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Research Article

Hematopoietic Stem Cell Transplant in Older Patients with MDS and Co-existing Myelofibrosis

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Abstract

Background: Myelodysplastic syndrome with co-existing bone marrow fibrosis is associated with a dismal prognosis with conventional therapy. Allogeneic hematopoietic stem cell transplant (HSCT) offers the sole treatment approach that offers curative potential. HSCT has been utilized in younger patients with this disorder however with the advent of reduced intensity conditioning (RIC) regimens it has allowed for expansion of this application up to the age of 70 years. The data on the outcomes of patients of older age undergoing RIC for MDS with fibrosis is unknown.

Methods: To identify patients who received HSCT at our center with the diagnosis of myelodysplastic syndrome with co-existing fibrosis (n=15). We conducted a retrospective review in regards to HSCT specific variables influencing outcome and classified them according to their age, degree of bone marrow fibrosis, cytogenetic abnormality, Jak2, engraftment, transplant-related mortality, relapse and overall survival.

Results: Higher median age, high risk cytogenetics and high grade bone marrow fibrosis in our study population was not associated with inferior survival in univariate analysis. The cumulative incidence of engraftment achieved at day+30 based on chimerism was 72.7% the 2-year overall survival was 78% in the patient cohort. There were no patients who developed graft failure and no reported cases of relapse post- transplant.

Conclusions: Among patients with myelodysplastic syndrome and co-existing bone marrow fibrosis, even in patients with older age, higher grade of marrow fibrosis or cytogenetic abnormality, overall survival after hematopoietic stem cell transplantation was not inferior. HSCT should be offered to patients even with older age and significant marrow fibrosis.

Introduction

The Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders [1]. There are several scoring systems that incorporate information based on the cytogenetics, number of cytopenias and the number or percentage of blasts (International Prognostic Scoring System, IPSS), or these variables integrated with transfusion dependency (WHO classification-based Prognostic Scoring System, WPSS) [2,3]. Currently there are no classification schemes that include marrow fibrosis as a risk parameter. The incidence of co-existing marrow fibrosis among patients with de novo MDS can ranges from as low as 2% to as high as 50% with secondary MDS [4,5]. With a very small subset of patients expressing the driver mutations Jak2V617F, CALR exon 9 and MPL515LK, the underlying pathophysiology in patients with co-existing fibrosis and MDS or Acute Myeloid Leukemia remains to be elicited. The significance of co-existing marrow fibrosis in regards to prognosis is also controversial. Different retrospective studies have shown overall survival in the fibrotic group to be inferior in multivariate analysis [6-8]. The only curative therapy for patients with MDS and co-existing bone marrow fibrosis is HSCT.

HSCT is usually reserved for patients with a Dynamic International Prognostic Scoring System (DIPSS) intermediate or high risk disease. However, based on the dismal prognosis in this patient population HSCT is considered to be the best treatment modality in patients with a Karnofsky performance status of at least 70%. With the advent of reduced intensity conditioning or reduced toxicity regimens such as the combination of fludarabine and busulfan allogeneic stem cell transplantation is more frequently offered in patients beyond the age of 60 as a curative therapeutic option for MDS. The major risk factors for outcome after allogeneic stem cell transplantation

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for patients with MDS are certain cytogenetic characteristics, number of blasts, and status of the disease at time of transplant, donor source and age of the patient at time of transplant. Data in regards to the impact of bone marrow fibrosis on outcome after allogeneic stem cell transplantation in patients with MDS especially over the age of 60 are limited. Here in we report the outcome of patients who underwent HSCT at our institution with MDS and co-existing bone marrow fibrosis.

Methods

We collected data from 15 patients who underwent HSCT at Henry Ford Cancer Institute after Intuitional Review Board approval with MDS and co-existing bone marrow fibrosis at diagnosis who underwent allogeneic stem cell transplantation between the time periods of 2005-20015. In this study we included only patients diagnosed with MDS and bone marrow fibrosis. Patients with primary Myelofibrosis or overlap syndrome, i.e. with MDS/myeloproliferative syndrome (MPS) were excluded. The primary endpoints of the study were overall survival (OS), non-relapse mortality NRM, time to neutrophil, platelet engraftment, rates of GVHD and primary graft failure. Time to achieve full donor chimerism was determined by the day of transplant, degree of fibrosis was determined by the hemato-pathologist at our institution. Age, gender, stem cell source, conditioning regimen, donor, disease status and cytogenetics were obtained on all patients.

Statistical analysis

Given our small sample size we used descriptive statistics to present our results as frequencies and percentages. Overall survival was defined as the date the therapy was started to date of death from any cause. Overall survival was stratified based on the type of conditioning regimen utilized: myeloablative (Busulfan and Cyclophosphamide) versus reduced intensity/toxicity conditioning (Fludarabine/Busulfan 40mg/m^2 i.v. x 4 days and 3.2mg/kg i.v. x 4 days or Fludarabine/Busulfan 40mg/m^2 i.v. x 4 days and 3.2mg/kg i.v. x 2 days) and cytogenetic risk category (normal, complex cytogenetics or JAK2 positive) For each of the aforementioned survival was tabulated as the percentage of patients that survived post-transplant. Kaplan-Meier curves for OS were generated based on the outcome of all patients.

Results

Patient and transplantation characteristics

A total of 15 patients were identified who underwent HSCT from 2005-2015. The baseline characteristics of these patients are presented in Table 1. Nine patients received a matched related donor graft, and six received a matched unrelated donor graft. The median age at time of transplant was 67.6 years and 13/15 (86%) underwent either a RIC or a reduced toxicity regimen with a combination of fludarabine 40 mg/m^2/day for 4 days and busulfan 3.2 mg/kg i.v. daily for 2-4 days depending on the regimen. Two patients received Cyclophosphamide 60mg/kg and Busulfan 3.2 mg/kg i.v. daily for 2 days. Graft versus host prophylaxis consisted of tacrolimus and methotrexate or tacrolimus and mycophenolate mofetil. Thymoglobulin (rabbit anti-thymocyte globulin) was administered to 9/15 patients.

Number of Patients		**15**
Age	Mean	67.6 (5.8)
	<65	6 (36.4%)
	>=65	9 (63.6%)
Gender	Male	11 (63.6%)
	Female	4 (36.4%)
Conditioning	Busulfan/Cyclophosphamide	2 (18.2%)
	Fludarabine/Busulfan x 4	8 (54.6%)
	Fludarabine/Busulfan x 2	5 (27.3%)
Graft failure	None	15 (100%)
Chimerism D+30	STR 100% donor	11 (73%)
	STR 85%D/15%R	2 (13%)
	STR 88%D/12%R	1 (6%)
	STR 94%D/6%R	1 (6%)
Cytogenics	Normal	8 (53%)
	Complex	3 (20%)
	JAK2	4 (26%)
Acute GVH	None	9 (60%)
	Present	6 (40%)
Chronic GVH	None	6 (40%)
	Present	9 (60%)
GVHD Prophylaxis		
	Methotrexate + Tacrolimus	9
	Cell Cept + Tacrolimus	6
Donor		
Related		6
Unrelated		9
Stem cell Source		
	G-CSF mobilized Peripheral blood stem cells	15
Cyto-reduction	Yes	9
	No	6

Table 1: Baseline Patient and Transplant Characteristics
Baseline Characteristics of 15 Patients with MDS and Co-existing MF Undergoing HSCT.

Engraftment and graft failure

At day 30 mean neutrophil engraftment (ANC >.5 x 10^9/L for 3 consecutive days) and platelet engraftment (>20,000 x 10^9/L for 7 consecutive days) were 92% and 80% respectively. Bone marrow or peripheral blood was collected post-transplant for donor chimerism assay studies at day +30, +100,+180 and +365. Chimerism was determined by comparative analysis of donor and recipient microsatellite markers utilizing multiplex polymerase chain reaction and differential fluorescence analysis measured in whole blood chimerism was not fractionated and was measured on whole blood samples. Patients were evaluated for donor chimerism if they achieved neutrophil engraftment and were in remission. At D+30 73% of patients achieved 100% full donor chimerism. There were no cases of graft failure defined as failure to engraft neutrophils within 35 days of stem cell infusion in our cohort.

Graft versus host disease

The cumulative incidences of grade II-IV and grade III/IV aGVHD at day 100 was 40% (95% C.I. 19-60%) and 18% (95% C.I. 5-22%) respectively. Sites affected by aGVHD included the skin, GI tract, and liver. Chronic GVHD developed in 6 patients

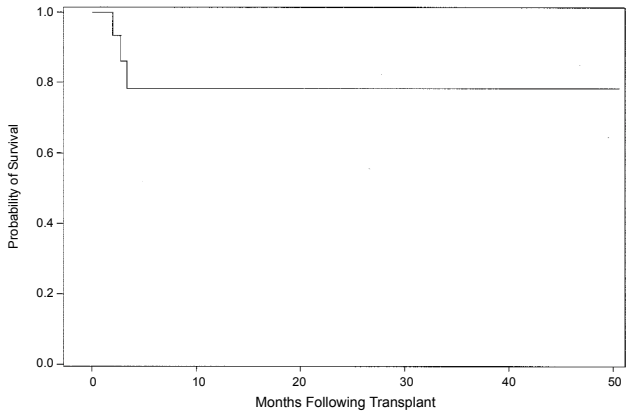

Figure 1: Overall Survival of 15 older patients with MDS and co-existing Myelofibrosis treated with HSCT.

40%. Using NIH criteria 4 had mild cGVHD, 2 had moderate cGVHD. Sites included ocular, oral and skin.

Survival

At a median follow up of 24 months the median OS for the entire cohort was 78% (Figure 1).

Causes of death

Of the 15 patients there were 3 deaths that occurred at day +63,+83 and one after day 100 respectively. One patient died of complications secondary to acute GVHD with sepsis. All patients had complex cytogenetics did not receive pre-transplant cyto-reduction and secondary to comorbid conditions received a RIC regimen.

Discussion

Allogeneic HSCT offers a potential curative therapy for many hematological disorders. The prognosis of patients with MDS is based on the percentage of myeloblast in the marrow and peripheral blood, peripheral blood cytopenias and clonal cytogenetics [5]. In patients with MDS and co-existing marrow fibrosis most reports especially in patients with early stage disease portrays an overall poor prognosis. Based on recent reports of encouraging results in younger patients undergoing HSCT and outcomes we set out to determine transplantation outcomes in a cohort of patients with MDS and co-existing bone marrow fibrosis of which the majority were of older age median age 67.6 years.

The feasibility of HSCT in adults over the age of 50 years and older with the advent of RIC has been encouraging based on several reports [6-8]. In patients with AML and MDS with controlled disease in older adult patient's OS estimates in the 35-40% range have been reported [6-9]. However, the utilization of HSCT in patients >60 and especially in >70 years and older are not offered this curative therapy.

Outcomes after HSCT in patients with co-existing marrow fibrosis have been mixed with some studies reporting that the presence of marrow fibrosis delayed time to engraftment significantly [10]. However, a more recent study in patients with AML and MDS and co-existing bone marrow fibrosis did not reveal a delay in regards to time for engraftment [11]. Current data does suggest in patients with MDS and co-existing fibrosis compared to those patients without fibrosis they tend to have a shorter life expectancy and tend to have high risk disease [10,11].

Our study utilized HSCT in 15 older patients with MDS and co-existing marrow fibrosis. Our outcomes in this small subset of patients were encouraging even when compared to publications in younger patients. With the advent of RIC and reduced toxicity conditioning TRM was 13% and OS was 80% at 4 years post-transplant in our patient cohort. The degree of marrow fibrosis or blast percentage did not have a negative impact on engraftment or OS. Based on these results further studies are warranted especially in older patients with this disorder who are candidates for HSCT.

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