Predictors and outcomes of flares in chronic Graft-Versus-Host Disease (cGVHD)

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INTRODUCTION

- cGVHD is the leading cause of non-relapse mortality (NRM) and morbidity after alloHCT
- cGVHD frequently requires prolonged immunosuppressive therapy (IST) with > 50% of patients still on IST at 5 years
- IST typically involves a slow taper of steroids often with flare of cGVHD, necessitating augmentation of previous therapy or addition of new IST
- Studies describing cGVHD flares are limited and are needed to identify those likely to flare and their subsequent outcomes
- We hence performed a retrospective analysis of a cohort of patients with cGVHD, who flared during the treatment with systemic IST, following matched sibling donor peripheral blood stem cell transplant (MSD PBSCT) and an umbilical cord blood transplant (UCBT), treated uniformly at the University of Minnesota

METHODS

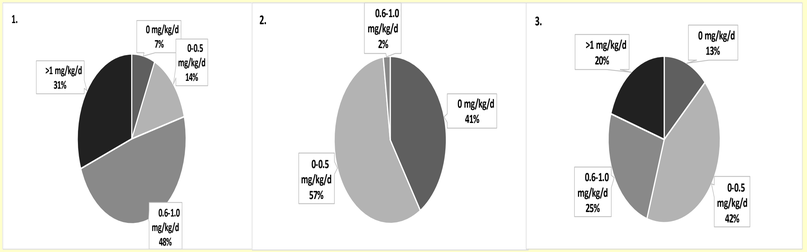
- Single center retrospective cohort study included adult recipients of allogeneic HCT between 2010-2017 using either MSD PBSCT or single/double UCBT and developed cGVHD (n=145)
- 2014 NIH Consensus Criteria were used to retrospectively classify organ and overall cGVHD severity at diagnosis
- Flare of cGVHD was defined as progression in cGVHD manifestations occurred after the initial response, which was less severe than at the diagnosis
- Descriptive analysis of cGVHD patients who flared and their outcomes (overall survival (OS), NRM and durable discontinuation of steroids (no steroid treatment ≥ 6 months).

STATISTICAL ANALYSIS

- Multivariate regression of flares was based on the Prentice, Williams and Peterson model for ordered multiple events (flares)
- Time-dependent effects on OS and NRM was analyzed by Cox, Fine and Gray regression with propensity scoring to control for confounding
- Variables included in multivariate analysis included:
  - *-gender*
  - *-age at transplant (continuous variable)*
  - *-donor type (MSD PBSCT vs UCBT)*
  - *-conditioning regimen (MA vs RIC)*
  - *-GVHD prophylaxis (CNI+MTX vs others)*
  - *-Lymphocytes at cGVHD diagnosis (<0.8x10e9/L vs ≥0.8x10e9/L)*
  - *-Eosinophils at cGVHD diagnosis (<0.7x10e9/L vs ≥0.7x10e9/L)*
  - *-Platelets at cGVHD diagnosis (<100x10e9/L vs ≥100x10e9/L)*
  - *-cGVHD onset (de-novo vs quiescent vs progressive)*
  - *-type of cGVHD (classic vs overlap)*
  - *-cGVHD global severity at dx (mild vs moderate vs severe)*
  - *-number of organs involved at diagnosis (1-2 vs 3+)*
  - *-days from transplant to diagnosis of cGVHD*
  - *-Karnofsky score at cGVHD (<90 vs>90)*
  - *-HCT-comorbidity index (low vs intermediate vs high risk)*

cGVHD PATIENT CHARACTERISTIC AND PREDNISONE DOSES AT CGVHD DIAGNOSIS (1), PRE-FLARE (2) AND POST FLARE (3)

Characteristics	MSD PBSCT, n(%)	UCBT, n(%)	p-value
N	104	41	
Age			0.06
Age, median (range)	54 (23-74)	50 (19-69)	
Gender			0.74
Male	69 (66%)	26 (63%)	
Donor type			
Matched sibling	104 (100%)	0 (0%)	
sUCBT	0 (0%)	9 (22%)	
dUCBT	0 (0%)	32 (78%)	
Conditioning regimen			0.02
Myeloablative with/without Total Body Irradiation	38 (37%)	25 (60%)	
Reduced intensity conditioning	66 (63%)	16 (39%)	
HCT-Comorbidity Index			0.75
Low risk: 0	41 (39%)	19 (46%)	
Intermediate risk: 1-2	31 (30%)	11 (27%)	
High risk: 3+	32 (31%)	11 (27%)	
Days from HCT to cGvHD			
Days (median range)	218 (88-1111)	224 (110-903)	
Prior aGvHD by grade			<0.01
No aGvHD	47 (45%)	6 (15%)	
Grade 1	6 (6%)	2 (5%)	
Grade 2	30 (29%)	12 (29%)	
Grade 3	15 (14%)	17 (41%)	
Grade 4	6 (6%)	4 (10%)	
Karnofsky score at cGvHD diagnosis			0.75
<90 at cGvHD diagnosis	28 (27%)	10 (24%)	
cGvHD onset			< 0.01
De-Novo	47 (45%)	6 (15%)	
Quiescent	34 (33%)	23 (56%)	
Progressive	23 (22%)	12 (29%)	
cGvHD type			0.58
Classic	71 (68%)	26 (63%)	
Overlap	33 (32%)	15 (37%)	
cGvHD global severity at diagnosis			0.01
Mild	12 (12%)	12 (29%)	
Moderate	62 (60%)	23 (56%)	
Severe	30 (29%)	6 (15%)	
Numbers of organs involved at cGvHD diagnosis			0.08
1 or 2	49 (47%)	26 (63%)	
3+	55 (53%)	15 (37%)	
Platelets count at cGvHD diagnosis			0.34
< 100x10e9/L	25 (24%)	13 (32%)	
≥ 100x10e9/L	79 (76%)	28 (68%)	
Eosinophil count at cGvHD diagnosis			0.05
< 0.7x10e9/L	79 (76%)	37 (90%)	
≥ 0.7x10e9/L	25 (24%)	4 (10%)	
Lymphocyte count at cGvHD diagnosis			0.63
< 0.8x10e9/L	27 (26%)	12 (29%)	
≥ 0.8-5.3x10e9/L	77(74%)	29 (71%)	
cGvHD treatment			0.33
Systemic	26 (25%)	13 (32%)	
Topical	7 (7%)	5 (12%)	



RESULTS

Figure 1: Organ involvement at flare

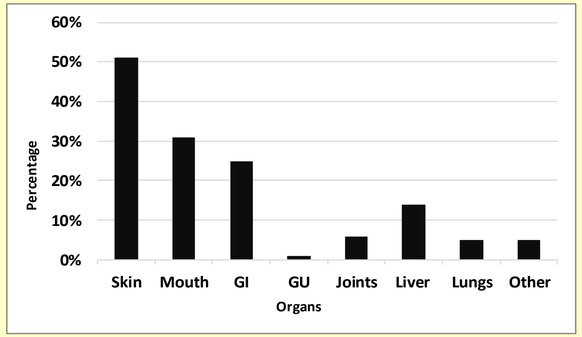


Figure 2: Forest plot with HR for flare predictors

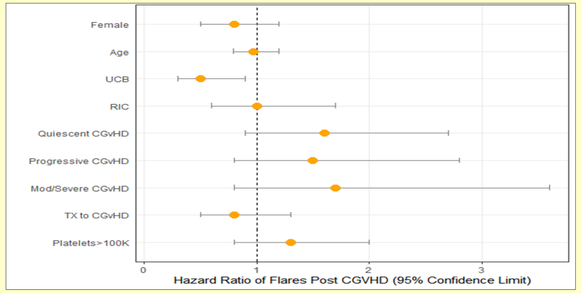
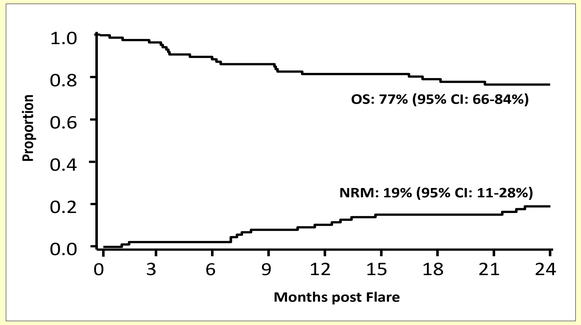


Figure 3: Non-relapse mortality and overall survival: outcomes post flare



- 87 patients developed flare, the cumulative incidence of flares - 60% (95% CI: 51-70%)
- Median time to flare 188 days (range 16-751); 32 (36%) experienced multiple flares (2 to 4)
- The median dose of prednisone at cGVHD diagnosis - 1 mg/kg/day (range 0-4.2)
- At flare: 36 (41%) were off prednisone, 50 (57%) were on 0.1-0.5 mg/kg/day, and 2 (2%) > 0.5 mg/kg/day
- The most common organs involved at flare were skin (n=45; 51%), mouth (n=27; 31%), GI tract (n=22; 25%) and liver (n=12; 14%)
- Flare was treated: 77 patients (88%) - increase in prednisone dose to 0.5 mg/kg/day (range 0.3-1.0); 48 (55%) - addition of another line of IST
- UCBT was associated with 2-fold lower probability of flaring (HR 0.5; 95% CI: 0.3-0.9; p=0.03) vs. MSD PBSCT
- OS was 77% (95% CI: 66-84%); NRM - 19% (95% CI: 11-28%) at 2 years
- Similar risk of NRM (HR 1.2; 95% CI: 0.2-6.1, p=0.86) and OS (HR 0.9; 95% CI: 0.4-2.3, p=0.85) in flare vs non-flare patients
- At 2 years from cGVHD onset, the cumulative incidence of discontinuation of IST was 31% (95% CI: 21-41%) in those who flared vs. 86% (95% CI: 75-96%) in those without flare.

CONCLUSIONS

- cGVHD patients with flare had similar risk of NRM and OS as those without a flare
- Patients with flare required extended steroids, along with clinical monitoring and intensified IST
- cGVHD after UCBT was associated with significantly lower risk of flaring compared to MSD PBSCT
- Patients with flare of cGVHD had a lower likelihood of durable discontinuation of steroids
- The ongoing burden of IST, risk of infection and morbidity of cGVHD is substantial and needs better approaches than chronic slow taper of steroids.

CONFLICT OF INTERESTS DISCLOSURE

D. J. Weisdorf: *Incyte (research funding); Fate Therapeutics & Pharmacyclics (consultancy)*
J. E. Wagner: *Magenta Therapeutics (consultancy and research funding), Gadeta (membership, advisory committees), BlueRock (research funding), Rocket Pharmaceuticals (consultancy, current equity holder)*
B. R. Blazar: *Magenta Therapeutics (consultancy), BlueRock Therapeutics (consultancy, research finding), Children's Cancer Research Fund (research funding), KidsFirst Fund (research funding), Tmunity (co-founder), Fate Therapeutics (research funding)*
M. L. MacMillan: *Talaris Therapeutics (consultancy), Fate Therapeutics (consultancy), Mesoblast (consultancy), Angiocrine Biosciences (consultancy), Equillium (consultancy)*
S. G. Holtan: *Incyte (consultancy), Bristol-Myers Squibb (consultancy), CSL Behring (consultancy), Jeneron (consultancy)*
C. G. Brunstein: *Gamida (research funding), Astex (research funding), Magenta (research funding), AlloVir (advisory board)*
B.C. Betts: *Pending patent WO2017058950A1: Methods of treating transplant rejection.*
V. Bachanova: *Gamida Cell (membership, advisory committees and research funding), Incyte (research funding), BMS (research funding), Fate (research funding), ding), Kite (membership, advisory committees), Karyopharma (membership, advisory committees)*
A. Rashidi: *Synthetic Biologics (DSMC member)*
M. Arora: *Fate Therapeutics (consultancy), Pharmacyclics (research funding), Kadmon (research funding), Syndax (research funding)*