Myeloablative reduced-toxicity IV busulfan-fludarabine and allogeneic hematopoietic stem cell transplant for patients with acute myeloid leukemia or myelodysplastic syndrome in the sixth through eighth decades of life

Gheath Alatrash, DO PhD[1,*], **Marcos de Lima, MD**[1,*], **Nelson Hamerschlak, MD**[2], **Matteo Pelosini, MD**[3], **Xuemei Wang, MS**[4], **Lianchun Xiao, MS**[4], **Fabio Kerbauy, MD**[2], **Alexandre Chiattone, MD**[1], **Gabriela Rondon, MD**[1], **Muzaffar H. Qazilbash, MD**[1], **Sergio A. Giralt, MD**[1], **Leandro de Padua Silva, MD**[1], **Chitra Hosing, MD**[1], **Partow Kebriaei, MD**[1], **Weiqing Zhang, MD**[1], **Yago Nieto, MD PhD**[1], **Rima M. Saliba, PhD**[1], **Richard E. Champlin, MD**[1], and **Borje S. Andersson, MD PhD**[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX

[2]Department of Hematology and Bone Marrow Transplant, Hospital Israelita Albert Einstein, Sao Paulo, Brazil

[3]Division of Hematology, Department of Oncology, Transplants and New Technologies in Medicine, University of Pisa, Pisa, Italy

[4]Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract

The optimal pretransplant regimen for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in patients 55 years of age remains to be determined. The myeloablative reduced-toxicity 4-day regimen IV busulfan (Bu) (130 mg/m^2)-IV fludarabine (Flu) (40 mg/m^2) is associated with low morbidity and mortality. We analyzed 79 patients 55 years of age (median, 58 years) with AML (n=63) or MDS (n=16) treated with IV Bu-Flu conditioning regimens between 2001 and 2009 (median follow-up, 24 months). The patients who received this regimen had a good performance status. The 2-year overall survival rates for patients in first complete remission (CR1), second CR (CR2), refractory disease and for all patients at time of transplantation were 71%, 44%, 32%, and 46%, respectively; 2-year event-free survival rates for

Correspondence: Borje S. Andersson MD PhD, Department of Stem Cell Transplantation and Cellular Therapy, Unit 0423, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; bandersson@mdanderson.org; phone (713) 794- 5743; fax: (713) 794-4747.
*Gheath Alatrash and Marcos de Lima contributed equally to this manuscript.

patients in CR1, CR2, or refractory disease at time of transplantation and for all patients were 68%, 42%, 30%, and 44%, respectively. One-year transplant-related mortality (TRM) rates for patients who were in CR or who had active disease at the time of transplantation were 19% and 20%, respectively. Grade II-IV acute graft-versus-host disease was diagnosed in 40% of the patients. Our results suggest that age alone should not be the primary reason for exclusion from receiving myeloablative reduced-toxicity conditioning with IV Bu-Flu preceding transplantation in patients with AML/MDS.

Introduction

Acute myeloid leukemia (AML) is primarily a disease of the elderly, with a median patient age at diagnosis of 70 years (1). AML is an aggressive disease with AML patients having a 5-year relative survival rate of 5% to 15%. Patient-, disease-, and donor-related issues limit and, at times, exclude the use of allogeneic hematopoietic stem cell transplantation (allo-SCT), which can be curative. Many factors contribute to the adverse outcomes of allo-SCT in elderly patients with AML (2-4). First, age-associated comorbid conditions, impact the tolerance to chemotherapy. Second, many pharmaceutically active agents are metabolized differently in older individuals (5, 6) and total systemic exposure of the conditioning therapy is not only related to overall toxicity, but also to acute graft-versus-host disease (GvHD), presumably through cytokine release from damaged organs (7). Third, the incidence of GvHD increases with age; this higher incidence of GvHD is partly due to an altered immune response, such as enhanced allogeneic stimulatory activities of antigen-presenting cells (8). Fourth, the potential of T-cells to mediate antileukemia activities is reduced in elderly patients, thereby limiting the beneficial graft-versus-leukemia effect. Additionally, the diversity in the naive T-cell repertoire is decreased after the seventh decade of life; this deficiency is compounded by a reduced ability of the thymus to rebuild a broad T-cell repertoire to target a wide range of antigens (9). Finally, stem cell homing, and therefore engraftment, may also be adversely affected by aging (10). These deficiencies underscore the critical need for a regimen that will maximize the eradication of residual leukemia cells and allow prompt engraftment with rapid reconstitution of immune response to mediate optimal antileukemia immunity.

Effective cytoreduction is critical in the treatment of elderly patients with AML, as it reduces the disease burden, permits rapid engraftment and immune reconstitution with long-term disease-control. If an ablative regimen can be safely delivered to patients up to and beyond 65 years of age, the currently held notion that reduced-intensity conditioning (RIC) is the optimal approach in this age group would be challenged. Paradoxically, from the antileukemia standpoint, and also in consideration of the immunological challenges imposed by aging, an optimally cytoreductive, myeloablative conditioning regimen may be even more desirable in older patients.

The reduced-toxicity IV busulfan (Bu)-fludarabine (Flu) regimen was shown to be a safe myeloablative conditioning program when compared with the more commonly used regimen of Bu-cyclophosphamide (Cy) in the treatment of patients with AML (11). In that study the outcome of 67 patients who received the Bu-Cy2 regimen were compared with 148 patients

who received the Bu-Flu conditioning regimen prior to allo-SCT for AML; patients whose disease was in first complete remission (CR1) who received Bu-Flu had significantly better 3-year overall survival (OS) and event-free survival (EFS) rates than those who received Bu-Cy, despite the higher median age of the Bu-Flu population (46 versus 39 years) (11). Of importance, the 3-year treatment-related mortality, which is often attributed to the conditioning regimen's toxicities, was significantly lower in the Bu-Flu group (14% versus 34%). In our early study (11), we had transplanted some patients who were in the 7th decade of life using the Bu-Flu regimen, and our impression was that the results would support the use of IV Bu-Flu in "elderly patients"-- in this report defined as being older than 50-55 years. Based on the success of Bu-Flu in this age bracket, we hypothesized that IV Bu-Flu might be a safe and effective conditioning therapy in elderly patients prior to allo-SCT for AML and MDS.

In view of this hypothesis, we retrospective analyzed 79 patients treated with the reduced-toxicity myeloablative regimen IV Bu-Flu. We critically examined the use of IV Bu-Flu followed by allo-SCT for AML and MDS patients in the 6th to 8th decades of life, and the present manuscript describes details of this investigation. Our data support the systematic use of the IV Bu-Flu conditioning regimen in high-risk patients older than 50-55 years, if they have a good performance status.

Materials and methods

Patients

We studied all patients 55 years or older who had been treated in 2 consecutive prospective protocols conducted at our institution (The University of Texas MD Anderson Cancer Center) and 5 patients treated with the same regimen in a prospective clinical trial at Hospital Israelita Albert Einstein (Sao Paulo, Brazil). The first protocol was a phase II study that investigated high-dose IV Bu-Flu with fixed dose delivery (12), while the second protocol compared a regimen of IV Bu-Flu with fixed-dose Bu with one containing dose-adjusted Bu in which pharmacokinetic monitoring targeted a systemic exposure of Bu as represented by the average daily area under the concentration vs. time curve for Bu of 6000 μMol*min for each of the 4 days of the regimen, similar to previous reports(13, 14). The studies were approved by institutional review board and all patients provided written informed consent as per institutional guidelines. IV busulfan was purchased from Otsuka America Pharmaceutical, Inc. (Princeton, NJ, USA).

To be eligible for these studies, patients were required to have adequate normal organ functions: hepatic function (SGPT 200 IU/mL, serum bilirubin and alkaline phosphatase within accepted laboratory standard normal limits or considered not clinically significant, and no evidence of chronic active hepatitis or cirrhosis); renal function (serum creatinine 1.5 mg/dL); cardiac function (left ventricular ejection fraction >45%; no uncontrolled arrhythmias or symptomatic cardiac disease); and pulmonary function (no symptomatic pulmonary disease, and FEV1, FVC and DLCO 50% of expected corrected for hemoglobin). AML patients were required to have disease status past first remission, primary induction failure, in first or subsequent relapse, or in first remission with intermediate or high-risk cytogenetics; MDS with intermediate or high risk International

Prognostic Scoring System score; no systemic therapy administered within 21 days prior to trial enrollment; no active infection; and ZUBROD performance status <2. Good-risk cytogenetics included patients with translocation (t)(8;21); inversion (inv)(16) or t(16;16); deletion (del)(9q); or t(15;17). Intermediate-risk cytogenetics included patient with a normal karyotype; -Y; del (5q); loss of 7q; t(9;11); +11; del(11q); abnormality (12p); +13; del(20q); or +21. High-risk cytogenetics included patients with a complex karyotype (3 abnormalities); inv(3) or t(3;3); t(6;9); t(6;11); -7; +8 (sole abnormality); or +8 with one other abnormality other than t(8;21), t(9;11), inv(16), or t(16;16); t(11;19)(q23;p13.1) (15).

The conditioning regimen consisted of IV Flu (40 mg/m^2) (Genzyme Inc., Cambridge, MA, USA) and IV Bu (130 mg/m^2) administered over a 3-hour period once a day on pretransplant days -6 to -3 (12). Tacrolimus and mini-methotrexate were used for GvHD prophylaxis (16), and pentostatin (Hospira Inc., Lake Forest, IL, USA) was administered in 13 cases (18%). Thymoglobulin (4 mg/kg) (Genzyme Inc., Cambridge, MA, USA) was administered to those who received grafts from mismatched related or unrelated donors on days -3 to -1. All donor-recipient pairs were fully typed at high resolution for the alleles of HLA-A, -B, -C, -DR, -DQ.

Statistical analysis

The primary outcomes of interest in the current analysis were OS and EFS rates, cumulative incidence of transplant-related mortality (TRM), and cumulative incidence of acute GvHD. All outcomes were evaluated from the date of transplantation, with the exception of monitoring for regimen-related adverse events, which included the days of chemotherapy administration. The probabilities of survival were estimated using the Kaplan-Meier method (17, 18). The log-rank test was used to compare survival probabilities between subgroups of patients. The cumulative incidence of TRM was estimated by considering death due to disease relapse and/or resistance or any other non-treatment-related cause as a competing risk. The cumulative incidence of acute GvHD was estimated by considering disease progression or death due to any cause as a competing risk. All statistical analyses were performed using SAS and S-plus software (SAS Institute Inc., Cary, NC). *P* values less than 0.05 were deemed statistically significant (17, 18).

Results

Patients

Seventy-nine patients 55 years or older with either AML (n = 63; secondary AML [n = 8]) or MDS (n = 16) underwent allo-SCT from September 2001 to May 2009. Pretransplant patient characteristics are presented in Table 1. The median age at the time of transplantation was 58 years (range, 55-76 years); 5 patients were older than 65. The median survival was 8 months (range, 1-82 months). Eighty percent (n=20) and 16% (n=4) of patients in CR1 had intermediate- and poor-risk cytogenetics, respectively, and cytogenetics were unknown in 1 patient. Six percent (n=1), 82% (n=14) and 6% (n=1) of patients in CR2 had good-, intermediate-, and poor-risk cytogenetics, respectively; cytogenetics were unknown in 1 patient. The median hematopoietic stem cell transplantation comorbidity index (HCT-CI) score was 1 (19).

Overall and event-free survival

The 2-year OS and EFS rates for the 25 patients who underwent transplantation while in CR1 were 71% and 68% respectively (Table 2; Figure 1 A-B). The 2-year OS and EFS rates for the entire cohort were 46% and 44%, respectively (Figure 1C-D). The 17 patients who underwent transplantation while their disease was in second complete remission (CR2) had 44% 2-year OS rate while the 37 patients who had active disease at the time of allo-SCT had 32% 2-year OS rate. Thirty-two percent of patients had disease progression (n=25). Disease status was the strongest predictor of OS time (P=0.006), with patients in CR1 having the longest OS time, followed by those in CR2 and those with active disease at time of transplantation.

Post-transplant outcomes, graft-versus-host disease and transplant-related mortality

Post-transplant outcomes are reported in Table 2. Engraftment was achieved in all patients. At day +30, 73% of patients (n=56) had achieved full donor chimerism and 23% (n=18) mixed chimerism (defined as the presence of any recipient cell or DNA as detected by cytogenetics, fluorescence in situ hybridization or DNA microsatellite polymorphisms); chimerism data was unavailable for 5 patients. Overall 100-day mortality was 6% (n=5) and was due to secondary graft failure (n=1), persistence of disease (n=1), liver failure (n=1), CNS bleed (n=1) and pre-existing radiation induced brain toxicity (n=1). Forty one percent of patients (n=32) developed grade II-IV acute GvHD, 7% (n=5) developed grade III-IV acute GvHD, and 43% (n=34) developed chronic GvHD. The cumulative incidence of acute GvHD (grades II-IV) is shown in Figure 2. Our analysis also showed that the HCT-CI score was higher (median score, 2) in patients with grade II-IV acute GvHD, compared with patients who had acute GvHD grades 0-1 (median score, 1) (P=0.02).

TRM was 1% at day +30 for all patients, and was highest in patients who underwent stem cell transplantation with active disease. TRM rates at day +100 for patients who underwent stem cell transplantation while in CR and for patients with active disease at time of stem cell transplantation were 5% for both groups. One-year TRM rates for patients who were in CR or who had active disease at the time of stem cell transplantation were 19% and 20%, respectively (Table 3).

Effects of age on overall survival

We further investigated whether age at the time of allo-SCT affected OS rates. For this analysis, we allocated the patients into 2 groups using the median age of 58 years as the cutoff (i.e.< 58 versus   58 years). Our results showed that OS was not significantly affected by age (median follow-up, 24 months) (Figure 3). Our data also showed that age alone did not affect outcome, regardless of disease status at the time of transplantation (Figure 4).

Discussion

In this analysis of 79 patients with AML or MDS who were   55 years of age at time of allo-SCT, we showed good outcomes including OS, EFS, TRM and GvHD rates following the use of the myeloablative, reduced-toxicity IV Bu-Flu regimen. Since it remains unknown if there should be an optimal age to use for excluding patients from allo-SCT or from receiving

this type of myeloablative regimens, and since many older adults with AML or MDS are offered RIC regimens prior to allo-SCT purely because of their age, our results challenge the current treatment tradition of offering mostly reduced-intensity programs for older patients with AML and MDS. Furthermore, our findings are especially important since AML and MDS are of intermediate sensitivity to the graft-versus-leukemia effect, and higher doses of chemotherapeutic agents are often required for effective disease control (20, 21). Therefore, we show that selected patients 55 years of age with AML or MDS can be safely treated with the reduced-toxicity IV Bu-Flu regimen, with acceptable overall outcomes and encouraging long-term disease control.

Our results are consistent with our prior report that employed IV Bu-Flu as a conditioning regimen for allo-SCT in a cohort of patients with a median age of 46 years (11, 12). The 2-year OS and EFS rates we observed here for patients whose disease was in CR1 were 71% and 68%, respectively; these rates were similar to the OS and EFS rates (78% and 74%, respectively) that we previously reported using this myeloablative IV Bu-Flu regimen (11, 12). Additionally, our outcomes compare favorably to RIC IV Bu-Flu (22, 23), which in older (60 years, median age, 63 years) leukemia patients (62% with AML or MDS) was shown to have 2-year cumulative incidence of non-relapse mortality NRM and OS of 10% and 46%, respectively (22).

It has lately become a practice to exclude older AML or MDS patients from myeloablative conditioning regimens. This is unfortunate, knowing that, in comparison with RIC regimens, a more potent disease eradication may yield a distinct benefit in patients. In one study, elderly patients (median age, 64 years) treated with the RIC regimens consisting of Flu, melphalan, and carmustine followed by allo-SCT achieved 1-year OS, disease-free survival, and NRM rates of 68%, 61%, and 22%, respectively (24). Another study in older patients (median age, 53 years) using a non-myeloablative conditioning regimen with IV Flu and oral Bu showed 4-year OS and EFS and 1-year NRM rates of 42%, 44%, and 16%, respectively (25). We have previously reported 3-year OS and EFS and 1-year NRM rates of approximately 40%, 20%, and 20%, respectively, in older patients (average age, 61 years) who received the non-myeloablative regimen Flu, cytarabine, and idarubicin (20).

Previous studies using myeloablative conditioning regimens prior to allo-SCT in elderly patients have reported poor outcomes secondary to high NRM rates. Wallen et al (26) evaluated ablative allo-SCT in adults 60 years or older (median age, 63 years) in which most patients received Bu-Cy (67%) or total-body irradiation (TBI)-Cy (21%), and only 10% of the patients received Bu-Flu; 3-year OS and relapse rates were estimated to be 34% and 24%, respectively; 100-day and 3-year NRM rates were 27% (versus 5% in our study) and 43%, respectively; and the acute GvHD (grade III-IV) rate was 20% (versus 7% in our study). In a subgroup analysis of older patients with AML who received unrelated donor grafts preceded by RIC or myeloablative conditioning regimens, Ringden et al (27) showed that patients 50 years or older (median age, 54 years) who received myeloablative conditioning regimens had 2-year leukemia-free survival, NRM, and acute GvHD (grade II-IV) rates of 43%, 39%, and 29%, respectively. However, similar to the study by Wallen et al (26), in the report by Ringden et al (27) only 14% of patients 50 years or older received Bu-Flu, whereas the majority of patients received either TBI-Cy (47%) or Bu-Cy (34%).

Cahn et al (28) retrospectively compared allo-SCT in AML patients over 40 years old to those age 40 and younger who underwent transplantation while their disease was in CR1 and reported similar relapse incidence and OS rates between the 2 groups; however, the rate of TRM was higher in patients older than 40 years, and most of these patients received Cy-TBI or Bu-Cy as their conditioning regimens. Likewise, in an analysis of 71 patients with de novo MDS who received Cy-TBI or Bu-Cy conditioning regimens, Sutton et al (29) reported shorter OS and EFS times and a higher relapse rate among patients who underwent transplantation at a later age (median, 37 years). We recognize the plethora of data that support RIC regimens in older AML and MDS patients, but when contrasted with these previous studies, our results highlight the need to re-evaluate age as an exclusion criterion for myeloablative regimens in light of the improved outcomes with IV Bu-Flu.

Recently, studies of patients 50 years or older with AML or MDS were conducted by the European Group for Blood and Marrow Transplantation and showed increased disease relapse rates following RIC compared with myeloablative conditioning regimens; in essence, the increase in disease relapse for RIC offsets the increase in TRM for the myeloablative regimens (27). Our analysis does not compare current data with historical controls, and in the absence of randomized trials, the issue of dose intensity remains unresolved. However, our findings suggest that older patients can benefit from the reduced-toxicity, myeloablative IV Bu-Flu regimen, which we showed likely to be less toxic and significantly safer than other commonly used myeloablative regimens. It is assumed that providing optimized cytoreduction contributes to improved long-term disease control (20, 30).

In view of our results, we recommend that the reduced-toxicity IV Bu-Flu regimen be considered for patients up to at least age 65, unless they suffer serious comorbid conditions. The tolerance for this therapy in elderly patients with serious comorbidities has not been evaluated under stringent, well-controlled conditions, and such patients may benefit from additional precautions. The regimen could however be considered for selected patients with comorbid conditions in this age group, if the treatment is given in a controlled clinical study to evaluate the tolerance to administered treatment in such a setting. As previously demonstrated in younger patients, the regimen seems especially fit for patients whose disease is in CR (11, 12). For patients whose disease is not in CR at the time of allo-SCT, to date, no regimen has been identified as the "standard conditioning regimen" and a variety of approaches are under investigation, including the replacement or supplementation of fludarabine with clofarabine (31) complementation of IV Bu-Flu with low-dose TBI (32) and/or post-allo-SCT maintenance therapy to prolong CR in high-risk patients (33).

Acknowledgments

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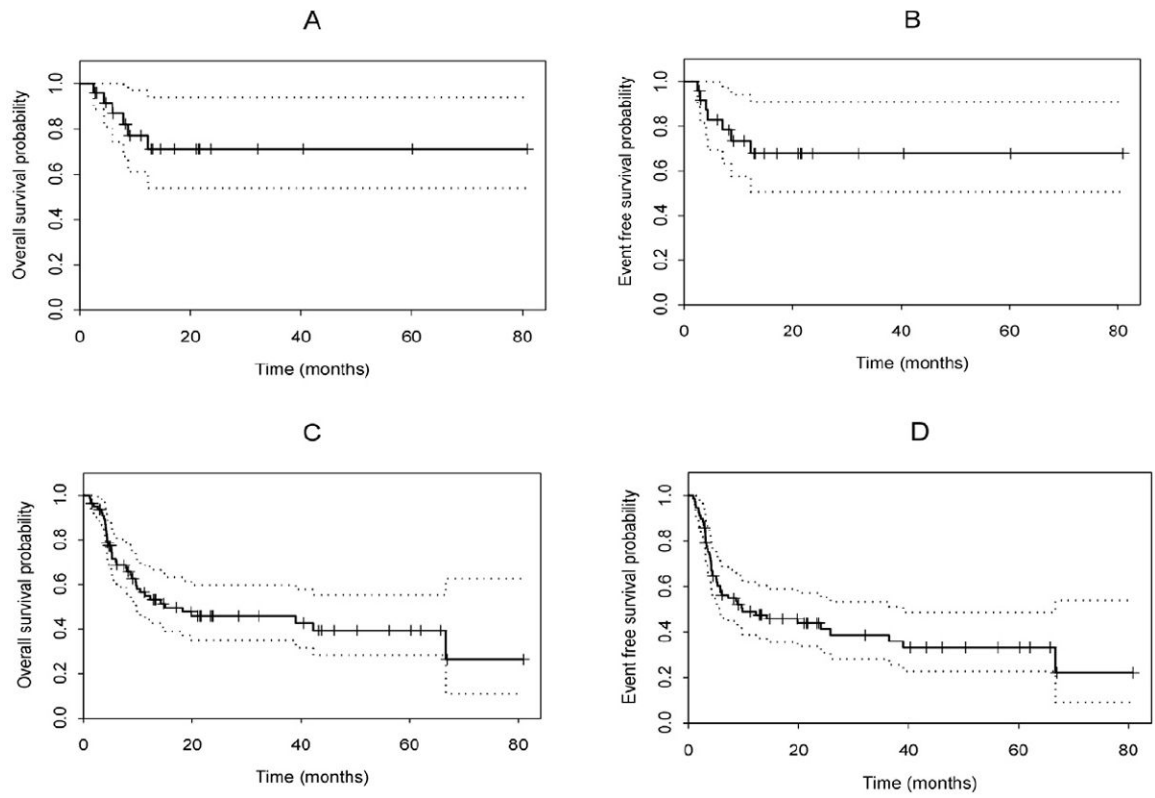
Figure 1. Kaplan-Meier curves for OS and EFS

OS and EFS probabilities for (A-B) patients in CR1 (n=25) and (C-D) for entire cohort (n=79).
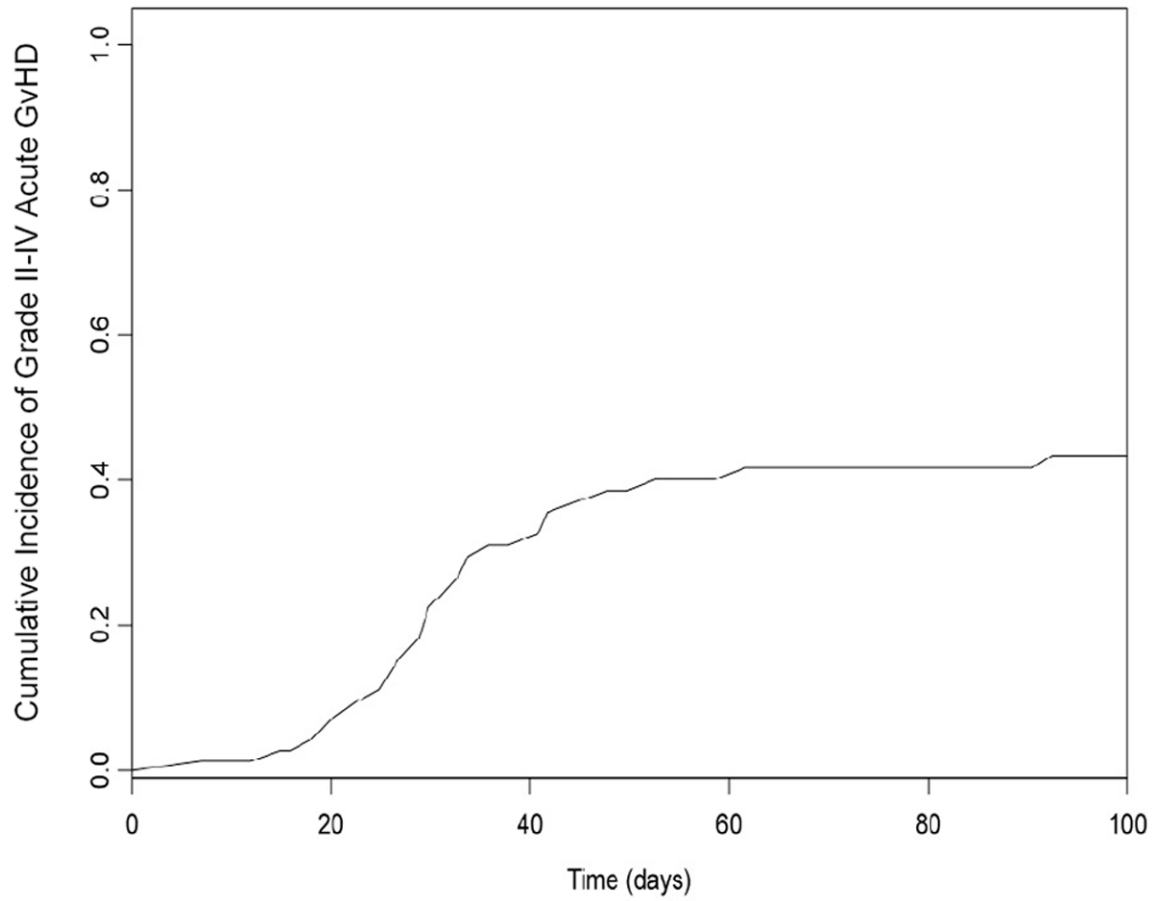
Figure 2. Cumulative incidence of grade II-IV acute graft-versus-host disease (GvHD)
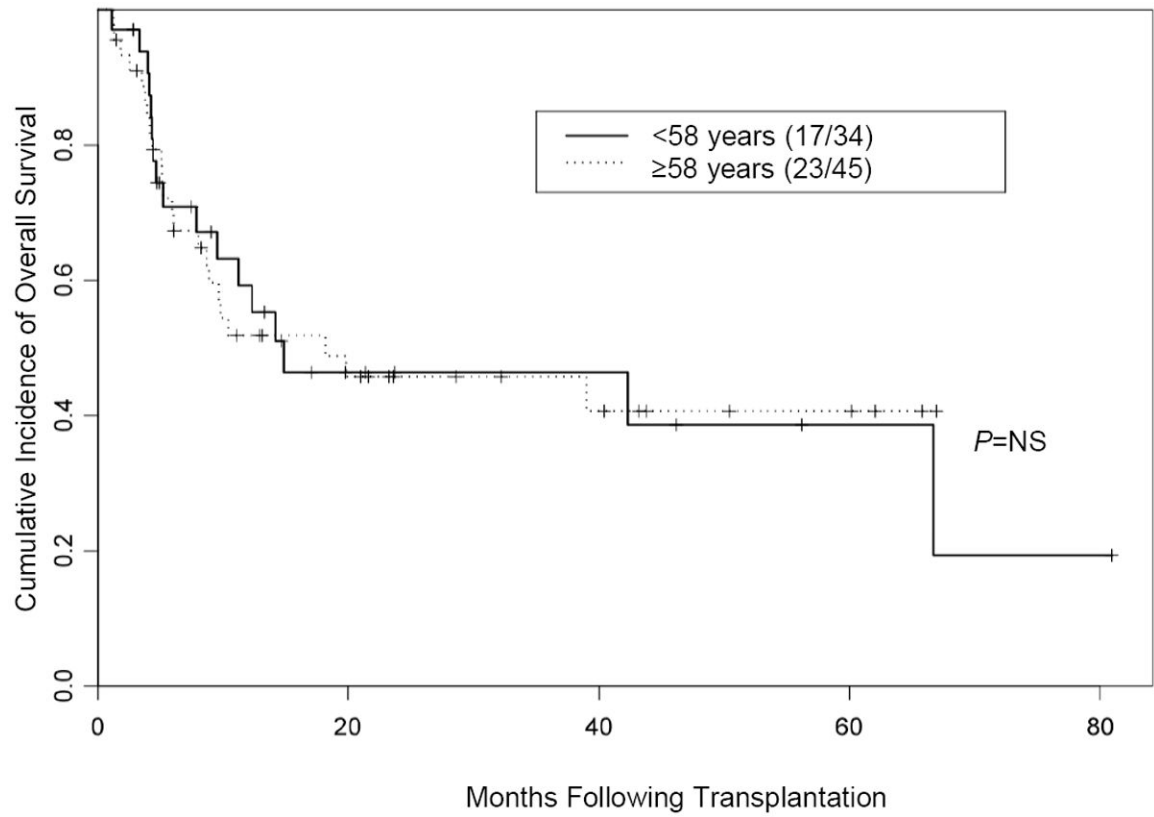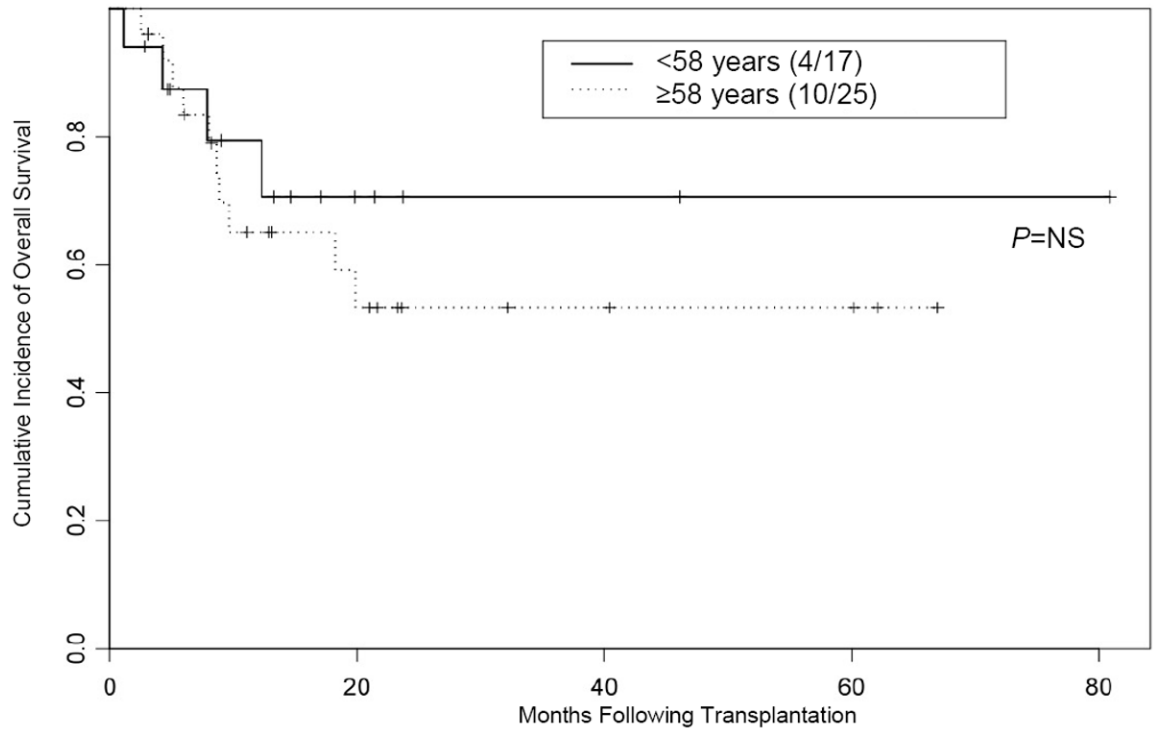
Figure 3. Overall survival in patients 58 years or older versus patients younger than 58 years
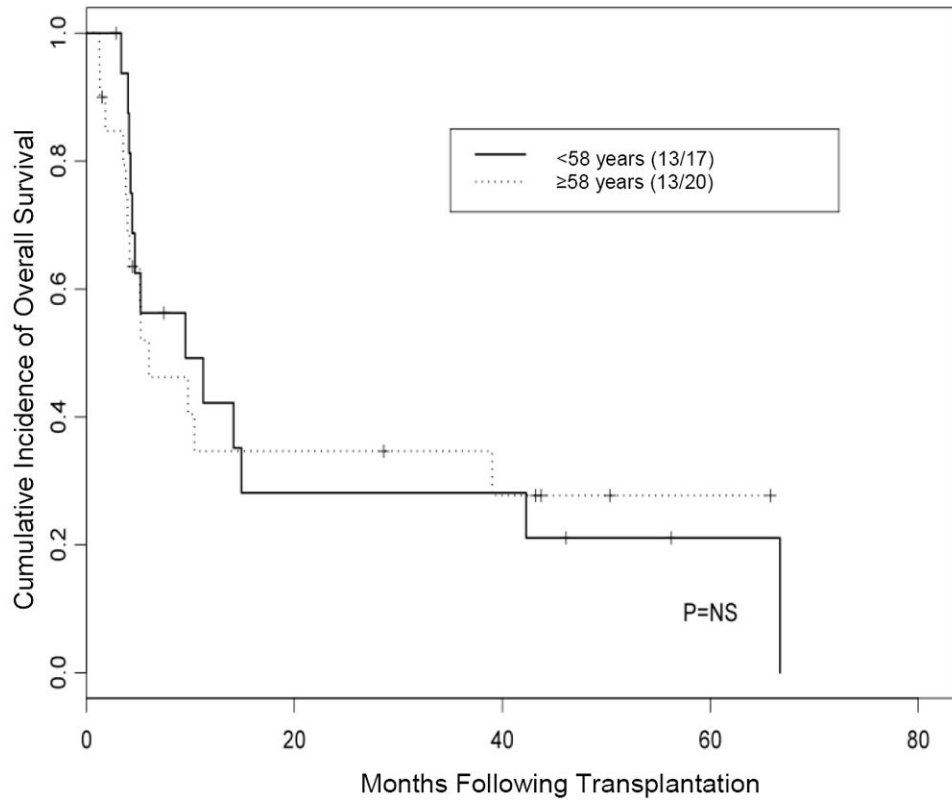NS indicates not significant.

A.

B.

Figure 4. Kaplan-Meier curve for overall survival according to remission status at time of transplantation
(A) Overall survival in patients 58 years or older versus patients younger than 58 years who underwent transplantation while their disease was in complete remission. (B) Overall survival in patients 58 years or older versus patients younger than 58 years who underwent transplantation while they had active disease.
NS indicates not significant.

Table 1

Pretransplant patient characteristics

Characteristic		Number (%)
Gender	Male	49 (62)
	Female	30 (38)
Age	>58	40 (51)
	58	39 (49)
Disease	AML	63 (80)
	MDS	16 (20)
Disease status at time of allo-SCT	CR	42 (53)
	CR1	25 (32)
	CR2	17 (22)
	Active disease	37 (47)
Cytogenetics	Good risk	4 (5)
	Intermediate risk	50 (63)
	Poor risk	20 (25)
	Unknown	5 (6)
Graft received	Related Donor	41 (52)
	Unrelated Donor	38 (48)
Stem cell source	Bone marrow	38 (48)
	Peripheral blood	41 (52)
HCT-CI Score[*]	1	41 (52)
	2	9 (11)
	3	27 (34)

Percentages listed are of the total number of patients (n=79).

[*] Data were unavailable for 2 patients.

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; allo-SCT, allogeneic stem cell transplantation; CR, complete remission; CR1, first complete remission; CR2, second complete remission; HCT-CI, hematopoietic stem cell transplantation comorbidity index(19).

Table 2

Post-transplant Outcomes

Characteristic		Number (%)
GvHD	Acute, Grade II-IV	32 (41)
	Acute, Grade III-IV	5 (7)
	Chronic	34 (43)
Cause of death[*]	Disease progression	23 (58)
	GvHD	9 (23)
	Infection	4 (10)
	Organ failure	3 (8)
		Kaplan-Meier estimate (95% CI)
2-year OS[†]	CR1	71% (54% -94%)
	CR2	44% (24% -81%)
	Active disease	32% (19% -53%)
2-year EFS[†]	CR1	68% (51% -91%)
	CR2	42% (23% -77%)
	Active disease	30% (18% -50%)

Except as noted, all percentages are calculated for the entire cohort (n = 79).

[*] Percentages reported in each cause of death category were calculated from the total number of patients who died (n = 40).

[†] Percentages reported for 2-year OS and EFS were categorized by disease status at the time of allo-SCT.

GvHD indicates graft-versus-host disease; OS, overall survival; CR1, first complete remission; CR2, second complete remission; and EFS, event-free survival.

Table 3

Transplant-related Mortality.

Transplant-related mortality	30 days	100 days	1 year	3 year
All patients (n=79)	1%	5%	19%	26%
All CR at allo-SCT (n = 42)	None	5%	19 %	26%
CR1 at allo-SCT (n = 25)	None	4%	14%	19%
Active disease (n = 37)	3%	5%	20%	27%

Percentages shown are calculated based on the total number of patients in each category.

CR indicates complete remission; allo-SCT, allogeneic stem cell transplantation; and CR1, first complete remission.