A Novel Chemo-Based Reduced Intensity Haploidentical Two-Step Allogeneic Hematopoietic Stem Cell Transplantation, Results of a Prospective Clinical Trial

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Introduction

- Allogeneic stem cell transplant is the standard of care for many hematologic malignancies. The typical conditioning process involves high-intensity chemotherapy associated with morbidity in mortality, particularly in older patients
- The two-step allogeneic hematopoietic stem cell transplant (HSCT) approach was developed at Thomas Jefferson University Hospital to isolate the graft's lymphoid and myeloid components, enabling a constant T cell dosage and protecting the stem cells from cyclophosphamide's effects.
- Here, we present the results of our clinical trial using a chemo-based **reduced-intensity conditioning (RIC)** regimen for older and frail patients.

Methods

- All patients received fludarabine 30mg/m^2 for 4 days and Thiotepa 5mg/kg for 3 days (n=15, 25%) or busulfan 3.2mg/kg for 2 days (n=45, 75%). Thiotepa was substituted with busulfan due to a national shortage.
- The patients then received one day of TBI (2 Gy), followed by 2 x 10*8/kg donor T-lymphocyte infusion on day –6, representing step 1.
- On days –3 and –4, patients received two doses of cyclophosphamide (CY) 60mg/kg to tolerize reactive lymphocytes, and 24 hours later, received CD34 selected stem cell infusion, representing step 2 .

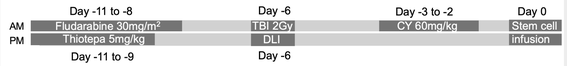


Figure 1a: Thiotepa-based regimen

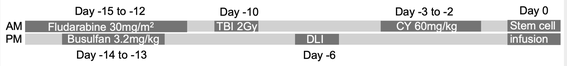


Figure 1b: Busulfan-based regimen

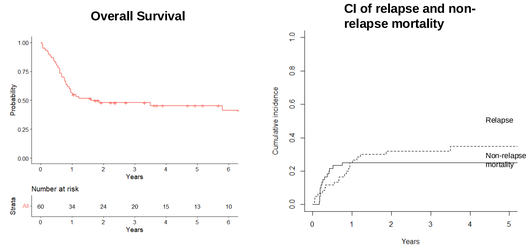
- The median time to neutrophil and platelet engraftment was 11 days (range 10 – 22) and 14 days (range 12 – 26), respectively.

Results

Table 1: Patient Characteristics

Variable	Patients (n = 60)
Age	62.5 (22 – 74 years)
Gender	
Male	42 (88%)
Female	18 (11%)
Race	
Caucasian	43 (70%)
African American	15 (25%)
Hispanic	1 (1.7%)
Asian	1 (1.7%)
Transplant type	
Haploidentical	53 (88%)
Matched Related	7 (11.7%)
HCT-Comorbidity Index	
0-2	27 (45%)
>=3	33 (55%)
Diagnoses	
Acute Myeloid Leukemia	19 (32%)
MPD	8 (13%)
MDS	9 (15%)
Hodgkin Lymphoma	5 (8.3%)
Multiple Myeloma	4 (6.7%)
DLBCL	3 (5.0%)
Other	12 (20%)
Chemotherapy regimen	
Busulfan-based	45 (75%)
Thiotepa-based	15 (25%)
Active disease at time of HSCT	
Yes	12 (20%)
No	48 80%)

Figure 2: Survival and mortality rates

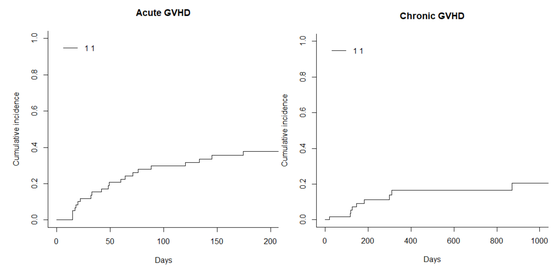


Overall Survival	Rate	95% CI	
1 year	57%	45%	71%
3 years	48%	37%	63%
Progression Free Survival	**Rate**	**95% CI**	
1 year	50%	39%	64%
3 years	45%	32%	58%

Relapse rate	Cumulative Incidence
1 year	25%
3 years	25%
Non-relapse mortality	**Cumulative Incidence**
1 year	25%
3 years	32%

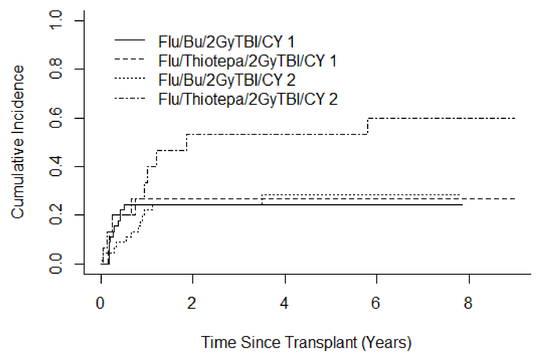
Results

Figure 3: Incidence of Graft Versus Host Disease



- The cumulative incidence of grade II to IV acute GVHD was 29.8% and 37.7% at 100 days and 6 months
- The cumulative incidence of chronic GVHD was 16.5% and 20.6% at 1 and 3 years

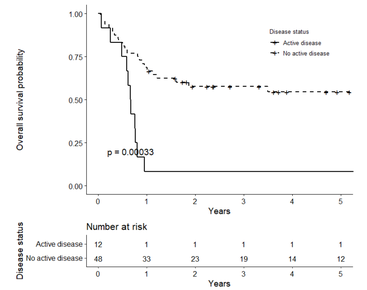
Figure 4: Busulfan versus Thiotepa



- The first 15 patients in the trial received thiotepa and the last 45 patients received busulfan
- Patients who received thiotepa based regimen had a much higher NRM than busulfan-based regimen (53% vs 28%, p = 0.05) at 5 years post-transplant, while relapse was similar (27% vs 24%, p = 0.84).

Results

Figure 5: Disease stage during transplant impacts survival and mortality



- Patients were labeled as having “active disease” (N=12) if in progressive disease (PD) at time of transplant or “non-active” (N=48) if in complete response/partial response/stable disease.
- The 3-year cumulative incidence of relapse was significantly lower for patients in CR/PR/SD at the time of transplant (19% vs 50%, p = 0.026) while NRM was similar (33% vs 42%, p = 0.66).
- There was significantly higher overall survival for patients transplanted in non-active disease (58% vs 8%, p = 0.00033). (Figure 4)

Conclusions

- Reduced intensity conditioning can be safely applied to the two-step haploidentical allogeneic stem cell transplant
- Quick engraftment and low rates of GVHD despite utilizing HI stem cell grafts are encouraging.
- Compared to a thiotepa-based regimen, the busulfan-based regimen is associated with lower rates of non-relapse mortality and overall survival, but has no impact on relapse rates

References

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