Reduced intensity conditioning for hematopoietic cell transplant for HLH and primary immune deficiencies: BMT CTN 1204

Supplemental Materials

Supplemental Table 1: Inclusion Criteria

1. Patient is ≥ 4 months and ≤ 45 years of age at time of enrollment.
2. Meets criteria for **one** of the following immune disorders (2A-2F) requiring HCT:

2A. HLH or related disorder with indication for HCT:
   a. Inherited gene mutation associated with HLH: *PRF1*, *UNC13D*, *MUNC18-2*, *STX11*, *RAB27A* (Griscelli syndrome, type 2), *SH2D1A* (XLP1), *XIAP* (XLP2), *LYST* (Chediak-Higashi syndrome).
   – OR –
   b. Meets clinical criteria for HLH (Table 1.2), refractory to therapy according to HLH-94 or HLH-2004 (dexamethasone/etoposide), or recurrent episodes of hyper-inflammation.
   – OR –
   c. Meets clinical criteria for HLH (Table 1.2), without identified gene defects, with affected sibling – OR – decreased or absent NK cell function at the last evaluation, – OR – a history of CNS inflammation as evidenced by pleocytosis in CSF or MRI evidence of hyper-inflammation in the CNS.

2B. CAEBV: Patients with chronic EBV infection (CAEBV) with or without associated lymphoma (in complete remission) or active HLH. Note that this diagnosis is distinct from post-transplant lymphoproliferative disorder/ EBV-associated lymphoproliferative disease (PTLD/LPD). Patients must meet <u>all</u> of the following:
   a. Severe progressive illness, usually with fever, lymphadenopathy and splenomegaly that either began as primary EBV infection or was associated with markedly elevated antibody titers to EBV viral capsid antibody (≥ 1:5120) or early antigen (≥ 1:640), or markedly elevated EBV DNA in the blood;
   – AND –
   b. Infiltration of tissues (e.g., lymph nodes, liver, lungs, CNS, bone marrow, eye, skin) with lymphocytes;
   – AND –
   c. Elevated EBV DNA, RNA or proteins in affected tissues;
   – AND –
   d. The absence of HIV or post-transplant lymphoproliferative disorder.

2C. Chronic granulomatous disease with indication for HCT:
   a. Oxidative burst < 10% normal with dihydrorhodamine (DHR) assay
   – AND –
   b. Documented CGD mutation(s) in *gp91^{phox}*, *p47^{phox}*, *p67^{phox}*, *p22^{phox}* or *p40^{phox}*
   – AND –
   c. Severe disease as evidenced by **one** or more of the following:
      i. history of one or more potentially life-threatening infections
      ii. inflammatory bowel disease
      iii. failure to thrive with height <10% for age (unless parent(s) height <10%)
      iv. autoimmune complication felt to be linked to CGD

2D. X-linked Hyper IgM Syndrome (HIGM1):
   a. Decreased serum IgG (more than 2 standard deviations below normal for age)
   – AND –
   b. Mutation in *CD40LG* – OR – family history of maternally related males with HIGM1.

2E. IPEX Syndrome:
   a. Absent FOXP3+ CD4+ T cells – OR – abnormal function of FOXP3+CD4+ T cells
   – AND –
   b. Disease-associated mutation in *FoxP3* (bi-allelic in females) – OR – family history of maternally related males with clinical diagnosis of IPEX.

2F. Severe Leukocyte Adhesion Deficiency, type I (LAD-I):
   a. Decreased CD18 expression on neutrophils (<5% normal for age)
   – AND –
   b. Mutation of *ITGB2* – OR – absence of *ITGB2* mRNA in leukocytes

3. Lansky or Karnofsky performance status ≥ 50%.
4. The patient's donor must be willing to give bone marrow stem cells and be:
   - An unaffected sibling donor who is a 6/6 match at HLA-A and –B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*
   - An unaffected related donor (other than sibling) who is a 7/8 or 8/8 match for HLA-A, -B, -C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*
   - An unrelated donor who is a 7/8 or 8/8 match at HLA-A, -B, -C, and –DRB1 (at high resolution using DNA-based typing).
5. Patient must have adequate organ function as measured by:
   a. Cardiac: Left ventricular ejection fraction (LVEF) > 40%; or LV shortening fraction (LVSF) > 26% by echocardiogram.
   b. Renal: Calculated or radioisotope GFR > 50 mL/min/1.73m^2
   c. Hepatic: Adequate liver function: serum conjugated (direct) bilirubin < 2x upper limit of normal for age as per local laboratory (with the exceptions of isolated hyperbilirubinemia due to Gilbert's syndrome, or hyperbilirubinemia as the result of liver inflammation in the setting of persistent, active HLH); ALT and AST < 10x upper limit of normal as per local laboratory (with the exception of elevated transaminase levels as the result of liver inflammation in the setting of persistent, active HLH).
   d. Pulmonary: Patient may not be on mechanical ventilation support or have progressive pulmonary infection at the time of transplant; Pulmonary Function Testing (PFT) with FEV1 <u>≥</u> 50% of normal and DLCO corrected for Hgb > 50% of normal. Patients unable to undergo PFTs should have stable respiratory status with SaO2 > 90% on a maximum of 2L/min supplemental oxygen.
6. Signed informed consent.

Supplemental Table 2: Last available chimerism data and DLI dosing information before reported DLI

ID	Day of DLI, post-transplant	Total CD3 dose ($x10^6$ cells/kg)	Day of Most Recent Unfractionated Sample	Unfractionated Sample, % Donor	Unfractionated type	Day of Most Recent T-cell Sample	T-cell Sample, % Donor	T-cell Sample Type
5	53	11.5	53	26	Blood	53	5	Blood
5	102	12	99	9	Blood	99	46	Blood
5	172	189	99	9	Blood	99	46	Blood
6	115					98	97	Blood
7	60	67	52	55	Blood			
8	73	35	70	24	Blood	70	37	Blood
8	86		83	14	Blood	83	27	Blood
10	90	22	83	81	Blood	76	63	Blood
10	115	66	98	75	Blood			
10	210	20	174	38	Blood	175	70	Blood
11	74	1	73	28	Blood	73	82	Blood
12	82	74	79	25	Blood			
13	100		100	38	Blood	100	88	Blood
15	126	31	101	64	Blood	101	57	Blood
16	123	50	88	30	Blood	88	14	Blood
22	138	9	105	15	Blood			
26	189					106	0	Blood
27	124		89	5	Blood	89	10	Blood
36	99	0.3	99	84	Blood			
36	115	1.1	99	84	Blood			
43	62	100				50	46	Blood
44	145		97	82	Blood	88	68	Blood
44	301		287	44	Blood	287	44	Blood

Supplemental Table 3A
Immune Reconstitution: QIgG, QIgA, and QIgM separately by IVIg status

	Primary Disease:	HLH						Other PID						Total					
	IVIg Prior to Assessment:	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
	Visit:	Baseline	Baseline	Day 100	Day 100	Day 365	Day 365	Baseline	Baseline	Day 100	Day 100	Day 365	Day 365	Baseline	Baseline	Day 100	Day 100	Day 365	Day 365
QIgG	n	26	8	10	20	1	25	8	4	4	6	1	6	34	12	14	26	2	31
	Mean (SD)	655.23 (340.97)	751.75 (451.7)	986.7 (434.41)	927.75 (345.65)	403 (NA)	630.4 (193.31)	587.75 (183.22)	482.75 (310.27)	369 (157.24)	1009.33 (678.74)	369 (NA)	621.83 (486.47)	639.35 (309.9)	662.08 (416.7)	810.21 (469.27)	946.58 (429.14)	386 (24.04)	628.74 (263.34)
	Median (Range)	707 (1379)	748 (1320)	926.5 (1271)	957.5 (1235)	403 (0)	659 (768)	603.5 (564)	364.5 (682)	362.5 (323)	926.5 (1757)	369 (0)	496 (1404)	645.5 (1379)	483.5 (1320)	836 (1396)	957.5 (1757)	386 (34)	656 (1404)
QIgA	n	24	7	7	13	1	15	8	4	1	5	0	5	32	11	8	18	1	20
	Mean (SD)	49 (50.26)	54.29 (56.74)	22.71 (32.55)	23.85 (27.23)	24 (NA)	32.47 (20.67)	76.63 (81.86)	41.25 (32.36)	8 (NA)	44 (60.67)	NA	81.6 (60.88)	55.91 (59.46)	49.55 (47.84)	20.88 (30.58)	29.44 (38.41)	24 (NA)	44.75 (39.64)
	Median (Range)	26 (202)	35 (136)	7 (91)	12 (90)	24 (0)	27 (64)	54 (201)	28.5 (70)	8 (0)	11 (141)	NA	52 (143)	30 (203)	33 (136)	7.5 (91)	11.5 (145)	24 (0)	43.5 (181)
QIgM	n	25	7	7	14	1	15	8	4	1	5	0	5	33	11	8	19	1	20
	Mean (SD)	45 (41.17)	57.57 (59.92)	27.43 (26.34)	31.07 (28.17)	59 (NA)	54.13 (54.22)	75.38 (58.46)	43.5 (23.23)	5 (NA)	154.2 (267.51)	NA	179.4 (313.71)	52.36 (46.84)	52.45 (48.65)	24.63 (25.65)	63.47 (139.92)	59 (NA)	85.45 (161.19)
	Median (Range)	27 (156)	37 (173)	24 (77)	27 (101)	59 (0)	42 (214)	71.5 (175)	37 (52)	5 (0)	26 (624)	NA	31 (732)	32 (181)	37 (173)	18.5 (77)	26 (624)	59 (0)	42 (732)

Yes = Received IVIg at any point before the measurement at a respective visit.

Supplemental Table 3B. NK Cell Function

	Baseline	Day 100	Day 365
NK Cell Function	**n (%)***	**n (%)***	**n (%)***
Missing or Form Not Submitted	5 (NA)	16 (NA)	18 (NA)
Present - Normal	8 (27.6)	13 (76.5)	8 (53.3)
Present - Decreased	13 (44.8)	3 (17.6)	6 (40.0)
Absent	8 (27.6)	1 (5.9)	1 (6.7)
Sample Uninterpretable	0 (NA)	1 (NA)	1 (NA)
Percentage of NK Cells			
n	21	16	12
Mean (Std. Dev.)	12.79 (16.6)	34.5 (25.55)	18.08 (11.32)
Median (Range)	6 (52)	27.5 (84)	15.5 (34)

*Percent of available samples (not missing or uninterpretable) given

Supplemental Figure 1. GVHD
Figure 1A. Acute GVHD (Grades II-IV)

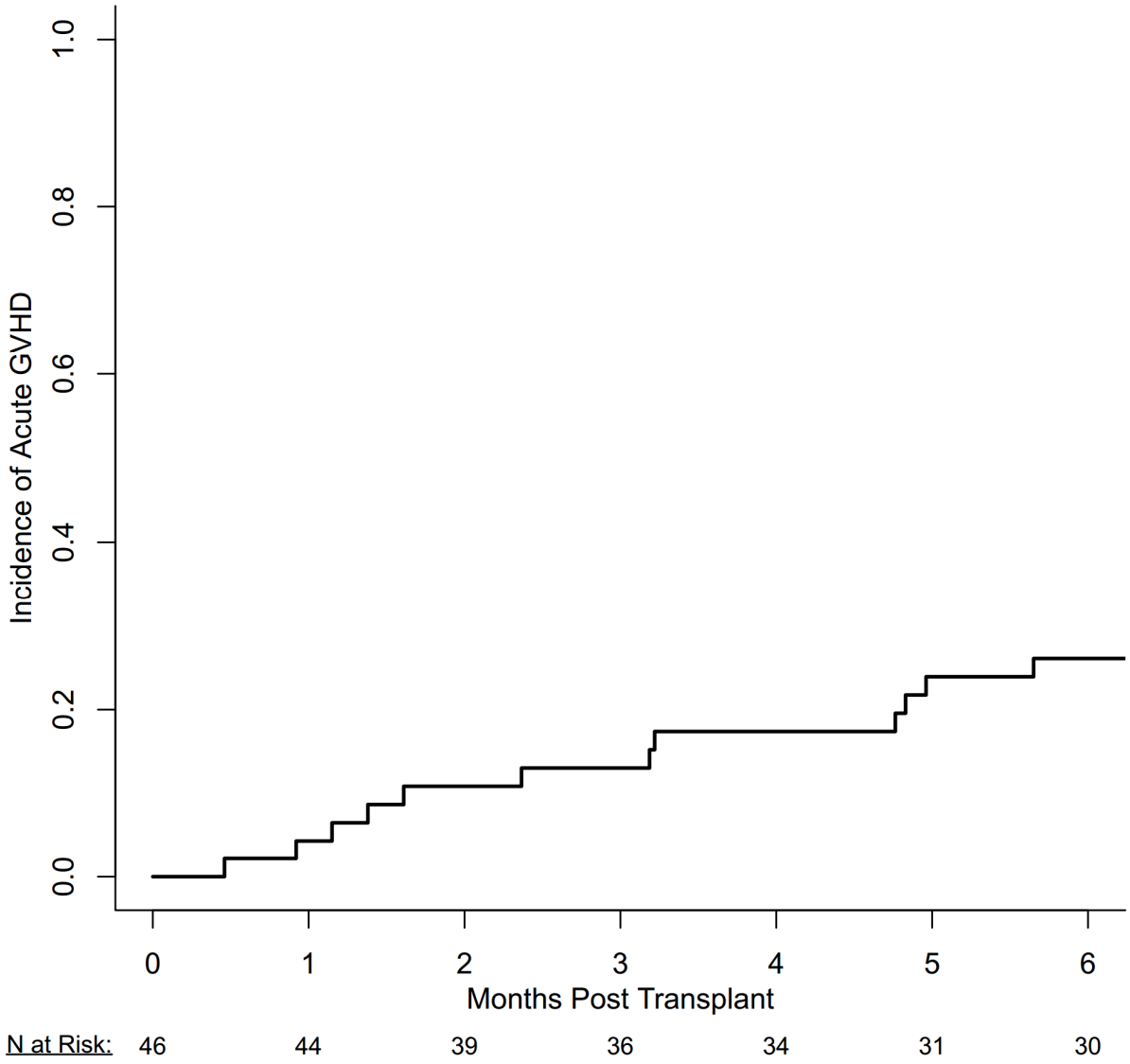

Figure 1B. Chronic GVHD