Nonmyeloablative allogeneic stem cell transplantation in elderly patients with hematological malignancies: Results from the GITMO (Gruppo Italiano Trapianto Midollo Osseo) multicenter prospective clinical trial

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This study aimed to evaluate the efficacy of a nonmyeloablative conditioning consisting of fludarabine and TBI in patients aged ≥60 years.A total of 32 patients (median age 62 years; range 60–70) with hematological malignancies were treated with fludarabine (30 mg/m^2 × 3–5 days) and 200 cCy TBI followed by allogeneic hematopoietic stem cell transplantation (HSCT) from a matched-sibling donor. GVHD prophylaxis consisted of cyclosporine and mycophenolate. Neutrophil recovery occurred in all patients at a median time of 16 days (range 9–34). Six patients did not become granulocytopenic. On day +30, 10 patients had >95% donor chimerism and 19 patients had mixed chimerism. The cumulative probabilities of Grade II–IV acute GVHD and chronic GVHD were 48 and 83%, respectively. Transplant-related mortality at 100 days and 1 year was 6 and 10%, respectively. The probabilities of 2-year overall (OS) and progression-free survival (PFS) were 39 and 35%, respectively. The estimated 2-year probability of OS and PFS for patients in early disease stages were 77 and 64%, respectively, which were significantly higher than the survival and PFS estimates of 0% obtained in patients with advanced disease stages at the time of transplant. Our analysis would suggest that for patients older than 60, this regimen is well tolerated and associated with a low incidence of transplant-related mortality. The leukemic burden at time of transplant has proven to be the most important risk factor for the outcome. Am. J. Hematol. 82:863–866, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established therapy for a variety of haematological malignancies, however even with the availability of HLA-matched sibling donors, conventional HSCT is associated with high rates of transplant-related mortality (TRM) in the region of 25–50% resulting at least partially from the toxicity of myeloablative preparative regimens [1]. The risk of TRM represents a major drawback in the allogeneic HSCT setting, especially in older patients [2]. Based on these considerations new strategies to reduce regimen-related toxicity have been investigated, prompting the development of less toxic, nonmyeloablative preparative regimens. This approach has the potential of extending allogeneic HSCT to a larger patient population including the elderly. Despite these considerations, data are scarce regarding the safety and efficacy of reduced intensity transplantation in patients over 60 years of age [3,4]. The present study addresses this issue by reporting our experience in 32 patients aged ≥60 years with haematological malignancies who received a reduced intensity HSCT.

Results

Patient characteristics

A total of 33 patients with various haematological malignancies were included in the study. Patients were transplanted between March 2000 and June 2005. Patient characteristics are outlined in Table I. Disease status was defined as early phase (acute leukaemia, myeloproliferative diseases, or poor-risk myelodysplasia in first complete remission, and lymphoid malignancy in first remission) in 17 patients (54%). In all, four patients had a prior autologous HSCT, and three a prior myeloablative allogeneic HSCT.

Hematologic recovery and chimerism

One patient died on day 5 with no signs of engraftment. In six patients neutrophil counts never decreased below 0.5 × 10^9/L. For the remaining 26 patients, the median time to neutrophil recovery was 16 days (range 9–34 days); median ANC nadir was 0.2 × 10^9/L. Thirty-two patients had chimersim evaluation on unsorted bone marrow aspirate. Three patients with low percentage of donor cells (1–9%

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Received for publication 19 January 2007; Revised 23 March 2007; Accepted 10 April 2007

Am. J. Hematol. 82:863–866, 2007.

Published online 6 July 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20990

TABLE I. Patient and Disease Characteristics

Characteristics	
No. of patients	33
Age (years), median (range)	62 (60–70)
Gender	
Male to female	17/16
Female to male	8
Underlying disease	
AML	12
MDS, RA	3
RAEB	5
RAEBt	3
CMML	2
AMM	1
NHL	2
CLL	3
ALL	2
Disease duration, median (range), days	184 (44–2855)
Disease phase at transplant	
Early	17
Advanced	16
Source of progenitors	
Peripheral blood stem cells	32
Bone marrow	1
Donor/recipient CMV-negative	1
TNC infused ($\times 10^8$/kg recipient BW), median (range)	11 (4–29)
CD34+ cells infused ($\times 10^6$/kg recipient BW), median (range)	7 (3–20)
CD3+ cells infused ($\times 10^8$/kg recipient BW), median (range)	3 (1–8)
Preparative regimen	
Fludarabine 90 mg/m^2, TBI 200 cGy	18
Fludarabine 150 mg/m^2, TBI 200 cGy	15

Abbreviations: AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukaemia; AMM, agnogeneic myeloid metaplasia with myelofibrosis; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia.

donor cells) had evidence of recurrence of their underlying disease shortly after the chimerism studies.

At the time of first testing after engraftment, 10 patients had complete donor chimerism, and 19 had mixed chimerism, ranging from 13 to 94% donor. Eight of the 19 patients with mixed chimerism converted spontaneously to complete chimerism, and 1 after donor lymphocyte infusion (DLI); 9 patients relapsed, 1 rejected the graft and received a second HSCT. The latter patient is alive and disease free.

The median time to platelet 20 $\times$ 10^9/L was 15 days (range 9–164 days); in 14 cases, platelet never decreased below 20 $\times$ 10^9/L.

Toxicity and GVHD

Among the 30 evaluable patients, Grade II–IV and III–IV acute GVHD occurred in 17 (57%) and 8 (27%) patients, respectively; the cumulative incidence is 48% (95% CI, 29–67%) and 20% (95% CI, 6–35%), respectively.

Of the 24 evaluable patients, 17 (71%) developed chronic GVHD, which was extensive in seven cases; the cumulative incidence of chronic GVHD was 83% (95% CI, 58–100%). Recurrence of the underlying disease occurred in nine patients (53%) with chronic GVHD and two patients (28%) with no signs of chronic GVHD.

Overall, TRM occurred in four patients with a cumulative incidence of 10% (95% CI, 1–20%) at 1 year after HSCT.

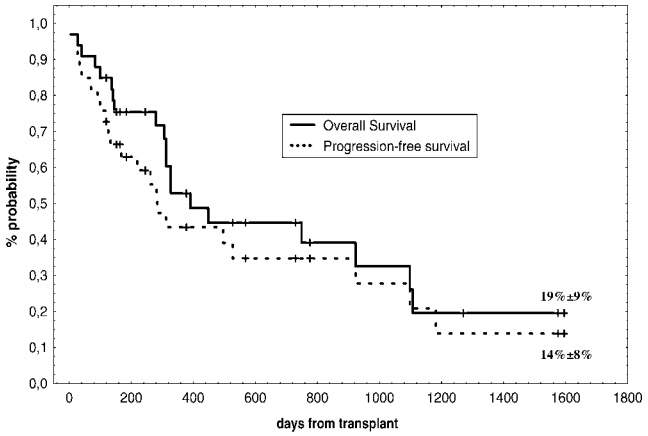

Figure 1. Kaplan–Meier analysis of overall survival and progression-free survival in 33 patients with haematological malignancies undergoing nonmyeloablative stem cell transplantation. The 2-year overall and progression-free survival were 39% ± 9% and 35% ± 9%, respectively.

Three patients died of complications (infection) related to acute (n = 1) or chronic GVHD (n = 2); one patient died of multiorgan failure on day 5 post-HSCT. Two of 17 patients (11%) with early disease stages and 2 of 16 patients (12%) with advanced disease stages died of transplant-related complications. Similarly, two patients (11%) who received fludarabine 90 mg/kg and two patients (13%) who received fludarabine 150 mg/kg died of transplant-related complications.

Responses and outcome

With a median follow-up of 527 days (range 119–1595 days), 13 patients are alive and 20 have died. Of these, four patients died of treatment-related complications, and 16 of disease relapse.

The 1-year and 2-year OS is 53% ± 9% and 39% ± 9%, respectively (Fig. 1). A total of 11 patients remain alive and disease free. Eighteen patients have relapsed, 16 with acute leukaemia/Myelodysplasia (MDS) and 2 with lymphomas, thus resulting in a relapse rate of 50% ± 9% and 60% ± 10%, respectively at 1- and 2-year post-transplant. Two patients with MDS and one patient with acute myeloid leukaemia (AML) were given DLI for disease recurrence, but did not respond.

Overall, the 1-year and 2-year PFS is 43% ± 9% and 35% ± 9%, respectively (Fig. 1).

At 1 year and 2 years, OS for patients with early disease stages was 77% ± 10%, with a median follow-up of 568 days (range 119–1,595 days) compared with 12% ± 9% and 0%, respectively for patients in advanced disease stages, with a median follow-up of 154 days (P = 0.0001) (Fig. 2).

PFS at 1 year and 2 years was 72% ± 11% and 64% ± 9%, respectively for patients in early disease stages and 14% ± 9% and 0% for patients in advanced disease stages (P = 0.003) (Fig. 3).

Relapse probability at 1- and 2-year post-transplant was 21% ± 9% and 30% ± 10%, respectively in patients with early disease and 81% ± 11% and 100%, respectively in patients with advanced disease (P = 0.0004).

Six of 18 patients (33%) conditioned with fludarabine 90 mg/kg were alive and disease free, as compared with 5 of 15 (33%) patients who received 150 mg/kg of fludarabine (P = 1.0).

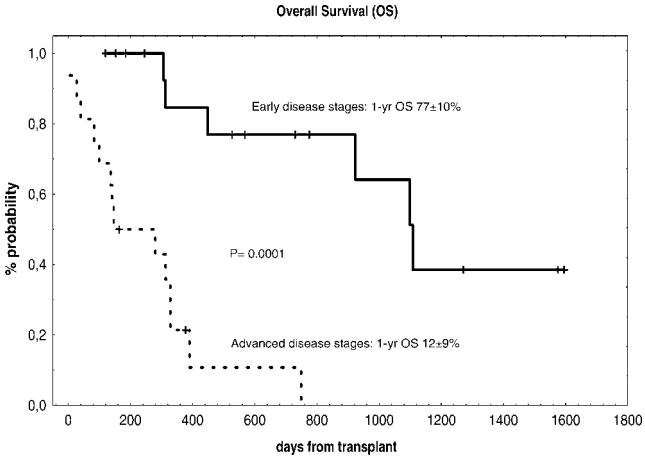

Figure 2. Comparison of post-transplant probability of survival for patients with early (continuous line) and advanced (broken line) disease stages. Estimated 1-year overall survival is 77% ± 10% for patients in early disease stages. Estimated 1-year overall survival for patients transplanted in advanced disease stages is 12% ± 9%.

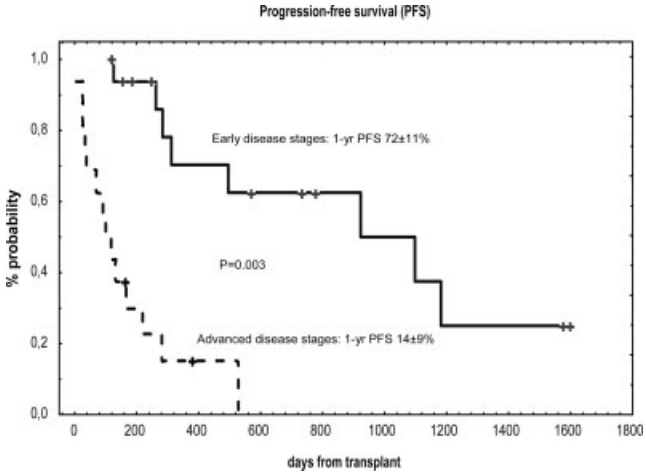

Figure 3. Comparison of post-transplant probability of progression-free survival for patients with early (continuous line) and advanced (broken line) disease stages. Estimated 1-year progression-free survival is 72% ± 11% for patients in early disease stages. Estimated 1-year progression-free survival for patients transplanted in advanced disease stages is 14% ± 9%.

When a more homogeneous subgroup of 26 patients with AML or MDS was analyzed, the OS at 1 and 2 years was 58% ± 10% and 49% ± 10%, respectively, and the PFS at 1 and 2 years was 46% ± 10% and 37% ± 9% respectively. Three (11%) of these selected patients died as a result of the transplant-related complications.

Discussion

Transplant strategies based on reduced intensity or non-myeloablative conditioning have expanded the patient-population eligible for HSCT. The results of our prospective clinical trial on 33 elderly patients receiving stem cell grafts after reduced intensity conditioning (RIC) for the treatment of haematological malignancies suggest that this approach offers the possibility of long-term disease-free survival among selected patients in this age group. We have adopted the preparative regimen originally described by the Seattle group [5] on the basis of the encouraging results in terms of low rates of nonfatal rejection and early mortality.

The rate of graft failure in our cohort of elderly patients was low at 3%: only one patient rejected the graft after receiving a stem cell dose of 7×10^6/kg and 90 mg/kg of fludarabine; the patient had an AML and received before the transplant standard chemotherapy treatment. A recent study from a Canadian group analyzed the outcomes of 24 patients aged $\geq$60 years with AML/MDS receiving RIC with fludarabine and low dose TBI [6]. The cumulative probabilities of acute and chronic GVHD were 45 and 74%, respectively. Acute and chronic GVHD remain a significant problem even in our patients: 48% of the patients developed severe acute GVHD, 83% of the patients had clinical signs of chronic GVHD and approximately half of these showed extensive chronic GVHD. Three of the four patients who died of transplant-related complications succumbed of GVHD (acute GVHD in one case and chronic GVHD in two cases) combined with infectious complications. Apparently, chronic GVHD did not have a protective effect on post-transplant relapses although the limited number of patients has to be taken into consideration when interpreting our results.

Of much greater clinical importance is the low TRM observed in our series: overall, the cumulative incidence was 10% at 1 year. This finding compares favourably with other studies including either ablative and nonmyeloablative preparative regimens. Shapira and coworkers [7] reported a TRM rate of 35% among 37 elderly patients (median age 60 years) with haematological malignancies treated with nonmyeloablative conditioning including fludarabine, low-dose busulphan, and antithymocyte globulin, while TRM rates were even higher in HSCT from unrelated donors [8]. Day-100 TRM was 27% in the study of Wallen et al. describing 52 older patients treated with myeloablative conditioning [9]. Similar results have been reported by Ditschkowski et al. in a group of 215 patients older than 50 years of age, receiving myeloablative allogeneic HSCT from matched sibling donors or matched unrelated donors [10].

Unfortunately the low TRM did not translate into a consistent survival because of the high rate of relapses. Nonetheless, it should be underscored that patients included in this report had underlying malignancies that were predictive of a poor outcome, mostly acute leukemias/MDS and relapsing malignancies after a prior stem cell transplant. Despite the high-risk status of the patients, our observations corroborate the results obtained from other studies demonstrating the feasibility of reduced intensity HSCT in elderly and confirm that the most relevant prognostic factor for post-transplant outcome is the disease status at the time of graft. Although our recipient cohort is small and the observation time limited, the 1-year PFS for patients with malignancies in early disease phase is 72% as compared with 14% for patients with high leukemic burden at HSCT. Interestingly, our findings indicate that the intensity of transplant conditioning was not a decisive factor in preventing post-transplant progression. Infact, we did not observe any significant difference in terms of PFS among patients who received fludarabine 90 mg/kg as compared with 150 mg/kg.

Design and Methods

Patient eligibility

Eligibility criteria for entry into this study included patients with a myeloid or lymphoid malignancy potentially treatable with an allogeneic transplant, who were $\geq$60-years old.

All patients provided written informed consent and the study was approved by all local institution review boards.

Donor selection

All patients received grafts from HLA-matched sibling donors. Donors were selected based on serologic typing of A and B antigens and high-resolution typing of DR antigens. For the most recently evaluated donor–recipient pairs, high-resolution typing of Class I antigens was also available. Donors' work-up was according to donor centre guidelines.

The median age of donors was 56 years (range 41–72 years). The source of stem cells was granulocyte colony-stimulating factor-mobilized peripheral blood stem cells in all patients except one who received bone marrow. The targeted cell number was at least 5×10^6 CD34+ cells/kg recipient body weight.

Conditioning regimen and GVHD prophylaxis

Patients were given reduced-intensity conditioning based on fludarabine 90–150 mg/m^2 intravenously and single dose TBI (200 cGy); unmanipulated stem cells were infused on day 0. The dose of Fludarabine (three doses vs. five doses) was selected based on disease type and disease status at the time of HSCT, physician discretion, and prior therapy.

Graft-versus-host disease (GVHD) prophylaxis consisted of MMF 15 mg/kg orally twice a day from day +1 to day 30 with no taper, and CSA 3 mg/kg orally twice a day from day −7 to day 30 with taper in absence of GVHD to day 180.

G-CSF was not routinely administered to the patients. The standard institutional regimen of antibiotics was employed for the prevention of bacterial, viral, fungal, and pneumocystis infections.

Definitions and evaluation of response

Myeloid and platelet engraftment were defined as the first of three consecutive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L and the first of 3 days with an unsupported platelet count $\geq 20 \times 10^9$/L.

The incidence and the time to development of Grades I–IV acute GVHD were evaluated in patients surviving 21 days with evidence of engraftment. The incidence and time to occurrence of any chronic GVHD were evaluated in patients surviving 100 days or longer after transplantation with evidence of engraftment. The diagnosis of acute and chronic GVHD was based on the characteristic clinical appearance of the symptoms of organ involvement, with histopatologic confirmation whenever possible. Grading of acute and chronic GVHD followed the commonly accepted criteria [11,12].

Chimerism status in the unfractionated bone marrow has been assessed regularly using fluorescence in situ hybridization to detect X and Y chromosome for recipients of sex mismatched transplants, polymerase chain reaction-based analysis of polymorphic microsatellite regions for recipients of sex matched transplants. Full donor chimerism was defined as the presence of >95% cells of donor origin, whereas mixed chimerism was defined as the presence of at least one and no more than 95% cells of donor origin.

Statistical analysis

Data were updated as of January 2006.

Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier method [13].

OS was defined as the time between stem cell infusion to death from any cause, and surviving patients were censored at last follow-up.

PFS was defined as the time from between stem cell infusion to a documented relapse or progression, death from any cause, or last follow-up.

The probability of TRM was calculated using cumulative incidence estimates [14]. For the endpoint of TRM, disease progression was regarded as a competing risk. Patients who died without disease progression were categorized as TRM, while patients alive without progression were censored at last follow-up and those who suffered disease progression were censored at progression.

The probabilities of acute and chronic GVHD were summarized using cumulative incidence estimates. In the analysis of GVHD rates death due to other causes were considered as competing risk.

In patients with disease progression, progression was listed as their primary cause of death regardless of the associated events.

In conclusion, the results of our study strengthen the concept that patients should not be deferred from a potentially curative therapeutic approach such as the allogeneic stem cell transplantation, exclusively because of older age. A reduced intensity preparative regimen including fludarabine and low dose TBI may be considered a viable option for selected patients with haematological malignancies transplanted in remission and early in the course of disease. Prospective studies with a larger patient group and longer follow-up are warranted to confirm our preliminary results.

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