BRIEF ARTICLE

Allogeneic Stem Cell Transplantation for Myelofibrosis with Leukemic Transformation

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Leukemic transformation (LT) from myelofibrosis has a very poor prognosis with the current treatment strategies. We hypothesized that allogeneic stem cell transplantation (ASCT) can improve outcomes for patients with LT, and reviewed 55 consecutive patients that were treated for myelofibrosis with ASCT at our institution. Fourteen patients (25%) were identified to have LT. Thirteen of these patients received induction chemotherapy and 6 achieved remission at the time of transplant. Conditioning regimen was melphalan (Mel)-based in 9 patients. All patients engrafted and achieved remission after transplant, whereas 4 subsequently relapsed. After a median follow-up of 31 months, 6 patients (49%) survived long term. Although limited by a small number of patients, this study suggests that patients with myelofibrosis and LT may achieve long-term remission after induction chemotherapy and ASCT.

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INTRODUCTION

Primary myelofibrosis (PMF) is a clonal myelogenous disease of unknown etiology characterized by neoplastic megakaryocyte proliferation, extensive bone marrow (BM) fibrosis, massive splenomegaly, mobilization of stem cells in circulation, and extramedullary hematopoiesis [1-3]. Secondary myelofibrosis (SMF) is the consequence of progression of polycythemia vera (PV) or essential thrombocythemia (ET) to a disease indistinguishable from PMF [4]. The disease evolves to a phase of extensive tumor burden, progressive cytopenias, followed eventually by a myelogenous blast phase that resembles acute myelogenous leukemia (AML), categorized by the World Health Organization (WHO) as myeloid leukemia evolving from a myeloproliferative neoplasm [1,5].

Leukemic transformation (LT) has a dismal prognosis with the current treatment strategies [6]. Allogeneic stem cell transplantation (ASCT) is a curative approach for patients with MF [7,8]; however, the outcomes of patients with LT are currently unknown. Here, we hypothesized that patients with myelofibrosis and LT can achieve durable long-term remission after ASCT.

PATIENTS AND METHODS

Selection of Patients

Of 55 consecutive patients with myelofibrosis who received an ASCT at the University of Texas M.D. Anderson Cancer Center between August 1994 and November 2008, 14 patients (25%) were identified to have LT (defined as >20% blasts in the BM or peripheral blood [PB]]). Patients with myelofibrosis and <20% blasts and patients with other myeloproliferative diseases transformed to AML were not included in this study. A retrospective study protocol, which included a waiver of informed consent, was approved by the M.D. Anderson Cancer Center institutional review board.

Characteristics of these patients are presented in Table 1. Thirteen patients received induction chemotherapy for LT, 8 with "3+7" regimen (idarubicin or daunorubicin plus cytarabine), 3 with cytarabine and either fludarabine (Flu) or azacytidine, and 2 with other agents. Six patients achieved complete remission (CR), 6 had a reduction in the percentage of BM blasts

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Table 1. Patient Characteristics

Number of patients	14
Age (median, range)	59 (50-67)
Sex	
Male	9
Diagnosis	
PMF	11
SMF	4
Lille Score at diagnosis of the time of LT	
0	4
1	7
2	3
Median time from MF to LT (months) (range)	38 (10-144) (n = 13)
Number of patients with prior splenectomy	5
Prior therapy for myelofibrosis	
Hydroxyurea	9
Thalidomide/lenalidomide	4
Interferon	3
Azacitidine/decitabine	2
Anabolic steroids	2
Erythropoietin	1
Bortezomib	1
Number of patients who received cytoreductive chemotherapy prior to transplant	13
Number of patients with LT in CR at transplant	6
Cytogenetics at LT	
Normal	3
CRS 1 abnormalities (+1, 1q-, t(1;6), der (1;19), t(1;17), dup(1), del(1))	7
CRS 7 abnormalities (del 7, 7q-, t(7;10))	3
CRS 8 abnormalities (+8, -8, t(3;8))	4
Complex karyotype	4

PMF indicates primary myelofibrosis; SMF, secondary myelofibrosis; LT, leukemic transformation; CR, complete remission from acute myelogenous leukemia; CRS, chromosome; MF, myelofibrosis.

(median final percentage of BM blasts prior to transplant was 7%, range: 0%-36%), and 1 had progressive disease (86% blasts) at the time of transplantation. Three patients had prior autologous (1) or ASCT (2) for myelofibrosis at different institutions.

Transplantation for acute leukemia was performed from matched siblings, unrelated or 1 antigen mismatched related donors (Table 2). Conditioning included reduced-intensity conditioning (RIC) preparative regimens in 9 patients using melphalan (Mel), Flu ± gemtuzumab ozogamicin, and myeloablative (MA) conditioning using busulfan (Bu)-based conditioning [9,10]. Although there are limitations to these terms, the conditioning regimens that included Bu 520 mg/m^2 total dose were considered MA conditioning whereas those including Mel 140 mg/m^2 or less were considered RIC. Antithymocyte globulin (ATG) was administered to patients who received a matched unrelated or mismatched related graft.

Definitions

Engraftment was defined as achieving an absolute neutrophil count (ANC) $> 0.5 \times 10^9$/L for at least 3 consecutive days before day 30, with donor derived cells detected by DNA microsatellite analysis. Platelet recovery was defined as the first day on which the platelet count was $>20 \times 10^9$/L unsupported by platelet transfusions for 7 days. Acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) were defined and graded according to previously described criteria [11,12].

Table 2. Transplant Characteristics

	Number
Donor	
MSD	8
MUD	4
1 antigen mismatched related	2
Cell type	
G-CSF mobilized peripheral blood stem cells	10
Bone marrow	4
Conditioning	
Reduced-intensity (Melphalan-based)	
Melphalan 140 mg/m^2 + fludarabine 120 mg/m^2 + Gemtuzumab (2, 4, 6, 9 or 16 mg/m^2)	8
Melphalan 100 mg/m^2 + fludarabine 120 mg/m^2	1
Myeloablative (Busulfan-based)	3
i.v. Busulfan 520 mg/m^2 + fludarabine 160 mg/m^2	1
i.v. Busulfan 520 mg/m^2 + clofarabine 120 mg/m^2 + fludarabine 40 mg/m^2	1
p.o. Busulfan 1 mg/kg × 10 doses + cyclophosphamide 120 mg/kg + thiotepa 750 mg/m^2	
GVHD prophylaxis	
Tacrolimus + methotrexate	13
Cyclosporine + methotrexate	1

MSD indicates matched sibling donor; MUD, matched unrelated donor; i.v., intravenous; p.o., oral; GVHD, graft-versus-host disease; G-CSF, granulocyte colony-stimulating factor.

Statistical Methods

Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method [13]. Days to engraftment for patients with or without splenectomy were compared using the Wilcoxon rank-sum test [14]. The incidence of disease progression, nonrelapse mortality (NRM), and GVHD was estimated using the cumulative incidence method to account for competing events. Death in the absence of disease progression, disease progression, and death without GVHD were considered as competing events for the respective outcomes. Statistical significance was defined at the .05 level.

RESULTS

Transplant outcomes are summarized in Table 2. Briefly, all patients engrafted after a median of 13 days for neutrophils and 21.5 days for platelets. Of 13 patients who had PB chimerism performed by PCR on day 30 after transplant, 10 had 100% donor myeloid and T cells. Three patients had a mixed chimerism (90% donor cells) on day 30, subsequently increased to 100% in 2 patients and decreased in 1 who subsequently relapsed.

Seven patients died after a median follow-up of 1 year, 3 of relapsed disease, 2 of infection, 1 of GVHD, and 1 secondary to decompensated liver