineurin inhibitor plus methotrexate versus ex vivo T cell depletion versus others), hematopoietic cell transplant to initial aGVHD interval (continuous), initial aGVHD to steroid-refractory aGVHD interval (<14 versus ≥14 days), steroid-refractory aGVHD organ involvement (multiple organs versus skin only versus gut or liver only), steroid-refractory aGVHD treatment (ATG versus etanercept versus MMF), transplant year (5-year intervals), and conditioning intensity (myeloablative without total body irradiation versus total body irradiation–based myeloablative versus reduced intensity). Graft source was not included because of its collinearity with donor type.

After identifying the most important predictors of OS and NRM, a subsequent objective was to evaluate whether day 28 response was associated with OS and NRM. Cox regression used landmark analysis (excluding deaths before day 28 for OS and a few relapses before day 28 for NRM) with mortality measured from day 28 of steroid-refractory aGVHD therapy. We used SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 for all analyses.

RESULTS

Two hundred three patients met the eligibility criteria and were included in the analysis (Table 1). Baseline characteristics of this group were similar to the 106 excluded patients (59% male, median age, 40 years [range, 1 to 75], 43% before year 2000, 45% acute leukemia, 15% nonmalignant). Organ stages at the time of initial diagnosis and steroid refractoriness are shown in Supplementary Table S1. As expected, stages 3 to 4 lower gut aGVHD was more common at the time of diagnosis of steroid-refractory aGVHD (38%) than initial aGVHD diagnosis (19%).

Outcomes of Steroid-Refractory aGVHD

Day 28 response after the initiation of therapy for steroid-refractory aGVHD was complete response (CR) in 47 patients (23%; 95% CI, 18% to 30%), partial response (PR) in 31 (15%; 95% CI, 11% to 21%), no response (NR) in 88 (43%; 95% CI, 36% to 51%), and death by day 28 in 37 patients (18%) who were treated as nonresponders. At 2 years after the diagnosis of steroid-refractory aGVHD, OS was 25% (95% CI, 20% to 32%) and NRM 65% (95% CI, 56% to 73%). The most common cause of death was steroid-refractory aGVHD (69% of deaths), followed by relapse of the underlying malignancy (18%). Seventy percent of patients dying of aGVHD had infection identified as a secondary cause of death.

Factors Associated with Steroid-Refractory aGVHD Outcomes

Variables associated with day 28 response were GVHD prophylaxis (odds ratio [OR] was .8 for calcineurin inhibitor/methotrexate, .6 for CsA/prednisone±ATG/other, and 1.0 for T cell depletion compared with the reference of CsA/MMF), initial aGVHD to steroid-refractory aGVHD interval (OR for ≥14 versus <14 days, 1.3), and organ involvement (OR for skin only, 1.4; OR for gut/liver only compared with multiorgan involvement, 1.2). The coefficients for all other factors shrank to 0 in lasso regression. The only variable associated with OS after steroid-refractory aGVHD was age, with a hazard ratio (HR) per decade of 1.04 for overall mortality. Similarly, age was the only variable associated with NRM (HR per decade, 1.02).

The results of conventional regression analyses are shown in Supplementary Table S2. GVHD prophylaxis regimen (with CsA/MMF being the best) and steroid-refractory aGVHD organ involvement (with multiple organ involvement being the worst) but not initial aGVHD to steroid-refractory aGVHD interval were associated with day 28 response in conventional regression. In contrast to lasso regression, umbilical cord blood was associated with a worse day 28 response than matched sibling donor in conventional regression (OR, .2; 95% CI, .4 to .7). Similar to lasso regression, age was associated with overall mortality and NRM in conventional regression. In contrast to lasso regression, transplant year between 2010 and 2016 was associated with higher overall mortality (HR, 2.5; 95% CI, 1.2 to 5.4) and NRM (HR, 3.3; 95% CI, 1.5 to 7.4) in conventional regression.

Relationship between Day 28 Response and Mortality

Two-year OS after steroid-refractory aGVHD was highest among patients with day 28 CR (45%, 95% CI, 30% to 58%), followed by those with a PR (35%; 95% CI, 19% to 52%) and NR (21%; 95% CI, 13% to 30%) (Figure 1A). Day 28 response and age (per decade, as the only variable associated with OS in lasso regression) were included in a regression model for OS (Table 2). In this analysis every decade increase in age was associated with a 10% increase in the risk of death. Overall, NR at day 28 more than doubled the risk of death (HR, 2.4; 95% CI, 1.5 to 3.7) compared with CR. This association was independent of age. Overall, the association between day 28 PR and mortality did not appear to be clinically important (compared with CR; HR, 1.1; 95% CI, .6 to 1.9). However, examination of survival curves in Figure 1A suggested a more apparent difference between CR and PR patients beyond 1 year, although the group sizes in the 1-year responders were modest (24 with CR and 14 with PR). Among the 3 late deaths in the CR group, 2 were after relapse and 1 after a GVHD flare. Among the 4 late deaths in the PR group, 3 were after a GVHD flare and 1 was infection related.

Two-year NRM after steroid-refractory aGVHD was lowest among patients with day 28 CR (43%; 95% CI, 28% to 59%),

Table 1
Day 28 Response and 2-Year OS and NRM

Variable	No. of Cases (%) or Median (Range)	Day 28 Response (%)*	2-Year OS (%)*	2-Year NRM(%)*
No. of cases	203	38 (32-46)	25 (25-32)	65 (56-73)
Gender				
Male	132 (65)	40 (32-49)	24 (17-32)	65 (55-76)
Female	71 (35)	35 (24-48)	28 (18-39)	63 (50-77)
Age at transplant, yr	35 (<1-75)			
<18	61 (30)	34 (23-48)	32 (21-44)	61 (47-75)
18-40	66 (33)	36 (25-49)	27 (17-38)	61 (47-75)
>40	76 (37)	43 (32-55)	18 (11-28)	71 (57-85)
Donor type				
Matched sibling	76 (37)	39 (28-51)	29 (19-39)	59 (46-72)
URD WM	26 (13)	38 (20-59)	14 (4-30)	82 (60-100)
URD PM	21 (10)	33 (15-57)	19 (6-38)	76 (52-100)
URD MM	34 (17)	32 (17-51)	32 (18-48)	59 (40-78)
UCB	46 (23)	43 (29-59)	24 (13-37)	63 (46-80)
Graft source				
BM	109 (15)	34 (25-44)	27 (19-36)	63 (51-74)
PB	48 (65)	44 (30-59)	23 (12-35)	69 (52-86)
UCB	46 (23)	43 (29-59)	24 (13-37)	63 (46-80)
Conditioning				
MAC, non-TBI	30 (15)	23 (10-42)	33 (17-50)	64 (44-84)
MAC, TBI	132 (65)	40 (32-49)	26 (19-33)	64 (54-75)
RIC	41 (20)	44 (29-60)	20 (9-33)	66 (48-84)
GVHD prophylaxis				
CsA/MMF	67 (33)	52 (40-64)	25 (16-36)	63 (49-77)
CNI/MTX	79 (39)	34 (24-46)	27 (17-37)	65 (52-78)
T cell depletion	21 (10)	33 (15-57)	17 (4-36)	73 (48-98)
CsA/prednisone ± ATG	18 (9)	28 (10-54)	17 (4-37)	78 (52-100)
Others	18 (9)	22 (6-48)	39 (17-60)	50 (26-74)
Sirolimus/MMF	2			
MTX/ATG/prednisone	12			
ATG	4			
Underlying disease				
Nonmalignant	32 (16)	34 (19-53)	31 (16-47)	69 (49-88)
ALL	30 (15)	47 (28-66)	33 (18-50)	57 (37-77)
AML	47 (23)	40 (26-56)	19 (9-31)	62 (45-78)
Lymphoma/CLL	22 (11)	50 (28-72)	36 (17-56)	50 (28-72)
MDS/MPN	18 (9)	28 (10-54)	17 (4-37)	67 (41-93)
Other malignancy	54 (27)	33 (21-48)	22 (12-34)	75 (51-83)
Treatment of steroid-refractory aGVHD				
ATG	166 (82)	37 (29-45)	24 (18-31)	67 (58-76)
Etanercept	10 (5)	20 (3-56)	30 (7-58)	70 (38-100)
MMF	27 (13)	56 (35-75)	33 (17-51)	48 (28-68)
HCT to initial aGHVD interval, days	30 (8-170)			
<28	82 (40)	33 (23-44)	22 (14-31)	68 (55-81)
≥28	121 (60)	42 (33-52)	28 (20-36)	62 (52-73)
Initial aGVHD to steroid-refractory aGVHD interval, days	11 (3-98)			
<14	113 (56)	34 (25-43)	28 (20-37)	65 (54-76)
≥14	90 (44)	44 (34-55)	22 (14-31)	64 (52-77)
aGVHD grade at initial diagnosis				
I	42 (21)	36 (22-52)	21 (11-35)	67 (49-84)
II	103 (51)	41 (31-51)	25 (17-34)	63 (52-75)
III	50 (25)	38 (25-53)	29 (17-42)	65 (49-81)
IV	8 (4)	25 (3-65)	25 (4-56)	75 (40-100)

(*continued*)

Table 1 (*Continued*)

Variable	No. of Cases (%) or Median (Range)	Day 28 Response (%)*	2-Year OS (%)*	2-Year NRM(%)*
Steroid-refractory aGVHD grade				
I	24 (12)	42 (22-63)	21 (8-39)	58 (35-82)
II	72 (35)	42 (30-54)	29 (19-40)	57 (44-70)
III	77 (38)	35 (25-47)	21 (13-31)	72 (59-85)
IV	30 (15)	37 (20-56)	30 (15-47)	70 (50-90)
MN risk score at initial diagnosis				
Standard	163 (80)	37 (30-45)	23 (17-30)	67 (58-76)
High	40 (20)	43 (27-59)	34 (20-49)	56 (38-73)
MN risk score at the diagnosis of steroid-refractory aGVHD				
Standard	118 (58)	40 (31-49)	26 (19-34)	61 (50-72)
High	85 (42)	36 (26-48)	24 (16-34)	70 (57-82)
Steroid-refractory aGVHD organ involvement				
Multiple organs	80 (39)	28 (18-37)	23 (15-32)	66 (53-79)
Skin only	70 (34)	46 (34-58)	29 (19-39)	59 (45-72)
Liver only	4 (2)	25 (1-81)	0	75 (37-100)
Gut only	49 (24)	47 (33-62)	26 (15-39)	70 (53-87)
Year of transplant				
1990-1994	59 (29)	29 (17-41)	31 (19-42)	59 (44-74)
1995-1999	41 (20)	32 (18-46)	17 (8-30)	73 (55-91)
2000-2004	41 (20)	54 (39-69)	32 (18-46)	56 (39-74)
2005-2009	20 (10)	55 (33-77)	40 (19-60)	40 (18-62)
2010-2016	42 (21)	36 (21-51)	13 (5-25)	85 (66-100)

HLA match definitions were according to published guidelines [24]. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CLL, chronic lymphocytic leukemia; CNI, calcineurin inhibitor; HCT, hematopoietic cell transplant; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MM, mismatched; MN, Minnesota; MPN, myeloproliferative neoplasm; MTX, methotrexate; PM, partially matched; PB, peripheral blood; RIC, reduced-intensity conditioning; TBI, total body irradiation; URD, unrelated donor; WM, well matched; HLA match definitions were according to published guidelines.

* Values in parentheses are 95% CIs.

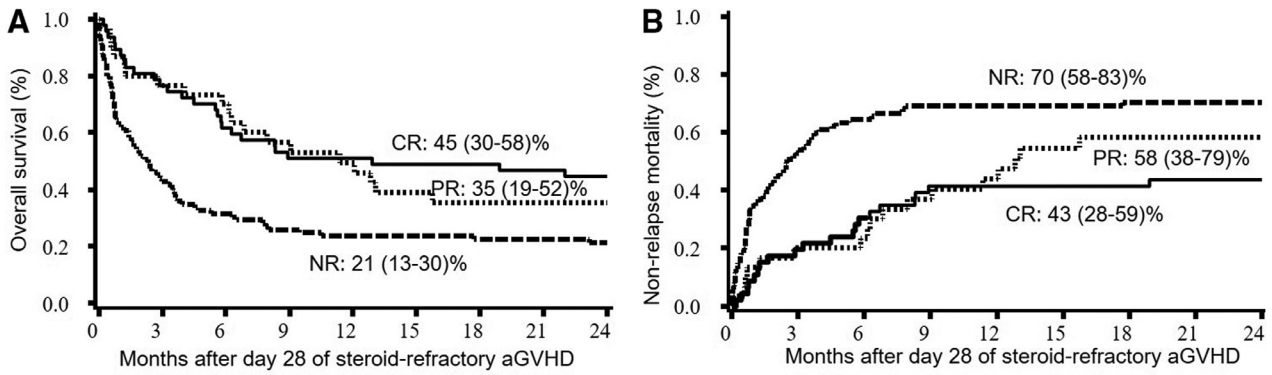

Figure 1. Two-year OS and NRM by day 28 response. Patients with a CR at day 28 of steroid-refractory aGVHD had similar 1-year but better 2-year OS (A) and NRM (B) compared with those with a PR or NR. Patients with NR did the worst.

Table 2
Landmark Cox Regression Analysis of Survival

Factor	No. of Cases	HR for Overall Mortality (95% CI)	No. of Cases	HR for Nonrelapse Mortality (95% CI)
Day 28 response				
CR	47	1.0 (reference)	46	1.0 (reference)
PR	30	1.1 (.6-1.9)	30	1.3 (.7-2.3)
NR	89	2.4 (1.5-3.7)	87	2.5 (1.5-4.1)
Age (per decade)		1.1 (1.0-1.2)		1.07 (.96-1.20)

followed by those with a PR (58%; 95% CI, 38% to 79%) and NR (70%; 95% CI, 58% to 83%) (Figure 1B). Day 28 response and age (per decade, as the only variable associated with NRM in lasso regression) were included in a regression model for NRM (Table 2). Overall, NR at day 28 more than doubled the risk of nonrelapse death (HR, 2.5; 95% CI, 1.5 to 4.1) compared with CR. This association was independent of age. Overall, the association between day 28 PR and mortality did not appear to be clinically important (compared with CR; HR, 1.3; 95% CI, .7 to 2.3). However, examination of the cumulative curves in Figure 1B suggested a more apparent difference between CR and PR patients beyond 1 year.

DISCUSSION

In a large cohort of steroid-refractory aGVHD patients with prospective and consistent GVHD scoring, we observed a 38% day 28 overall response (23% CR). This disappointing response rate, although consistent with prior reports [5,6,16], highlights the shortcomings of current therapies and the importance of novel therapeutics. Over the study period we used ATG as the drug of choice for steroid-refractory aGVHD when a clinical trial was not available. The poor response rates in steroid-refractory aGVHD are partly due to the high frequency of lower gut involvement in steroid-refractory aGVHD, 38% in this analysis. As expected [5,17,18], steroid-refractory aGVHD was highly fatal, with only one-fourth of patients surviving 2 years after diagnosis.

Our study was novel in the approach we adopted from bioinformatics when the presence of many potential predictors increases the likelihood of finding false-positive results. Lasso regression is a more conservative approach than conventional regression in that it more aggressively eliminates variables that are unlikely to be associated with outcome. This approach is particularly valuable in exploratory analyses like this study with no a priori hypotheses. Lasso regression identifies variables that are most likely to be associated with outcome to suggest future hypothesis-driven analyses using those variables. Lasso does not produce *P* values or CIs, making it suitable for exploratory analysis without overemphasizing false leads. In our analyses conventional regression overall resulted in more complex models including more variables associated with outcome.

Although day 28 response in our series seemed to depend on the choice of treatment in univariate analysis, with MMF yielding the highest response (56%) and etanercept the lowest response (20%), CIs were large and the associations did not hold in lasso regression. The largest previous study (n = 58) of etanercept in steroid-refractory aGVHD reported a response rate of 38% at day 28 [16]. However, the extent of organ involvement was, as expected [5,16,19], associated with day 28 response. Patients with only skin involvement had the best response rate, followed by those with only gut or liver involvement, followed by those with multiorgan disease. Our analysis suggests that response to steroid-refractory aGVHD may also depend on the GVHD prophylactic regimen used after transplant. This observation is worthy of further investigation in other cohorts because the GVHD prophylaxis regimens used at our institution are associated with graft source and conditioning intensity. We also found that a shorter interval ($<$14 days) between the initial diagnosis of aGVHD and steroid-refractory aGVHD predicts poor response. Patients with a combination of all high-risk features (CsA/prednisone $\pm$ ATG as GVHD prophylaxis, multiorgan involvement, and initial aGVHD to steroid-refractory aGVHD interval $<$ 14 days) had a day 28 response rate of 29%, whereas those with a combination of all low-risk features (CsA/MMF as GVHD prophylaxis, skin only steroid-refractory aGVHD, and initial aGVHD to steroid-refractory aGVHD interval $\geq$ 14 days) had a day 28 response rate of 71%.

We found that age and day 28 response were the only variables associated with OS. Each additional decade of age increased the risk of death by about 5% to 10%. Age was associated with OS in some previous reports [20,21]. The relationship with age and poor OS may be related to cumulative comorbidities or worsening physiologic reserves because of the aging process. NR at day 28 more than doubled the risk of death compared with CR, consistent with previous reports [19].

In conclusion, we applied an underused statistical tool to identify the most likely correlates of steroid-refractory aGVHD treatment outcomes among many potential variables. We found that multiorgan involvement, short interval between initial and steroid-refractory aGVHD, and GVHD prophylactic regimens other than CsA/MMF were associated with poor response, whereas older age and poor response predicted higher mortality. The group at highest risk for poor response and/or mortality was elderly patients developing multiorgan steroid-refractory aGVHD within 2 weeks of the initial diagnosis of GVHD. We considered the 3 most commonly used agents for the treatment of steroid-refractory aGVHD in the study period. Future studies with other therapeutic agents would be valuable to assess the generalizability of our results. Most importantly, this analysis further emphasizes the disappointing results from current steroid-refractory aGVHD treatments and the need for novel therapeutics. Several such therapies are being tested in clinical trials [22,23].

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.07.017.

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