ALLOGENEIC STEM CELL TRANSPLANT WITH MYELOABLATIVE FRACTIONATED BUSULFAN, FLUDARABINE AND THIOTEPA CONDITIONING REGIMEN IN OLDER PATIENTS WITH HIGH RISK MDS

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Introduction

To reduce non-relapse mortality and relapse rate in older patients with MDS undergoing stem cell transplantation, we developed a novel myeloablative conditioning regimen. We gave the conditioning regimen over a 3-week period instead of conventional 4-6 days. This fractionation and lengthening of the regimen's duration reduced toxicity and non-relapse mortality, allowing us to give a myeloablative regimen to older patients. We hypothesized that this intensified regimen will not only be safe but also reduce relapse after transplant.

Patients and Methods

The conditioning regimen included outpatient busulfan 80 mg/m^2 on days -20 and -13, thiotepa 5 mg/kg on day -7, fludarabine 30-40 mg/m^2, and busulfan pharmacokinetically dosed to achieve total exposure (including outpatient busulfan) of 16,000±12% µmol.min on days -6 to -3. Graft-versus-host disease (GVHD) prophylaxis was post-transplant cyclophosphamide 50 mg/kg on days +3 and +4, and tacrolimus ± MMF.

Results

Between 2019-2023, 58 patients with MDS with a median age of 65.5 years (29-74) were treated. Most patients had received prior hypomethylating agents (98%) and 53% were male. Fifty percent of recipients were older than 65 years of age. Twenty-two patients (38%) had IPSS-R >3.5. Thirty-seven (68%) had moderate-high, high, or very high IPSS-M score. Eighteen patients (31%) had mutated TP53. Donor was a matched sibling in 9 (15%), matched unrelated in 30 (52%), mismatched unrelated in 7 (12%), and haploidentical related in 12 (21%). The comorbidity score was ≥3 in 71% of patients.

Results

Results are summarized in **Table 1**. With a median follow up of 36 months, 1 and 3-year overall survival were 70% and 57% in patients without TP53 mutation and 33% and 22% in patients with mutated TP53. In multivariate analysis, TP53 mutation (HR=2.4, P=0.03) was the only significant predictor of progression-free survival (PFS). Median PFS was 6 and 40 months (P=0.007) in patients with and without TP53 mutation, respectively. One and 3-year relapse rates were 12% and 18% in patient without TP53 mutation and 56% and 56% in patients with mutated TP53, respectively.

Table 1. Patient Outcomes.

N=58	Outcomes at 1 Year	Outcomes at 3 Years
Outcome	% (95% CI)	% (95% CI)
Overall Survival	59% (45-70)	46% (32-58)
TP53 mutated (n=18)	33% (14-54)	22% (7-43)
TP53 wild type (n=40)	70% (53-82)	57% (40-71)
Progression-Free Survival	52% (38-64)	42% (29-54)
TP53 mutated (n=18)	22% (7-43)	22% (7-43)
TP53 wild (n=40)	65% (48-78)	51% (35-66)
Cumulative Incidence of Progression	26% (17-40)	30% (20-45)
TP53 mutated (n=18)	56% (37-84)	56% (37-84)
TP53 wild (n=40)	12% (5-28)	18% (9-36)
Cumulative Incidence of NRM	21% (12-34)	26% (17-41)
Neutrophil Engraftment, ANC > 500 mm3: Median (range) days	17 (13-33)	
Platelet Engraftment > 20,000 mm3: Median (range) days	23 (10-225)	
T Cell % Chimerism at Day 30: Median (range) days	100 (80-100) N=53	
Myeloid % Chimerism at Day 30: Median (range) days	100 (98-100) N=53	
Cumulative Risk cGVHD	16% (9-29)	23% (15-38)
Cumulative Risk aGVHD, 6m		
Grade 2-4	45% (33-59)	
Grade 3-4	10% (5-22)	

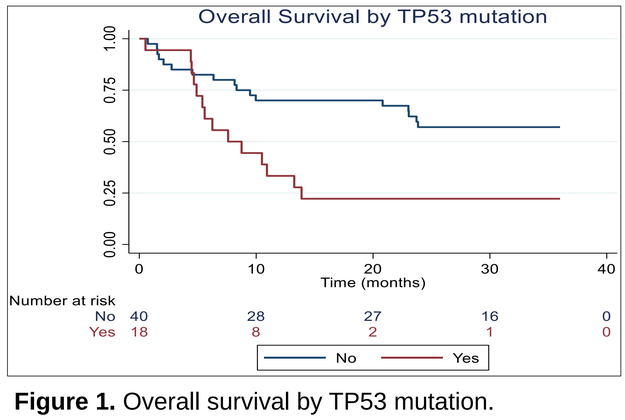


Figure 1. Overall survival by TP53 mutation.

Conclusion

Our results are encouraging in this very high-risk older patient population, particularly for patients without TP53 mutation.