First reported Evaluation of Outcomes and Safety of using "Flipped" Conditioning Regimens of Fractionated total body irradiation followed by fludarabine vs cyclophosphamide for Allogeneic-Hematopoietic Stem Cell Transplant at the University of Southern California

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Introduction

- Use of Fludarabine (Flu) or Cyclophosphamide (Cy) followed by fractionated total body irradiation (FTBI) as conditioning regimens have been well-studied in allogeneic hematopoietic stem cell transplant (allo-HSCT) yielding good engraftment, low mortality and clinically significant graft versus host disease (GVHD) rates (1-5)
- Currently no data using a "flipped" conditioning strategy of FTBI followed by Fludarabine (FTBI/Flu) pre-transplant
- Limited data using FTBI then Cy (FTBI/Cy) (6)
- Due to logistics and with approval from our investigational review board/patient consent-process, we started using flipped conditioning strategies with adjustment to the timing of donor stem cell infusion
- We now report outcomes and safety data using "flipped" conditioning regimens: FTBI/Flu and FTBI/Cy

Objectives

- **Primary Outcomes:**
  - Over-all survival (OS) and event-free survival (EFS) since transplant, stratified by FTBI/Flu and FTBI/Cy, transplant type, disease risk index (DRI) and stage of disease at transplant: complete response achieved within first induction (CR1) after salvage chemotherapy for first or second relapse (CR2/3) or refractory
- **Secondary Outcomes:**
  - Patient/ treatment characteristics, associated graft versus host disease (GVHD) and (non-)relapse related mortality rates (NRM) rates and time to engraftment engraftment

Materials & Methods

- This is a retrospective, single institution chart review study Included adults ≥18 years, male/female patients with any benign or malignant hematologic diseases who underwent allo-HSCT at our institution using FTBI/Flu or Cy (2015-2021)
- Distribution of time-to-event end points/outcomes were calculated with Kaplan-Meier (KM) method and OS and EFS reported through KM curves. Patient demographics, treatment, response and adverse event characteristics presented with descriptive statistics. Two-sided p value ≤0.05 was considered significant.

Table 1. Patient and transplant characteristics for all patients and by conditioning/type of regimen

Variable	All Patients (n=40)	Conditioning/Type of Regimen		P-value
		FTBI then Flu (n=36)	FTBI then Cyclo (n=4)	
Age at Diagnosis	48.5 (17.3) (21, 63)	50.5 (16.5) (25, 63)	35.5 (13.0) (21, 52)	**0.049***
Gender				0.999
Male	22 (55.0%)	20 (55.6%)	2 (50.0%)	
Female	18 (45.0%)	16 (44.4%)	2 (50.0%)	
Ethnicity				**0.022***
White/non-Hispanic	14 (35.0%)	14 (38.9%)	0	
African American	0	0	0	
Hispanic	17 (42.5%)	14 (38.9%)	3 (75.0%)	
Asian	8 (20.0%)	8 (22.2%)	0	
Others	1 (2.5%)	0	1 (25.0%)	
BMI at Transplant	29.2 (5.9) (19.1, 42.9)	28.9 (6.6) (19.1, 42.9)	31.6 (4.4) (20.8, 33.8)	0.528
Hepatic Steatosis				0.999
Yes	9 (23.1%)	9 (25.0%)	0	
No	30 (76.9%)	27 (75.0%)	3 (100%)	
Cirrhosis only	0	0	0	
Both HS & cirrhosis	0	0	0	
Disease				0.177
AML	18 (45.0%)	18 (50.0%)	0	
ALL	17 (42.5%)	13 (36.1%)	4 (100%)	
CML	1 (2.5%)	1 (2.8%)	0	
MDS	1 (2.5%)	1 (2.8%)	0	
NHL	1 (2.5%)	1 (2.8%)	0	
BM Failure	0	0	0	
Congenital immune	0	0	0	
Mixed Leukemia	1 (2.5%)	1 (2.8%)	0	
MPN	1 (2.5%)	1 (2.8%)	0	
Stage of Disease at Tx				0.999
CR1	26 (68.4%)	23 (67.7%)	3 (75.0%)	
CR2/3	9 (23.7%)	8 (23.5%)	1 (25.0%)	
Refractory	3 (7.9%)	3 (8.8%)	0	
Disease Risk Index (DRI)				0.648
Low	10 (25.0%)	10 (27.8%)	0	
Intermediate	21 (52.5%)	18 (50.0%)	3 (75.0%)	
High	9 (22.5%)	8 (22.2%)	1 (25.0%)	
Type of Allo-SCT				**0.009***
MRD/MSD	8 (20.0%)	5 (13.9%)	3 (75.0%)	
MUD	14 (35.0%)	13 (36.1%)	1 (25.0%)	
Haplo	18 (45.0%)	18 (50.0%)	0	
Donor SCT Source				0.999
BM	3 (7.5%)	3 (8.3%)	0	
PB	37 (92.5%)	33 (91.7%)	4 (100%)	
Cord	0	0	0	
Recipient CMV Status				0.999
Positive	33 (82.5%)	29 (80.6%)	4 (100%)	
Negative	7 (17.5%)	7 (19.4%)	0	
GVHD PPX				**<0.001***
PTCY/tac/mmf	35 (87.5%)	35 (97.2%)	0	
Tacro+MTX	5 (12.5%)	1 (2.8%)	4 (100%)	
Other	0	0	0	

Table 2. GVHD characteristics for all patients and by conditioning/type of regimen

Variable	All Patients (n=40)	Conditioning/Type of Regimen		P-value
		FTBI then Flu (n=36)	FTBI then Cyclo (n=4)	
Any Acute GVHD				0.602
No	14 (35.0%)	12 (33.3%)	2 (50.0%)	
Yes	26 (65.0%)	24 (66.7%)	2 (50.0%)	
Type of Acute GVHD				
Skin	15 (57.7%)	15 (62.5%)	0	0.113
Gut	16 (61.5%)	14 (58.3%)	2 (100%)	0.999
Liver	2 (7.7%)	2 (8.3%)	0	0.999
Grade of Acute Skin GVHD				-------
1	6 (40.0%)	6 (40.0%)	0	
2	9 (60.0%)	9 (60.0%)	0	
Grade of Acute Gut GVHD				
1	10 (62.5%)	8 (57.1%)	2 (100%)	0.999
2	3 (18.8%)	3 (21.4%)	0	
3	2 (12.5%)	2 (14.3%)	0	
4	1 (6.2%)	1 (7.1%)	0	
Grade of Acute Liver GVHD				-------
1	1 (50.0%)	1 (50.0%)	0	
3	1 (50.0%)	1 (50.0%)	0	
Any Chronic GVHD				0.584
No	27 (67.5%)	25 (69.4%)	2 (50.0%)	
Yes	13 (32.5%)	11 (30.6%)	2 (50.0%)	
Type of Chronic GVHD				
Skin	7 (53.8%)	5 (45.5%)	2 (100%)	0.190
Gut	3 (23.1%)	3 (27.3%)	0	0.999
Liver	3 (23.1%)	3 (27.3%)	0	0.999
Grade of Chronic Skin GVHD				0.999
1	6 (85.7%)	4 (80.0%)	2 (100%)	
2	1 (14.3%)	1 (20.0%)	0	
Grade of Chronic Gut GVHD				
1	1 (33.3%)	1 (33.3%)	0	-------
2	1 (33.3%)	1 (33.3%)	0	-------
3	1 (33.3%)	1 (33.3%)	0	-------
Grade of Chronic Liver GVHD				
1	2 (100%)	2 (100%)	0	-------

Table 3. Outcomes and Responses all patients and by conditioning/type of regimen

Variable	All Patients (n=40)	Conditioning/Type of Regimen		P-value
		FTBI then Flu (n=36)	FTBI then Cy (n=4)	
Time to Engraftment for ANC ≥500 x3 days	18.0 (4.8) (11, 23)	18.0 (4.8) (11, 23)	13.0 (3.0) (12, 18)	**0.037***
Time to PLT ≥20k, >3 days w/o Blood Transfusion	20.0 (8.0) (8, 48)	20.0 (7.0) (11, 48)	13.0 (6.0) (8, 20)	**0.040***
Relapsed Post-SCT				**0.043***
No	36 (90.0%)	34 (94.4%)	2 (50.0%)	
Yes	4 (10.0%)	2 (5.6%)	2 (50.0%)	
Any Death				0.999
No	33 (82.5%)	29 (80.6%)	4 (100%)	
Yes	7 (17.5%)	7 (19.4%)	0	
Alive 100 days from Transplant				0.999
No	4 (10%)	4 (11.1%)	0	
Yes	36 (90.0%)	32 (88.9%)	4 (100%)	
Alive 1-year from Transplant				0.999
No	6 (18.8%)	6 (20.7%)	0	
Yes	26 (81.2%)	23 (79.3%)	3 (100%)	
Transplant Related Mortality				-------
GVHD	2 (28.6%)	2 (28.6%)	0	
Infection	3 (42.9%)	3 (42.9%)	0	
HSCT related VOD	1 (14.3%)	1 (14.3%)	0	
Other	1 (14.3%)	1 (14.3%)	0	

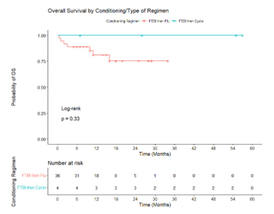


Fig.1- Over-all survival using "flipped" conditioning regimens: Fractionated Total Body Irradiation (FTBI) then Fludarabine (Flu) vs FTBI then Cyclophosphamide (Cy)

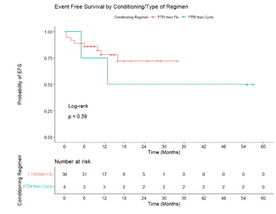


Fig.2- Event-free survival using "flipped" conditioning regimens: Fractionated Total Body Irradiation (FTBI) then Fludarabine (Flu) vs FTBI then Cyclophosphamide (Cy)

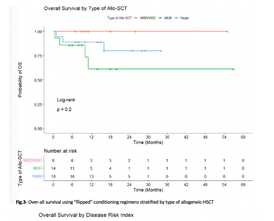


Fig.3- Over-all survival using "flipped" conditioning regimens stratified by type of allogeneic-HSCT

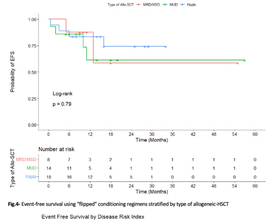


Fig.4- Event-free survival using "flipped" conditioning regimens stratified by type of allogeneic-HSCT

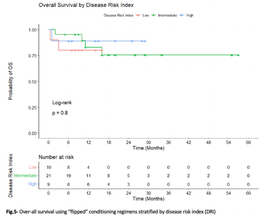


Fig.5- Over-all survival using "flipped" conditioning regimens stratified by disease risk index (DRI)

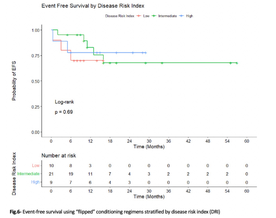


Fig.6- Event-free survival using "flipped" conditioning regimens stratified by disease risk index (DRI)

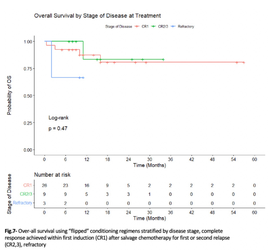


Fig.7- Over-all survival using "flipped" conditioning regimens stratified by disease stage, complete response achieved within first induction (CR1) after salvage chemotherapy for first or second relapse (CR2,3), refractory

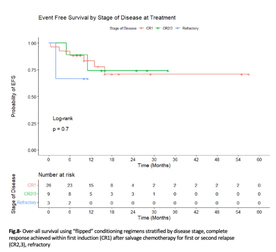


Fig.8- Over-all survival using "flipped" conditioning regimens stratified by disease stage, complete response achieved within first induction (CR1) after salvage chemotherapy for first or second relapse (CR2,3), refractory

Results

- In 40 patients, 36 underwent FTBI/Flu, 4 FTBI/Cy, median age 48.5 years, 50% had AML, 36.1% ALL in the FTBI/Flu group while 100% had ALL in FTBI/Cy (n=0.18) (Table 1)
- In the FTBI/Flu group, 68.4% had CR1, 23.7% had CR2/3 at transplant vs 75% CR1 and 25% CR 2/3 in FTBI/Cy (n=0.99). 50% had intermediate and 22.2% had high DRI in FTBI/Flu; 75% had intermediate and 25% had high DRI in FTBI/Cy (n=0.65) (Table 1)
- 13.9% had MSD, 26.1% MUD and 50% Haplo in the FTBI/Flu group vs 75% MSD and 25% MUD transplant in FTBI/Cy (n=0.01) (Table 1)
- GVHD PPX: 97.2% used post-transplant cyclophosphamide/tacrolimus/mycophenolate in the FTBI/Flu group; 100% used Tacrolimus/methotrexate in the FTBI/Cy group (n=0.001) (Table 2)
- In FTBI/Flu, median neutrophil engraftment was at 18 days vs 13 days (FTBI/Cy) (n=0.037). Median PLT engraftment was 20 days (FTBI/Flu) vs 13 days (FTBI/Cy) (n=0.04). 5.6% had relapsed disease post-transplant (FTBI/Flu), none in FTBI/Cy group (n=0.04) (Table 3)
- 88.9% alive at d+100 vs 100% in FTBI/Cy (n=0.99). 79.3% were alive after 1 year in the FTBI/Flu group vs 100% in FTBI/Cy (n=0.99). Death in the FTBI/Flu group was attributed to GVHD (28.6%), infection (42.9%) and VOD (14.3%) (Table 3)
- 66.7% FTBI/Flu vs 50% FTBI/Cy had any grade, any type, acute GVHD (p=0.6). Among 14 FTBI/Flu patients with acute gut GVHD, 14.3% experienced G3 while 1 of 2 patients with acute liver GVHD had G3, no G4. No G3/4 in FTBI/Cy. 30.6% FTBI/Flu patients had any grade, any type chronic GVHD vs 50% in FTBI/Cy patients (p=0.58). In 3 FTBI/Flu with chronic gut GVHD, 33.3% had G3, no G4. No G3/4 in FTBI/Cy (Table 2)
- Since transplant, over-all, 3y OS was 78.2% with 3y-EFS of 69.3%. If stratified by conditioning, FTBI/Flu 2y-OS was 75.3% vs 100% in FTBI/Cy (p=0.33); FTBI/Flu 2y-EFS was 72.2% vs 50% in FTBI/Cy (p=0.39) (Fig 1-2)
- 3y OS was 100% for MSD, 61.2% MUD, 2y OS was 80% in Haplo (p=0.2). 3y EFS was 58.3% MSD, 61.2% MUD and 2y EFS was 74.1% in Haplo (p=0.79). No difference when survival stratified by DRI (p=0.69-0.8) or transplant disease stage (p=0.47-0.7) (Fig 3-8)

Discussion & Conclusion

- Given most of our patients had intermediate/high DRI, using flipped conditioning strategies yielded appreciable 3y-OS (78.2%) and EFS (69.3%), even when further stratified based on conditioning types, DRI, disease status and stage at treatment
- Based on our data, using FTBI followed by Flu or Cy appears to be a safe strategy if needed, and did not show significantly more toxicity or inferior outcomes

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