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blood advances

Steroid-dependent acute GVHD after allogeneic hematopoietic cell transplantation: risk factors and clinical outcomes

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Key Points

- Steroid-sensitive and steroid-dependent acute GVHD groups have similar risks of overall and nonrelapse mortality.
- Steroid-dependent acute GVHD does not have an intermediate prognosis between the steroid-sensitive and -resistant groups.

Acute graft-versus-host disease (aGVHD) has various risk factors and outcomes. We defined distinct aGVHD treatment response groups based on response to first-line corticosteroids: steroid sensitive (SS), steroid resistant (SR), and the rarely studied steroid dependent (SD) aGVHD. In 1143 consecutive adult and pediatric allogeneic hematopoietic cell transplant recipients, 385 (34%) developed aGVHD, with 10% having SS aGVHD, 9% SD aGVHD, and 14% SR aGVHD. The only factor significantly associated with SD in comparison with SS was older age (odds ratio [OR], 3.9; 95% confidence interval [CI], 1.4-11.3, when comparing 18- to 60-year-olds with <18-year-olds). Factors significantly associated with SR in comparison with SS were unrelated donor (OR, 3.0; 95% CI, 1.2-7.4) and Minnesota high-risk aGVHD (OR, 2.4; 95% CI, 1.3-4.6). SR aGVHD was independently associated with higher risk for 2-year overall mortality (hazards ratio [HR], 1.8; 95% CI, 1.2-2.8) and nonrelapse mortality (NRM; HR, 2.1; 95% CI, 1.2-3.9). SS and SD GVHD groups had similar overall survival and NRM. The cumulative incidence of chronic GVHD was highest in the SD group, followed by the SR and SS groups (46%, 41%, and 29%, respectively). SD and SS GVHD had similar prognoses, both markedly better than those of the SR groups.

Introduction

Graft-versus-host disease (GVHD) remains the major cause of nonrelapse mortality (NRM) and morbidity after allogeneic hematopoietic cell transplantation (HCT). However, the response to corticosteroids or other treatments can extend survival and control recurrence of malignant disease through the associated graft-versus-tumor effect.[1-3] It is known that steroid-resistant (SR) acute GVHD (aGVHD) is associated with high NRM and poor overall survival (OS). However, a distinct group with steroid-dependent (SD) GVHD, in whom steroid tapering is difficult or leads to a flare of GVHD symptomatology, has an uncertain prognosis and outcome. Characterization and better understanding of this often clinically encountered group may better inform prognosis and preferred management strategies. We compared 3 aGVHD treatment response cohorts: SS, SD, and SR aGVHD. To contrast these 3 disease states, we analyzed each group's patient, transplant, and GVHD characteristics and compared outcomes between the cohorts.

Methods

Study design and inclusion criteria

The objective of this retrospective, single-institution, cohort study was to assess the incidence, risk factors, and clinical outcomes of patients with aGVHD who were SS, SD, or SR after initial steroid therapy. The study population included 1143 consecutive adult and pediatric allogeneic HCT recipients from the University of

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Minnesota who underwent HCT for malignant or nonmalignant disorders between 2008 and 2016. Only the first allogeneic transplants were included. Bone marrow (BM), peripheral blood stem cell (PBSC), and umbilical cord blood (UCB) graft sources and all related and unrelated donors (URDs) were included. Recipients received myeloablative (MAC) or reduced-intensity conditioning (RIC) regimens. All GVHD prophylaxis strategies were included. GVHD cases were considered only if systemic steroid treatment was the first-line therapy.

GVHD therapy and response assessment

Per our standard protocol for initial treatment of aGVHD, all patients received initial therapy with oral prednisone at ~2 mg/kg per day for adults or 60 mg/m^2 per day for children (or the intravenous equivalent of methylprednisolone). The initial treatment dose regimen was divided into 3 doses a day for the first 7 days and then a single dose for the next 7 days, with scheduled tapering over the following 8 weeks.[4] Therefore, the tapering schedule was completed within 70 days from the initial treatment. In this analysis, up to 10 additional days (through day 80) were added, to account for variation in scheduling and clinical follow-up assessments.

The response was determined by comparing the initial aGVHD stage and grade in each organ to the best recorded stage and grade at day 28 (±7 standard deviation [SD]) after initiation of corticosteroid treatment. Complete response (CR) was defined as the complete resolution of aGVHD symptoms in all organs without need for secondary GVHD therapy. Partial response (PR) was defined as improvement in GVHD stage in 1 or more initial target organs, without resolution in all organs and without worsening in any other GVHD target organs or the need for secondary GVHD therapy at any time.

aGVHD response group definitions and distribution

SR aGVHD was defined by any of the following: (1) an increase in GVHD stage in any organ or developing in a new organ after 3 days of steroid therapy; (2) no improvement in ≥1 organ after 7 days; (3) GVHD with no CR or PR after 14 days of treatment; (4) development of GVHD in a new organ or progression during tapering while still receiving ≥50% of the starting corticosteroid dose; (5) a need for the addition of any new systemic treatment of aGVHD before day 56; or (6) death before treatment day 80 of GVHD treatment.

SS aGVHD was defined by any of these CR or PR criteria: CR by day 56 of initial therapy, plus both of the following: alive with successful tapering of steroids with complete discontinuation by day 80 of aGVHD treatment and no flare of GVHD requiring any new systemic therapy for aGVHD before the onset of chronic GVHD (cGVHD). A flare of aGVHD controlled with an increase in steroid dose of <25% of the immediately preceding dose between days 56 and 80 after treatment was still considered SS.

SD aGVHD was defined by any of the following: (1) PR by day 56 of initial therapy; (2) SS, but still receiving >10 mg/m^2 per day of prednisone by day 56 (averaged over 2 days and assessed within a ±3-day window from day 56); (3) SS, but still receiving steroids beyond day 80 of aGVHD treatment; or (4) a flare requiring a ≥25% increase in steroid dose without the addition of other new systemic therapy for aGVHD before the onset of cGVHD.

In total, 385 patients developed aGVHD and were reviewed individually to determine their classification as SS (n = 114), SD (n = 103), and SR (n = 168). GVHD was defined based on clinical presentation and supported by biopsy of the involved organ if clinically indicated. Initial staging among patients with aGVHD was defined as the maximum stage noted in each organ 1 to 7 days before the day of initiation of systemic steroids. Of 65 (17%) patients with no staging clearly documented in the 7-day pre-treatment window, the maximum stage for 45 (12%) was recorded within 3 days of treatment and, for the remaining 20 (5%), within 7 days of initial treatment.

Patient and transplant characteristics

The clinical factors examined as potential covariates included sex, age, year of HCT (2008-2011 or 2012-2016), prior autologous

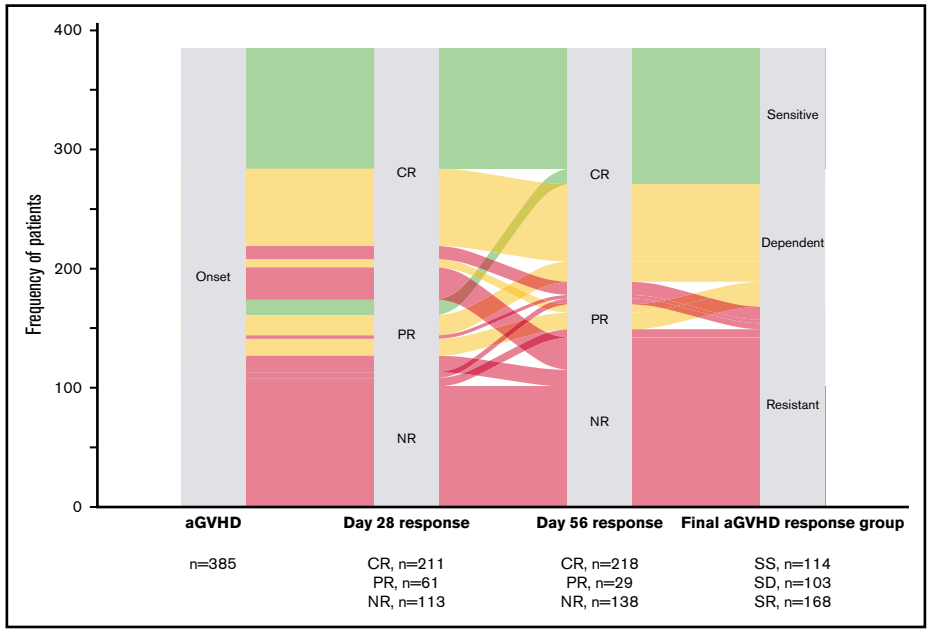

Figure 1. A Sankey plot of patients with aGVHD stratified by response at days 28 and 56 and final response group classification. Green, SS; yellow, SD; red, SR. This plot graphically displays the response distribution and transition between response groups. CR, PR, and NR (no response) at days 28 and 56 and final response group classification into SS, SD, and SR aGVHD.

Table 1. Frequency of aGVHD response groups by demographic subset of patients with aGVHD

Factor	n	Frequency		
		Sensitive aGVHD	Dependent aGVHD	Resistant aGVHD
Overall	385	114 (30)	103 (27)	168 (43)
Sex				
Male	242	71 (29)	65 (27)	106 (44)
Female	143	43 (30)	38 (27)	62 (43)
Age, y				
<18	67	28 (42)	10 (15)	29 (43)
18-40	83	21 (25)	29 (35)	33 (40)
41-60	145	42 (29)	45 (31)	58 (40)
61+	48	23 (26)	19 (21)	48 (53)
Year of transplant				
2008-2011	158	45 (28)	49 (31)	64 (41)
2012-2016	227	69 (30)	54 (24)	104 (46)
Donor type				
Sibling match	112	31 (28)	35 (31)	46 (41)
Haploidentical	10	3 (30)	3 (30)	4 (40)
URD*	60	11 (18)	10 (17)	39 (65)
Single/double UCB	203	69 (34)	55 (27)	79 (39)
Prior autologous transplant				
No	357	107 (30)	93 (26)	157 (44)
Yes	28	7 (25)	10 (36)	11 (39)
Pre-transplant conditioning				
MAC	178	55 (31)	50 (28)	73 (41)
RIC	207	59 (29)	53 (26)	95 (46)
GVHD prophylaxis				
CsA/MTX	50	19 (38)	13 (26)	18 (36)
CsA/MMF	290	81 (28)	84 (29)	125 (43)
Sirolimus/MMF	3	0	1 (33)	2 (67)
Other	42	14 (33)	5 (12)	23 (55)
Diagnosis				
Aplastic/Fanconi anemia	11	3 (27)	4 (36)	4 (36)
Other nonmalignant†	29	13 (45)	4 (14)	12 (41)
ALL	68	23 (34)	20 (29)	25 (37)
AML	130	38 (29)	34 (26)	58 (45)
CML/CLL/JCML	34	11 (32)	8 (24)	15 (44)
MDS	42	9 (21)	9 (21)	24 (57)
Myeloproliferative disorder	8	1 (13)	2 (25)	5 (63)
NHL/HL	36	9 (25)	13 (36)	14 (39)
Multiple myeloma	18	4 (22)	7 (39)	7 (39)
Other malignancy	9	3 (33)	2 (22)	4 (44)
DRI				
Low risk	47	14 (30)	14 (30)	19 (40)
Intermediate risk	244	67 (27)	71 (29)	106 (43)
High/very high risk	54	17 (31)	10 (19)	27 (50)
Nonmalignant	40	16 (40)	8 (20)	16 (40)

Frequency data are number of patients (percentage of subgroup), unless otherwise indicated.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CsA, cyclosporine; HL, Hodgkin lymphoma; JCML, juvenile chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MTX, methotrexate; NHL, non-Hodgkin lymphoma.

*Well-matched, partially matched, and mismatched donors.

†Hemoglobinopathy, immune deficiency, storage disorder, and epidermolysis bullosa.

HCT, diagnosis, donor type (matched sibling donor [MSD], matched unrelated donor [URD], partially matched or mismatched URD, haploidentical, or umbilical cord blood [UCB]), conditioning intensity (MAC vs RIC), GVHD prophylaxis (cyclosporine [CsA] with methotrexate, CsA with mycophenolate mofetil [MMF], sirolimus with MMF, and others, including T-cell depletion), disease risk index for malignant disorders (DRI; low, intermediate, or high/very risk or nonmalignant),[5] HCT comorbidity index[6] (HCT-CI; low, risk, or high risk), and Karnofsky performance status (<90 or ≥90).

NRM was defined as death in the absence of disease relapse or progression, accounting for relapse as a competing risk. OS was defined as time from transplantation to death from any cause. All patients or their guardians signed a written informed consent for the use of their medical data in clinical research analysis. This study was reviewed and approved by the University of Minnesota Institutional Review Board.

Statistical analysis

A Sankey diagram was used to graphically display the distribution and transition of patients between response groups from days 28 to 56 in defining the final classification of aGVHD severity.[7] Time to onset of aGVHD was calculated from the date of HCT. The distribution of aGVHD severity among the clinical factors was estimated by using simple proportions. To measure the independent impact of clinical risk factors on the severity of aGVHD, a multinomial logit model was used, treating aGVHD as a categorical nonordinal end point. The odds ratios (ORs) from this model represented independent assessments of factors on SD and SR aGVHD, treating SS aGVHD as the reference category.[8]

When evaluating outcomes, overall survival after day 80 of initial GVHD treatment was estimated by Kaplan-Meier curves.[9] NRM and cGVHD were analyzed by using cumulative incidence, treating relapse, and non-GVHD death as competing risks, respectively.[10] We completed univariate comparisons with the log-rank test or the Gray test for survival and NRM, relapse, or cGVHD, using a landmark analysis in which patients who died before day 80 after aGVHD were excluded. Cox regression was used to assess the independent effect of the type of aGVHD response on 2-year OS.[11] Fine and Gray proportional hazards regression was used to assess the independent effect of the states on NRM, relapse (excluding nonmalignant diseases) and cGVHD.[12] Factors considered in regression models included sex, age (by decade), donor type (MSD vs URD vs haploidentical vs UCB), DRI (low risk vs intermediate risk vs high/very risk vs nonmalignancy), HCT-CI (low risk vs intermediate risk vs high risk), conditioning (MAC vs RIC), and transplant year (2008-2011 vs 2012-2016). The Minnesota (MN) aGVHD risk score (standard risk vs high risk) was also used in assessment of patients with aGVHD.[3] All reported *P*-values were 2 sided. All analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC) and R, version 3.6.3.

Results

Patient and treatment characteristics of the entire study population

Of 1143 patients with HCT, 385 (34%) developed aGVHD requiring systemic corticosteroid therapy and were included in the analysis. Initial aGVHD treatment led to 114 patients (10%) with SS aGVHD, 103 (9%) SD aGVHD, and 168 (14%) SR aGVHD. Of the 385 patients with aGVHD, 78% had MN standard-risk disease at onset and 22% had high-risk disease. aGVHD at onset of treatment was grade 1 (11%), 2 (52%), 3 (31%), and 4 (6%). Figure 1 is a Sankey plot of patients with aGVHD showing the response

Table 1. (continued)

Factor	n	Frequency		
		Sensitive aGVHD	Dependent aGVHD	Resistant aGVHD
HCT-CI				
Low risk	192	59 (31)	54 (28)	79 (41)
Intermediate risk	95	34 (36)	25 (26)	36 (38)
High risk	98	21 (21)	24 (24)	53 (54)
Karnofsky performance status				
<90	61	18 (30)	10 (16)	33 (54)
≥90	324	96 (30)	93 (29)	135 (42)
MN GVHD risk (at onset)				
Standard	301	97 (32)	83 (28)	121 (40)
High	84	17 (20)	20 (24)	47 (56)
GVHD grade (at onset)				
1	42	12 (29)	10 (24)	20 (48)
2	201	70 (35)	59 (29)	72 (36)
3	121	31 (26)	31 (26)	59 (49)
4	21	1 (5)	3 (14)	17 (81)
Length of follow-up among survivors, median mo (range)		31 (6.5-103.6)	34.8 (9.2-99.6)	27 (6.9-101)

Frequency data are number of patients (percentage of subgroup), unless otherwise indicated.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CsA, cyclosporine; HL, Hodgkin lymphoma; JCML, juvenile chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MTX, methotrexate; NHL, non-Hodgkin lymphoma.

*Well-matched, partially matched, and mismatched donors.

†Hemoglobinopathy, immune deficiency, storage disorder, and epidermolysis bullosa.

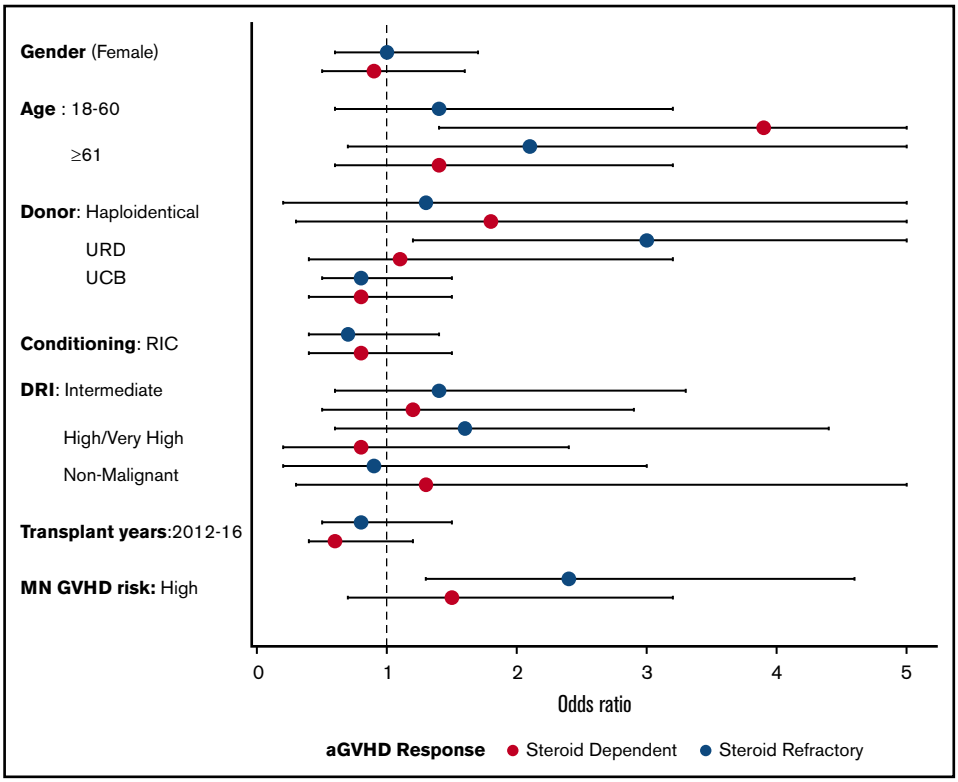

Figure 2. Multinomial logistic regression for acute GVHD state, treating each group as a nonordinal dependent categorical variable. Reference group is patients with SS aGVHD. PM-MM, partially matched–mismatched; WM, well matched.

distribution and transition in the response groups at days 28 and 56 and the final response group classification as SS, SD, and SR aGVHD.

Characteristics of the SS, SD, and SR aGVHD cohorts

Median time to onset of GVHD was similar in all 3 groups: 41 days in the SS group (range, 14-153), 37 days in the SD group (range, 11-166), and 35 days in the SR group (range, 10-170). Demographic and transplant characteristics for each GVHD cohort are shown in Table 1. More patients with high-risk HCT-CI (54%) developed SR aGVHD vs 21% and 24% in the SS and SD groups, respectively. MN high-risk aGVHD was more frequent in the SR group: 56%, compared with only 20% in the SS group and 24% in the SD group. At onset, grade 3 aGVHD led to 49% SR compared with 26% in both the SS and SD groups; grade 4 ended up at 81% in the SR group vs only 14% and 5% in the SD and SS groups, respectively.

Risk factors for aGVHD groups

We examined the independent impact of clinical factors on the severity of aGVHD, treating each of the following groups as a nonordinal, categorical, dependent variable: SS, SD, and SR aGVHD (Table 1). Older age (18-60 vs <18 years; OR, 3.9; 95% confidence interval [CI], 1.4-11.3; $P = .02$) was associated with SD aGVHD. URD (OR, 3.0; 95% CI, 1.2-7.4; $P = .02$) and MN high-risk aGVHD (OR, 2.4; 95% CI, 1.3-4.6; $P < .01$) were each associated with SR aGVHD. From our regression model, Figure 2 shows the comparative independent ORs for factors distinguishing SD and SR vs SS.

Survival, NRM, relapse, and chronic GVHD

Table 2 summarizes the landmark multiple regression analysis of outcomes by aGVHD response group. Within each aGVHD response group, we conducted a landmark analysis starting at day 80 of steroid treatment, the time point when classifications were established with certainty. The 2-year OS was similar in the SS and SD aGVHD groups (68% vs 68%, respectively) and lowest in the SR group at 46% OS ($P < .01$; Figure 3). The 2-year OS among pediatric-only patients in the SS, SD, and SR aGVHD groups were 88% (95% CI, 66-96), 70% (95% CI, 33-89), and 43% (95% CI, 20-64), respectively ($P < .01$). Despite the small samples, the trend to worse OS was also noted in those with nonmalignant disorders: 2-year OS of 91% (95% CI, 51-99), 100%, and 36% (95% CI, 11-63), respectively ($P < .01$), in those developing SS, SD, and SR aGVHD.

Table 2. Landmark Cox regression analysis of outcome by aGVHD response group

		Mortality		cGVHD			NRM		Relapse	
aGVHD response group	n	HR (95% CI)	*P*	HR (95% CI)	*P*	n*	HR (95% CI)	*P*	HR (95% CI)	*P*
Steroid sensitive	113	1.0 (reference)	—	1.0 (reference)	—	97	1.0 (reference)	—	1.0 (reference)	—
Steroid dependent	102	0.9 (0.5-1.5)	.61	1.7 (1.1-2.7)	<.01	94	1.0 (0.5-2.0)	.97	1.1 (0.6-2.1)	.80
Steroid resistant	110	1.8 (1.2-2.8)	.01	1.5 (1.0-2.4)	.06	99	2.2 (1.2-3.9)	.01	0.8 (0.4-1.8)	.84

*Excludes nonmalignant diagnoses.

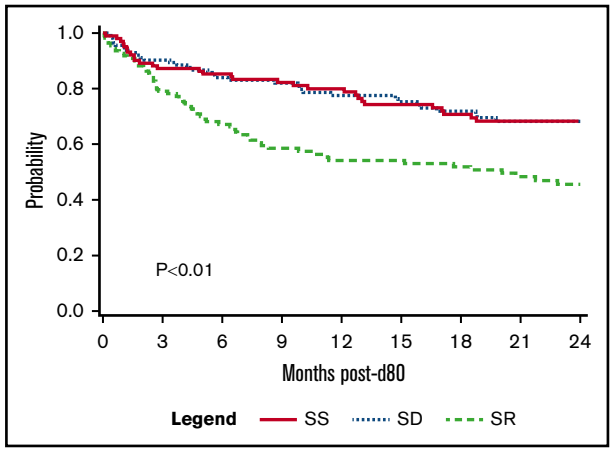

Figure 3. Kaplan-Meier estimates of OS after day 80 of aGVHD treatment initiation. The 2-year OS in the SS, SD, and SR groups were 68% (95% CI, 58-76), 68% (95% CI, 58-77), and 46% (95% CI, 35-55), respectively.

Among patients with malignant disease, 2-year NRM was 40% in the SR group and was significantly higher than that in the SS and SD aGVHD groups (19% and 20%, respectively; $P < .01$; Figure 4A). Relapse risk was similar in all 3 groups (22%, 28%, and 23% in the SS, SD, and SR groups, respectively; $P = .72$; Figure 4B). In a regression analysis, the risk of NRM for SD was similar to that of SS (hazards ratio [HR], 1.0; 95% CI, 0.5-2.0), whereas SR aGVHD was significantly associated with greater NRM (HR, 2.2; 95% CI, 1.2-3.9; $P = .01$) as was high (≥3) HCT-CI (HR, 2.0; 95% CI, 1.2-3.5; $P < .01$).

The cumulative incidence of cGVHD was highest in the SD group, followed by the SR and SS groups (46%, 41%, and 29%, respectively; $P < .01$; Figure 4C). In the regression analysis, the aGVHD response group was independently associated with the risk of cGVHD ($P < .05$), with SD aGVHD associated with more cGVHD than SR aGVHD (HR, 1.7; 95% CI, 1.1-2.7; $P = .02$, vs SS (HR, 1.5; 95% CI, 1.0-2.4; $P = .06$, respectively). This may be related, in part, to a marginally higher competing risk of non-GVHD mortality in the SR group (HR, 1.6; 95% CI, 1.0-2.7; $P = .07$) compared with the SD group (HR, 1.0; 95% CI, 0.5-1.7; $P = .88$) vs SS. Older age was associated with higher risk of cGVHD (HR, 1.17; 95% CI, 1.02-1.35; $P = .03$), whereas RIC (HR, 0.5; 95% CI, 0.3-0.8; $P < .01$), URD (HR, 0.5; 95% CI, 0.3-0.9; $P = .02$), UCB (HR, 0.5; 95% CI, 0.3-0.7; $P < .01$), and higher DRI (intermediate risk [HR 0.6; 95% CI, 0.4-0.9; $P = .01$], for high/very risk [HR, 0.3; 95% CI, 0.1-0.9; $P < .01$], and nonmalignant diagnosis [HR, 0.3; 95% CI, 0.1-0.9; $P = .03$]) were each associated with a lower risk of cGVHD. Malignant disease relapse was a competing risk for development of cGVHD in those with a high or very high DRI (HR, 6.9; 95% CI, 1.4-33.4). cGVHD was infrequent among the pediatric and nonmalignant disorder cohorts, precluding subgroup analysis. Among patients with cGVHD requiring systemic immune suppression, 77% (95% CI, 54-100) had discontinued treatment 3 years after diagnosis in the SS groups compared with 62% (95% CI, 43-82) in the SD group and 38% (95% CI, 21-56) in the SR group ($P = .02$).

Causes of death in the SR group were most often attributed to aGVHD (43%), but not in the SS and SD groups (6% and 13%, respectively). Infection caused death at similar rates in the 3 groups (13% vs 16% vs 16%). Disease relapse was the primary cause of death in the SS group (69%), whereas it accounted for only 47% and 23% of deaths in the SD and SR groups, respectively.

Discussion

We classified 3 clinically encountered aGVHD response states in patients who developed aGVHD after allogeneic HCT. In our large consecutive cohort, 10% experienced SS aGVHD, 9% SD aGVHD, and 14% SR aGVHD, with slightly earlier onset of aGVHD in the SR cohort. Advanced age, donor type, and malignant disease diagnosis were associated with SR GVHD.

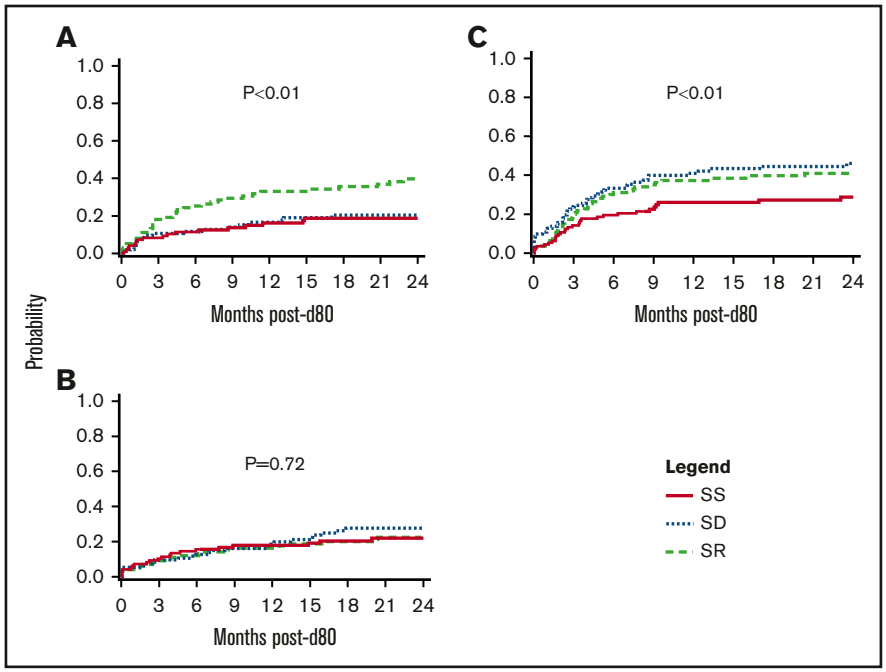

Figure 4. Landmark analysis of cumulative incidence of NRM, relapse, and cGVHD after day 80 of aGVHD treatment initiation. NRM (A), relapse (B), and cGVHD (C). The 2-year NRM in the SS, SD, and SR groups were 19% (95% CI, 11-27), 20% (95% CI, 12-29), and 40% (95% CI, 29-50), respectively. The 2-year relapse risk in the SS, SD, and SR groups were 22% (95% CI, 13-31), 28% (95% CI, 18-37), and 23% (95% CI, 14-31), respectively. The 2-year incidence of cGVHD in the SS, SD, and SR groups were 29% (95% CI, 20-38), 46% (95% CI, 35-57), and 41% (95% CI, 31-51), respectively.

Although we had hypothesized that SD GVHD would have an intermediate prognosis between the SS group and SR groups, our data showed no distinct outcomes between SS and SD patients with GVHD who had similar 2-year OS and NRM. We did observe that SD aGVHD was uniquely associated with higher risks of subsequent cGVHD, without increased risks of 2-year OS, NRM, or relapse. Although we are unable to explain this pathophysiologically, we surmise that the prolonged need for steroids leads directly or indirectly to the development of cGVHD. This prolonged immune suppression in the SD group was also associated with more frequent serious infections. The development of SR aGVHD led to greater NRM and mortality, yet did not modify relapse risk, as aGVHD was the cause of death in nearly half of our SR patients.

Most factors that are associated with more advanced SD and SR aGVHD are not easily modifiable. Although early referral for transplant is highly encouraged, patient age is fixed. The choice and intensity of conditioning regimens is generally dependent on age, comorbidities, and previous therapies, including prior autologous HCT and possibly measurable residual disease (MRD) before HCT. The donor source for some patients can be modifiable and may influence GVHD risk. However, the optimal donor choice in the absence of an available MSD is complex and continues to be based on genetic factors, as well as institutional experience and preference. Because of a strong correlation with donor and graft type, we could not examine any impact of GVHD prophylaxis on the different GVHD response groups.

We acknowledge that there is no established definition for classification of aGVHD based on response to first-line steroid treatment, and the literature on SD aGVHD is sparce.[13-15] In our cohort, the use of a standard and clearly defined steroid dose and taper schedule facilitated this unique analysis with limited bias related to practice variation. Mohty et al recently proposed a definition for ruxolitinib-resistant aGVHD, highlighting the importance of the steroid tapering schedule in aGVHD treatment, but without offering any definition for steroid or ruxolitinib dependent aGVHD states.[16]

Refining aGVHD classification into these 3 response groups, each having different risk factors and prognosis, could be used to guide future therapeutic strategies. Future analyses should examine the impact of alternate initial GVHD therapies[17] on the risk of development of these different disease response states and how the risk factors defined herein can help tailor best management of acute GVHD.

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Authorship

Contribution: N.E.J. and D.J.W. performed the literature search and wrote the first version of the manuscript; N.E.J., D.J.W., and M.L.M. contributed to the design of the study; T.E.D. performed the statistical analysis; and all other authors edited and revised the manuscript.

Conflict-of-interest disclosure: S.G.H. reports consulting for Incyte, Bristol Myers Squibb, and Generon. D.J.W. reports research support from Incyte and FATE Therapeutics. The remaining authors declare no competing financial interests.

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References

1. Jagasia M, Arora M, Flowers MED, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood*. 2012;119(1):296-307.
2. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant*. 2002;8(7):387-394.
3. MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. *Biol Blood Marrow Transplant*. 2015;21(4):761-767.
4. Hings IM, Filipovich AH, Miller WJ, et al. Prednisone therapy for acute graft-versus-host disease: short- versus long-term treatment. A prospective randomized trial. *Transplantation*. 1993;56(3):577-580.
5. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;123(23):3664-3671.
6. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.
7. Kennedy ABW, Sankey HR. The thermal efficiency of steam engines. Report of the committee appointed to the council upon the subject of the definition of a standard or standards of thermal efficiency for steam engines: with an introductory note (including appendixes and plate at back of volume). *Minutes Proc Inst Civ Eng*. 1898;134(1898):278-312.
8. Läuter H, Agresti A. Analysis of ordinal categorical data. *Biometrical J*. 1987;29(1):70.
9. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc*. 1958;53(282):457-481.
10. Lin DY. Non-parametric inference for cumulative incidence functions in competing risks studies. *Stat Med*. 1997;16(8):901-910.
11. Cox DR. Regression Models and Life-Tables. *J R Stat Soc B*. 1972;34(2):187-202.
12. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94(446):496-509.

13. Shapira MY, Resnick IB, Bitan M, et al. Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute graft-versus-host disease: a preliminary report. *Bone Marrow Transplant*. 2005;36(12):1097-1101.

14. Schoemans HM, Lee SJ, Ferrara JL, et al; EBMT (European Society for Blood and Marrow Transplantation) Transplant Complications Working Party and the "EBMT−NIH (National Institutes of Health)−CIBMTR (Center for International Blood and Marrow Transplant Research) GvHD Task Force". EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant*. 2018;53(11):1401-1415.

15. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood*. 1990;76(8): 1464-1472.

16. Mohty M, Holler E, Jagasia M, et al. Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness. *Blood*. 2020;136(17):1903-1906..

17. Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood*. 2020;135(2):97-107.