UNIVERSITÀ DEGLI STUDI DI TORINO

Long-term Outcomes Among Older Patients Following Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation for Advanced Hematologic Malignancies

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ABSTRACT

Context A minimally toxic nonmyeloablative regimen was developed for allogeneic hematopoietic cell transplantation (HCT) to treat patients with advanced hematologic malignancies who are older or have comorbid conditions.

Objective To describe outcomes of patients 60 years or older after receiving minimally toxic nonmyeloablative allogeneic HCT.

Design, Setting, and Participants From 1998 to 2008, 372 patients aged 60 to 75 years were enrolled in prospective clinical HCT trials at 18 collaborating institutions using conditioning with low-dose total body irradiation alone or combined with fludarabine, 90 mg/m2, before related (n = 184) or unrelated (n = 188) donor transplants. Postgrafting immunosuppression included mycophenolate mofetil and a calcineurin inhibitor.

Main Outcome Measures Overall and progression-free survival were estimated by Kaplan-Meier method. Cumulative incidence estimates were calculated for acute and chronic graft-vs-host disease, toxicities, achievement of full donor chimerism, complete remission, relapse, and nonrelapse mortality. Hazard ratios (HRs) were estimated from Cox regression models.

Results Overall, 5-year cumulative incidences of nonrelapse mortality and relapse were 27% (95% CI, 22%-32%) and 41% (95% CI, 36%-46%), respectively, leading to 5-year overall and progression-free survival of 35% (95% CI, 30%-40%) and 32% (95% CI, 27%-37%), respectively. These outcomes were not statistically significantly different when stratified by age groups. Furthermore, increasing age was not associated with increases in acute or chronic graft-vs-host disease or organ toxicities. In multivariate models, HCT-specific comorbidity index scores of 1 to 2 (HR, 1.58 [95% CI, 1.08-2.31]) and 3 or greater (HR, 1.97 [95% CI, 1.38-2.80]) were associated with worse survival compared with an HCT-specific comorbidity index score of 0 (P = .003 overall). Similarly, standard relapse risk (HR, 1.67 [95% CI, 1.10-2.54]) and high relapse risk (HR, 2.22 [95% CI, 1.43-3.43]) were associated with worse survival compared with low relapse risk (P < .001 overall).

Conclusion Among patients aged 60 to 75 years treated with nonmyeloablative allogeneic HCT, 5-year overall and progression-free survivals were 35% and 32%, respectively.

Increasing age has been historically implicated in higher mortality after high-dose allogeneic hematopoietic cell transplantation (HCT) for patients with hematologic malignancies.1 Such transplants are preceded by intense, cytotoxic conditioning regimens aimed at reducing tumor burden. The risk of organ toxicities has limited the use of high-dose regimens to younger patients in good medical condition. Therefore, age cutoffs of 55 to 60 years have been in place for decades for high-dose HCT. This excluded the vast majority of patients from allogeneic HCT, given that median ages of patients at diagnoses of most hematologic malignancies range from 65 to 70 years.2,3

To circumvent this limitation, a nonmyeloablative conditioning regimen for allogeneic HCT was developed. The regimen relies on graft-vs-tumor effects to cure cancer and consists of fludarabine and a low dose of total-body irradiation before HCT and a course of immunosuppression with mycophenolate mofetil and a calcineurin inhibitor after HCT.4,5 This regimen has allowed extension of allogeneic HCT to a previously unserved population of older or medically infirm patients. Use of this regimen also has contributed to improving allogeneic HCT outcomes over the past decade.6 Herein, we describe outcomes among 372 patients aged 60 years or older with advanced hematologic malignancies who underwent allogeneic HCT in prospective clinical trials.

METHODS

Patients

Between March 4, 1998, and December 24, 2008, 372 patients aged 60 to 75 years underwent allogeneic HCT for advanced hematologic malignancies after nonmyeloablative conditioning per multi-institutional protocols executed at 18 centers coordinated through the Fred Hutchinson Cancer Research Center, Seattle, Washington. The primary differences between protocols were the addition of fludarabine to 2-Gy total-body irradiation, the use of HLA-matched related or unrelated or HLA-mismatched grafts, variations in the duration and intensity of posttransplantation immunosuppressive medications, and disease-specific protocols (eTable 1). These changes were aimed at reducing the risks of graft-vs-host disease (GVHD) and graft rejection.

All protocols were approved by the institutional review boards of the Fred Hutchinson Cancer Research Center and the collaborating sites. All patients provided written informed consent using forms approved by the local institutional review boards.

Inclusion criteria included diagnoses of hematologic malignancy with disease-specific high-risk features favoring allogeneic HCT; older than 55 to 60 years; younger than 55 to 60 years but at high risk for

nonrelapse mortality due to failed prior high-dose HCT or preexisting comorbid conditions; failure of 1 or more front-line therapies for B-cell malignancies; and morphologic remission (<5% bone marrow blasts) for acute myeloid leukemia (AML) or myelodysplastic syndrome. Exclusion criteria included older than 75 years; pregnancy; cardiac ejection fraction less than 40% for related recipients and less than 35% for unrelated recipients; pulmonary diffusion capacity less than 35%; decompensated liver disease (fulminant hepatic failure, liver cirrhosis with portal hypertension); Karnofsky Performance Status Scale (KPS) values less than 50% to less than 70%; and serologic evidence of infection with the human immunodeficiency virus.

HCT Methods

Three hundred fifty-one patients were conditioned with 2-Gy total-body irradiation alone on day 1 before HCT (n = 40) or with 2-Gy total-body irradiation with fludarabine, 30 mg/m2 per day, on days 4, 3, and 2 before HCT (n = 311) (eTable 1). Twenty-one patients received 3-Gy or 4-Gy total-body irradiation in addition to fludarabine. Postgrafting immunosuppression included mycophenolate mofetil plus a calcineurin inhibitor (cyclosporine or tacrolimus) in different schedules (eTable 1). Patients and their donors were matched for HLA-A, HLA-B, and HLA-C by at least intermediate resolution DNA typing, and for HLA-DRB1 and HLA-DQB1 by high-resolution techniques.7 All but 3 patients, who had marrow grafts, received peripheral blood mononuclear cells.5 Infection prophylaxis and treatment were performed according to each institution's standard practice guidelines.

Definition of Terms and Risk-Assessment Instruments

Complete remission was defined as complete disappearance of disease. Progression was defined as 50% or greater increase in disease burden compared with pretransplant status, while relapse was defined as emergence of minimal residual disease after achievement of complete remission.

Pretransplant comorbid conditions were evaluated and scored by a single investigator (M.L.S.) per the HCT-specific comorbidity index (HCT-CI) (eMethods).8 Physical functions before and after HCT (at last contact) were assessed prospectively by clinicians using the KPS. Scores for risk of relapse were classified retrospectively according to the published categorization for patients receiving the nonmyeloablative conditioning regimen (eMethods).9

Graft-vs-Host Disease

The peak severity of acute GVHD was graded by protocol principal investigators.10 Chronic GVHD was diagnosed and staged according to published criteria11 and was labeled as extensive if treated with systemic steroids in addition to continuation of the study immunosuppressive medications. Thirty days after last use of any immunosuppressive medication was designated as date of resolution of chronic GVHD.

Statistical Analyses

Outcome data were determined as of June 23, 2010. Overall and progression-free survivals were estimated by the Kaplan-Meier method. Cumulative incidence estimates were calculated for acute and chronic GVHD, graft rejection, toxicity, complete remission, relapse or progression, nonrelapse mortality, and discontinuation of immunosuppression.12 Prevalence of chronic GVHD was estimated by methods previously described.13 Hazard ratios were estimated from Cox regression models. Rate ratios for infection were estimated from Poisson regression models. Deaths were treated as competing events in analyses of graft rejection, GVHD, complete remission, toxicity, discontinuation of immunosuppression, and disease progression.

Progression and nonrelapse mortality were the components of progression-free survival and were treated as competing events. The association of age with time-to-event outcomes was based on a Cox regression analysis using age as a continuous variable. Comparisons of infection rates were performed similarly using Poisson regression. Comparison of rates of hospitalization was based on the x2 test. Comparison of CD3 and CD34 chimerism was based on the Kruskal-Wallis test. Factors tested in univariate models prior to inclusion in the multivariate model included recipient age, donor age, recipient/donor sex combinations, recipient/donor ABO matching degree, recipient/donor cytomegalovirus serostatus, donor type, HCT-CI scores,8 pretransplant KPS percentages, interval between diagnosis and HCT, number of prior regimens, prior radiation treatment, prior HCT, relapse risk,9 graft CD3 cell dose, graft CD34 cell dose, and dose of total-body irradiation.

The multivariate models included all factors associated with a given outcome at the .10 level of significance. Multivariate P values for a variable were based on adjustment for all other variables in the model. All P values were derived from likelihood ratio statistics and were 2-sided. Statistical analysis was performed using SAS version 8. Expected population mortality rates were based on sex-specific 2001 US life table data from the National Center for Health Statistics.

RESULTS

Table 1. Patient Characteristics

Characteristic	All Patients (N = 372)	Age, y			P Value
		60-64 (n = 218)	65-69 (n = 121)	70-75 (n = 33)	
Donor age, median (range), y[a]	50 (18-83)	49 (18-74)	47 (20-83)	62 (23-78)	.007
Interval from diagnosis to HCT, median (range), mo	15 (2-242)	17 (3-242)	15 (2-223)	8 (3-158)	.01
No. of prior regimens, median (range)	3 (0-14)	3 (0-14)	3 (0-13)	2 (0-10)	.06
CD34+ cells, median (range), $\times 10^6$/kg	7.1 (1.1-33.8)	7.4 (1.5-33.8)	6.9 (1.1-25.0)	7.5 (2.3-16.8)	.56
CD3 cells, median (range), $\times 10^8$/kg	3.0 (0.0-196.2)	3.0 (0.2-196.2)	3.1 (0.0-19.4)	3.2 (1.3-6.7)	.60
Diagnosis, No. (%)					
Acute leukemia	109 (29.30)	67 (30.73)	43 (35.54)	15 (45.45)	.05
Chronic leukemia	67 (18.01)	31 (14.22)	17 (14.05)	3 (9.09)	
Lymphoma/multiple myeloma	95 (25.54)	68 (31.19)	24 (19.83)	3 (9.09)	
MDS/MPD	98 (26.34)	49 (22.48)	37 (30.58)	12 (36.36)	
Other[b]	3 (0.81)	3 (1.38)	0	0	
Disease risk for relapse, No. (%)[c]					
Low	67 (18.01)	42 (19.27)	20 (16.53)	5 (15.16)	.38
Standard	179 (48.12)	108 (49.54)	59 (48.76)	12 (36.36)	
High	126 (33.87)	68 (31.19)	42 (34.71)	16 (48.48)	
Prior HCT, No. (%)					
Failed	54 (14.52)	41 (18.18)	1 (3.03)	1 (3.03)	.02
Planned	25 (6.72)	18 (8.26)	6 (4.96)	1 (3.03)	
None	293 (78.76)	159 (72.94)	103 (85.12)	31 (93.94)	
Donor, No. (%)					
HLA-matched sibling	183 (49.20)	106 (48.62)	56 (46.28)	21 (63.64)	.50
HLA-matched unrelated	155 (41.70)	89 (40.83)	56 (46.28)	10 (30.30)	
HLA-mismatched	34 (9.10)	23 (10.55)	9 (7.44)	2 (6.06)	
Donor/recipient sex combination, No. (%)					
Female donor to male recipient	105 (28.30)	59 (27.06)	33 (27.27)	13 (40.63)	.27
All others	266 (71.70)	159 (72.94)	88 (72.73)	19 (59.37)	
Conditioning, No. (%)					
2-Gy total-body irradiation	40 (10.75)	24 (11.01)	11 (9.09)	5 (15.15)	.14
2-Gy total-body irradiation + fludarabine	311 (83.60)	186 (85.32)	98 (80.99)	27 (81.82)	
3-4–Gy total-body irradiation + fludarabine	21 (5.65)	8 (3.67)	12 (9.92)	1 (3.03)	
HCT-CI scores, No. (%)[d]					
0	80 (21.86)	49 (22.79)	24 (20.34)	7 (21.21)	.53
1-2	115 (31.42)	65 (30.23)	42 (35.59)	8 (24.24)	
3-4	117 (31.97)	72 (33.49)	31 (26.27)	14 (42.43)	
≥5	54 (14.75)	29 (13.49)	21 (17.80)	4 (12.12)	
KPS %, No. (%)[e]					
<80	31 (8.73)	19 (9.13)	10 (8.47)	2 (6.90)	.63
80	105 (29.58)	55 (26.44)	41 (34.75)	9 (31.03)	
90	161 (45.35)	96 (46.15)	53 (44.92)	12 (41.38)	
100	58 (16.34)	38 (18.28)	14 (11.86)	6 (20.69)	
Degree of donor/recipient ABO blood group matching, No. (%)					
Matched	230 (61.80)	135 (61.93)	74 (61.16)	21 (63.64)	.75
Minor mismatched	62 (16.70)	37 (16.97)	22 (18.18)	3 (9.09)	
Major mismatched	80 (21.50)	46 (21.10)	25 (20.66)	9 (27.27)	
Donor/recipient CMV serostatus combinations, No. (%)					
Recipients+	230 (62.16)	126 (58.33)	78 (64.46)	26 (78.79)	.24
Recipient–/donor+	46 (12.43)	30 (13.89)	14 (11.57)	2 (6.06)	
Recipient–/donor–	94 (25.41)	60 (27.78)	29 (23.97)	5 (15.15)	
Prior radiotherapy, No. (%)					
Yes	60 (16.13)	42 (19.27)	14 (11.57)	4 (12.12)	.15
No	312 (83.87)	176 (80.73)	107 (88.43)	29 (87.88)	

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic cell transplantation; HCT-CI, HCT comorbidity index; KPS, Karnofsky Performance Status Scale; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease.
[a] Donor age was not available for 2 patients.
[b] Other diagnoses included 1 patient with aplastic anemia, 1 with melanoma, and 1 with renal cell carcinoma.
[c] See Kahl et al[2] for details.
[d] HCT-CI scores could not be assigned for 6 patients because of lack of comorbidity information.
[e] KPS percentages were not available for 17 patients.

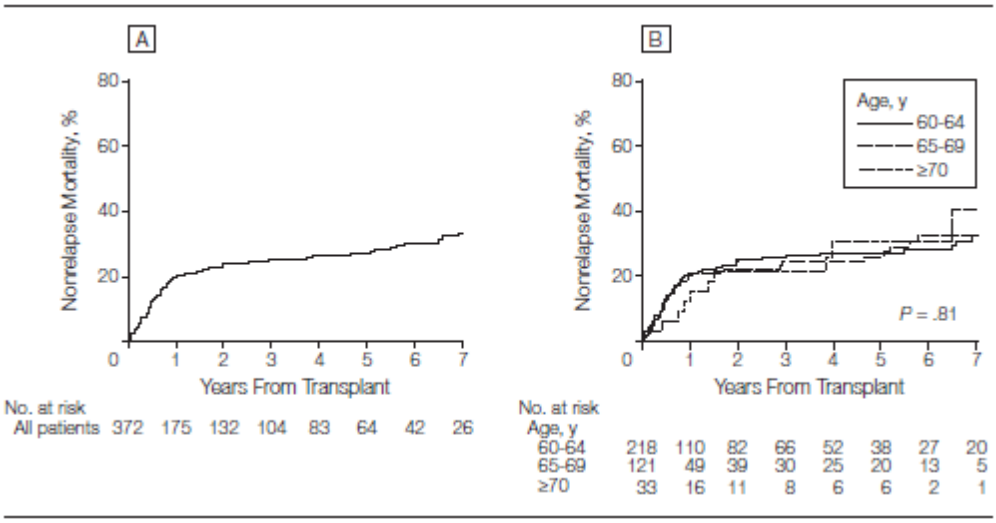
The median age of patients was 64.1 (range, 60.1-75.1) years. Table 1 shows demographic, disease, and transplant characteristics for all patients, as stratified by age groups. Older patients more frequently underwent transplantation for acute leukemia and myelodysplastic syndromes (MDS)/myeloproliferative diseases and less frequently for multiple myeloma/lymphoma. Older patient age was associated with older

donor age, shorter times between diagnosis and HCT, and fewer preceding chemotherapy regimens or prior HCT. Differences between age groups did not reach statistical significance for other variables (Table 1). Median pretransplant KPS percentage was 90% (range, 50%-100%), while the median HCT-CI score was 2 (range, 0-11).

Overall Outcome Measures

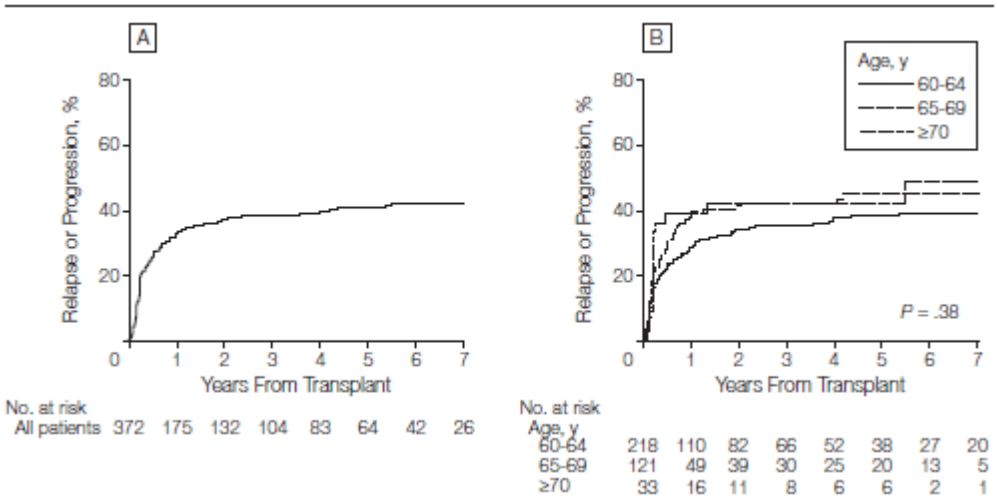
As of June 23, 2010, 133 of the 372 patients were alive, with a median follow-up of 55 (range, 12-133) months. By 120 days, cumulative incidences of acute GVHD were 52% (95% CI, 47%-57%) for grades II-IV and 13% (95% CI, 10%-17%) for grades III-IV. The cumulative incidence of extensive chronic GVHD at 2 years was 42% (95% CI, 37%-47%). Cumulative incidences of nonrelapse mortality were 7% (95% CI, 4%-10%) at 100 days after HCT, 20% (95% CI, 16%-24%) at 1 year, and 27% (95% CI, 22%-32%) at 5 years (Figure 1). Relapse rates were 33% (95% CI, 29%-37%) at 1 year after HCT and 41% (95% CI, 36%-46%) at 5 years (Figure 2). Five-year rates of overall survival (Figure 3) and progression-free survival (eFigure 1) were 35% (95% CI, 30%-40%) and 32% (95% CI, 27%-37%), respectively. Among 3-year survivors (n = 121), the subsequent 5-year survival was 61% (95% CI, 49%-72%), compared with 88% expected for an age- and sex-matched general population.

Figure 1. Nonrelapse Mortality in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older



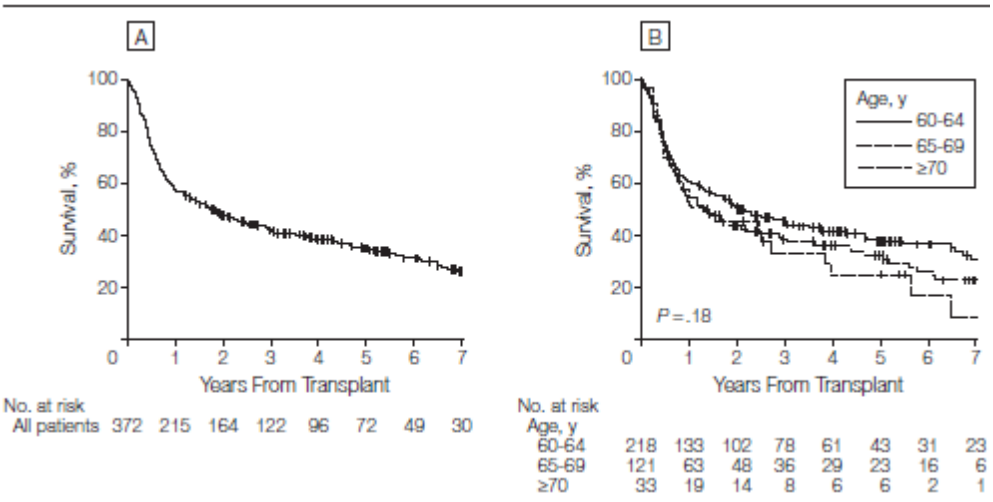
A, Cumulative incidence of nonrelapse mortality of 27% at 5 years among 372 patients 60 years or older treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .81, likelihood ratio statistics from Cox regression model) detected in cumulative incidences of nonrelapse mortality among patients 60 through 64, 65 through 69, and 70 years or older.

Figure 2. Disease Progression or Relapse in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older



A, Rate of disease progression or relapse of 41% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .38, likelihood ratio statistics from Cox regression model) detected in rates of disease progression or relapse among patients 60 through 64, 65 through 69, and 70 years or older.

Figure 3. Overall Survival in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older



Vertical lines indicate censored events. A, Kaplan-Meier estimate of overall survival of 35% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .18, likelihood ratio statistics from Cox regression model) detected in rates of overall survival among patients 60 through 64, 65 through 69, and 70 years or older.

Overall, disease progression or relapse has been the most common cause of death (n = 135). Nonrelapse deaths occurred among 104 patients, mainly due to infections, GVHD, and multiorgan failure (eTable 2). In aggregate, the time-point order of causes of death, per median onset, was organ failure followed by GVHD, infections, cerebrovascular accidents, and second cancers.

Outcome Measures by Age Groups

Cumulative incidences for nonrelapse mortality at 5 years (Figure 1) were comparable among the 3 age groups (27% [95% CI, 21%-33%] for patients aged 60-64 vs 26% [95% CI, 18%-34%] for those aged 65-69 vs 31% [95% CI, 14%-47%] for those 70 or older). The hazard ratio for nonrelapse mortality per 5 years of age was 1.04 (95% CI, 0.78-1.38; P = .78). Likewise, the 5-year rates of relapse were similar (38% [95% CI, 32%-45%] vs 45% [36%-54%] vs 42% [26%-59%], respectively) (Figure 2). The hazard ratio for relapse per 5 years of age was 1.19 (95% CI, 0.95-1.49; P = .15).

Complete remission rates at 5 years among the 3 age groups were 40% (95% CI, 31%-49%), 40% (95% CI, 28%-52%), and 63% (95% CI, 39%-86%), respectively. The hazard ratio for remission per 5 years of age was 1.30 (95% CI, 0.96-1.76; P = .10).

Five-year rates of overall survival were 38% (95% CI, 31%-45%) for patients aged 60 through 64, 33% (95% CI, 24%-41%) for those aged 65 through 69, and 25% (95% CI, 9%-41%) for those 70 years or older (Figure 3). The hazard ratio for mortality per 5 years of age was 1.16 (95% CI, 0.97-1.38; P = .12). The 5-year rates of progression-free survival were 34% (95% CI, 28%-41%), 29% (95% CI, 20%-38%), and 27% (95% CI, 11%-44%), respectively (eFigure 1). The hazard ratio for progression-free survival per 5 years of age was 1.13 (95% CI, 0.94-1.34; P = .20).

HCT Complications as Stratified by Age Groups

GVHD. At 120 days, the 3 age groups had comparable incidences of grades II-IV acute GVHD (54% [95% CI, 47%-60%] for patients aged 60-64 vs 50% [95% CI, 41%-59%] for those aged 65-69 vs 52% [34%-69%] for those 70 years or older) or grades III-IV acute GVHD (15% [95% CI, 10%-20%] vs 12% [95% CI, 6%-17%] vs 9% [95% CI, 1%-17%], respectively). The hazard ratio for grade II-IV acute GVHD per 5 years of age was 0.86 (95% CI, 0.70-1.05; P = .14) and for grade III-IV GVHD was 0.70 (95% CI, 0.46-1.05; P = .07). Rates of chronic GVHD at 2 years were also comparable (42% [95% CI, 36%-49%] vs 41% [95% CI, 32%-50%] vs 49% [95% CI, 31%-66%], respectively). The hazard ratio for extensive chronic GVHD per 5 years of age was 1.14 (95% CI, 0.91-1.42; P = .27).

Organ Toxicities. Grades III and IV organ (nonhematologic) toxicities within the first 100 days were comparable among the 3 age groups (grade III: 24% [95% CI, 18%-29%] for patients aged 60-64 vs 30% [95% CI, 22%-39%] for those aged 65-69 vs 32% [95% CI, 16%-49%] for those 70 years or older; grade IV: 12% [95% CI, 8%-17%] vs 16% [95% CI, 9%-22%] vs 6% [1%-14%], respectively). The hazard ratio for grade III

toxicity per 5 years of age was 1.12 (95% CI, 0.84-1.48; P = .45), and for grade IV toxicity was 1.03 (95% CI, 0.68-1.55; P = .90).

Infections. Rates of bacterial infection episodes per 100 patient-days of risk within the first 100 days varied among the 3 age groups (0.75 [95% CI, 0.63-0.87] for patients aged 60-64 vs 1.12 [95% CI, 0.92-1.32] for those aged 65-69 vs 0.98 [95% CI, 0.62-1.35] for those 70 years or older, respectively). The rate ratio for bacterial infection per 5 years of age was 1.19 (95% CI, 1.01-1.40; P = .04).

The rates of viral infection episodes were similar among the 3 age groups (0.67 [95% CI, 0.55-0.78] vs 0.77 [95% CI, 0.61-0.94] vs 0.63 [95% CI, 0.34-0.92], respectively), as were rates of fungal infection episodes (0.17 [95% CI, 0.11-0.22] vs 0.18 [95% CI, 0.10-0.26] vs 0.14 [95% CI, 0.01-0.28], respectively). The rate ratio for viral infection per 5 years of age was 1.00 (95% CI, 0.83-1.22; P = .96) and for fungal infection was 1.05 (95% CI, 0.71-1.54; P = .80).

Hospitalization. Overall, 54% (95% CI, 47%-60%) of patients aged 60 through 64, 36% (95% CI, 28%-45%) of those aged 65 through 69, and 55% (95% CI, 38%-72%) of those 70 years or older (P = .007) were either never hospitalized or hospitalized only overnight for unrelated donor stem cell infusion within the first 100 days after HCT.

Chimerism and Graft Rejection. Median percentages of CD33 donor chimerism at day 28 were 98% (range, 0%-100%) for patients aged 60 through 64, 99% (range, 0%-100%) for those aged 65 through 69, and 97% (range, 10%-100%) for those 70 years or older (P = .36), and all reached 100% at day 180. Median percentages of CD3 donor chimerism at day 28 were 82% (range, 0%-100%), 84% (range, 0%-100%), and 73% (range, 34%-97%) (P = .27), respectively, and all reached 99% at day 180. Rates of graft rejection were similar among patients in the 3 age groups (4% [95% CI, 1%-7%] vs 4% [95% CI, 1%-8%] vs 3% [95% CI, 1%-9%], respectively). The hazard ratio for rejection per 5 years of age was 0.96 (95% CI, 0.45-1.03; P = .91).

Resolution of Chronic GVHD, Duration of Immunosuppressive Therapy, and Last-Contact Physical Condition

Overall, at 5 years after HCT, an estimated 14% of patients (approximately 39% of surviving patients) continued to require immunosuppressive medications, while 21% of patients (61% of surviving patients) had all immunosuppressive medications discontinued, in a median of 30 (5.5-119) months, indicating resolution of chronic GVHD. Among the 158 patients who developed extensive chronic GVHD, the rates of discontinuation of immunosuppressive drugs within 5 years after onset of chronic GVHD were 43% (95% CI, 29%-54%) for patients aged 60 through 64 vs 33% (95% CI, 18%-47%) for those aged 65 through 69 vs 20% (95% CI, 1%-41%) for those 70 or older. The hazard ratio for discontinuation of immunosuppression per 5 years of age was 0.80 (95% CI, 0.52-1.22; P = .28). Among 133 patients alive at last contact, 115 (86%) were assessed by physicians for physical function using the KPS, with a median value of 90% (range, 60%-100%) for patients both with or without chronic GVHD.

Associations Between Pretransplant Factors and HCT Outcomes

Multiple risk factors were analyzed for their associations with nonrelapse mortality, relapse, overall survival, and progression-free survival using univariate analyses. Patient age, patient/donor sex combinations, CD34 cell dose, CD3 cell dose, pre-HCT KPS percentages, number of preceding chemotherapy regimens, prior radiation, and total-body irradiation dose (2 vs 3-4 Gy) were not significantly associated with any of the 4 outcomes at the .10 level of significance. The remaining factors that were associated with each outcome in univariate analyses at the .10 level of significance were entered in multivariate analyses (Table 2). Increasing HCT-CI scores and major ABO-mismatch were associated with higher hazard ratios for nonrelapse mortality, whereas the relapse-risk score9 was the only factor associated with increased progression or relapse. As a result, the same 3 factors were independently associated with overall and progression-free survival.

Table 2. Cox Regression Models for Assessment of Risk Factors for NRM, Relapse or Progression, Overall Survival, and Progression-Free Survival Among 372 Patients 60 Years and Older Treated With Nonmyeloablative Conditioning Followed by Allogeneic Hematopoietic Cell Transplantationa

	Survival						Relapse or Progression			Nonrelapse Mortality		
	Overall			Progression-Free								
	EVR[b]	HR (95% CI)	*P* Value	EVR[b]	HR (95% CI)	*P* Value	EVR[b]	HR (95% CI)	*P* Value	EVR[b]	HR (95% CI)	*P* Value
Blood group compatibility												
Matched	0.34	1 [Reference]		0.46	1 [Reference]					0.18	1 [Reference]	
Minor mismatch	0.21	0.70 (0.48-1.03)	.02	0.33	0.72 (0.50-1.04)	.05				0.11	0.60 (0.34-1.08)	.04
Major mismatch	0.47	1.27 (0.93-1.74)		0.56	1.20 (0.89-1.63)					0.24	1.39 (0.87-2.22)	
Donor age, y												
<50							0.24	1 [Reference]	.29	0.22	1 [Reference]	.59
≥50							0.30	1.27 (0.92-1.77)		0.14	0.92 (0.37-2.29)	
CMV serostatus												
Donor−/recipient−										0.10	1 [Reference]	
Donor+/recipient−										0.22	2.27 (1.10-4.66)	.03
Recipient+										0.20	2.00 (1.12-3.56)	
Donor type												
HLA-matched related										0.14	1 [Reference]	
HLA-matched unrelated										0.18	1.24 (0.49-3.14)	.10
HLA-mismatched										0.44	2.42 (0.84-6.94)	
HCT-CI scores												
0	0.17	1 [Reference]		0.29	1 [Reference]					0.08	1 [Reference]	
1-2	0.32	1.58 (1.08-2.31)	.003	0.43	1.45 (1.01-2.09)	.01				0.16	1.69 (0.91-3.14)	.06
≥3	0.47	1.97 (1.38-2.80)		0.57	1.62 (1.15-2.27)					0.25	2.01 (1.12-3.60)	
Interval from diagnosis to HCT, mo												
<18	0.39	1 [Reference]	.23	0.49	1 [Reference]	.36	0.32	1 [Reference]	.30			
≥18	0.29	0.85 (0.65-1.11)		0.40	0.89 (0.69-1.15)		0.23	0.84 (0.60-1.17)				
Prior HCT												
None										0.18	1 [Reference]	
Planned										0.04	0.31 (0.07-1.27)	.10
Failed										0.25	1.19 (0.70-2.03)	
Relapse risk												
Low	0.17	1 [Reference]		0.24	1 [Reference]		0.11	1 [Reference]		0.13	1 [Reference]	
Standard	0.33	1.67 (1.10-2.54)	<.001	0.46	1.66 (1.12-2.46)	.001	0.30	2.32 (1.31-4.11)	.003	0.15	1.08 (0.62-1.87)	.10
High	0.48	2.22 (1.43-3.43)		0.61	2.07 (1.37-3.14)		0.35	2.49 (1.37-4.54)		0.26	1.66 (0.94-2.94)	

Abbreviations: CMV, cytomegalovirus; EVR, events per person-year at risk; HCT, hematopoietic cell transplantation; HR, hazard ratio; NRM, nonrelapse mortality.
[a] For each outcome, factors with significance of .10 in univariate analyses were considered in the multivariate model.
[b] EVR during first 3 years after HCT (the first 3 years captures more than 90% of all events; these are univariate event rates, and the hazard ratio analysis uses the entire period of follow-up).

Overall, patients aged 60 to 75 years who had HCT-CI scores of 0 vs 1 to 2 vs 3 or greater experienced 5-year overall survival of 48% (95% CI, 37%-60%) vs 38% (95% CI, 29%-47%) vs 27% (95% CI, 20%-35%), respectively (P < .001) (eFigure 2). Patients with low vs standard vs high relapse risk had 5-year overall survival of 55% (95% CI, 42%-69%) vs 35% (95% CI, 28%-42%) vs 25% (95% CI, 16%-33%), respectively (P < .001) (eFigure 2). Grafts from HLA-matched related, HLA-matched unrelated, and HLA-mismatched donors resulted in 5-year overall survival of 36% (95% CI, 29%-44%) vs 37% (95% CI, 29%-46%) vs 17% (95% CI, 1%-34%), respectively (P = .22). Patients diagnosed with AML, MDS or myeloproliferative disease, and chronic myeloid leukemia had 5-year overall survival of 40% (95% CI, 30%-49%) vs 28% (95% CI, 19%-38%) vs 31% (95% CI, 9%-53%), respectively (P = .40) (eFigure 2), while those diagnosed with lymphoma, chronic lymphocytic leukemia, and multiple myeloma had 5-year overall survival of 53% (95% CI, 38%-68%) vs 33% (95% CI, 16%-50%) vs 30% (95% CI, 15%-44%), respectively (P = .41) (eFigure 2).

Given that comorbidity and disease risk were the most influential factors for overall survival, we stratified outcomes of all patients based on these 2 risk factors (eTable 3). Patients with low comorbidity burden and low relapse risk had 5-year overall survival of 69% (95% CI, 44%-95%), compared with 23% (95% CI, 11%-35%) for patients with high comorbidity burden and high relapse risk.

COMMENT

This study reports on long-term outcomes among 372 patients aged 60 years or older with advanced hematologic malignancies who were enrolled in multicenter, prospective clinical trials of allogeneic HCT after a uniform nonmyeloablative conditioning regimen. Regardless of age, 5-year survivals ranged from 23% in patients with high comorbidity scores and high disease risk to 69% in patients with low comorbidity score and low disease risk, with the majority of patients having discontinued all immunosuppressive medications. While there is much room for improvement, particularly with regard to relapse, these results are encouraging given the poor outcomes with nontransplantation treatments, especially for patients with high-risk AML,14 fludarabine-refractory chronic lymphocytic leukemia,15 or progressive lymphoma.16 The older population is increasing; demographic changes in the United States suggest that 20% of the population will be 65 years or older by 2030. Furthermore, increases of up to 77% in the number of newly diagnosed hematologic malignancies among the older population are expected to occur in the next 20 years.17 Greater age is also associated with increased medical comorbid conditions.18,19 Thus, establishing treatment options with curative outcomes and near-normal long-term physical function have become an important future goal for older patients with hematologic malignancies.

Two registry studies reported allogeneic HCT outcomes among older patients with AML or MDS who were given various reduced-intensity regimens. In a study from the European Group of Blood and Marrow Transplantation (EBMT),20 449 patients older than 60 years had 4-year nonrelapse mortality of 39% and overall survival of 27%. In a study from the Center of International Blood and Marrow Transplantation Research (CIBMTR),21 376 patients older than 60 years had 2-year nonrelapse mortality between 34% and 39% and overall survival of 34% to 36% among patients with AML and MDS, respectively. A relatively large group of 154 patients older than 65 years are included in the current study, compared with 118 patients in the CIBMTR study and an unknown number in the EBMT study.

Our study is distinguished from the 2 registry studies at least 3 ways. First, our study includes consecutive patients entered in prospective, registered clinical trials with a uniform conditioning regimen vs retrospective analyses registry data from patients given multiple regimens. Second, we introduce a stratification model based on comorbidity and relapse risk that provides guidance for future patient counseling and enrollment in trials. Last, we report details on organ toxicities, infections, hospitalization, and the course of chronic GVHD, including its resolution among older patients.

Also, while the number of patients is small (n = 33), to our knowledge this study is the first to report on allogeneic HCT among patients older than 70 years, 82% of whom had AML or MDS with otherwise predictably poor outcomes after conventional chemotherapy (predicted 5-year overall survival <10%).22 Thus, the 24% 5-year overall survival is encouraging. In the current study, no differences could be detected in nonrelapse mortality, relapse, or survival when age was tested as a categorical or continuous variable. Therefore, severe organ malfunctions but not age should be used as protocol exclusion criterion.

Greater age was associated with increased bacterial infections and subsequently increased rate of hospitalization. This might have been in part because of age-related decline of the host immune system,23 which provides infection control early after HCT while the donor immune system is attempting to establish itself. Also, approximately half of the older patients received grafts from older sibling donors, whose immune systems might have similarly regressed. Last, thymic neogeneration of T cells remains low for patients 60 years or older,24 resulting in low levels of circulating naive T cells required for immune responses.25 However, rates of fungal and viral infections were similar between age groups, and, importantly, the increase in bacterial infections with age did not translate into increased nonrelapse mortality, consistent with successful antibiotic intervention policies.

An important limitation of this study is the absence of a control group receiving conventional therapy or supportive care. Observational studies are needed to compare the outcomes between patients who receive or do not receive allogeneic HCT, since conducting a randomized clinical trial would be difficult because these patients have mostly exhausted all conventional therapies. Furthermore, the number of patients studied is not large enough to accurately detect a definitive age effect.

Chronic GVHD is a complication of allogeneic HCT that requires extended immunosuppressive therapy and has associated morbidity, which is particularly concerning for older and medically frail patients. There are no published data on the course of chronic GVHD among older patients, even though such data are increasingly important for adequate assessment of risk-benefit ratio.26 Our study shows that approximately two-thirds of patients living at 5 years who were affected by chronic GVHD had complete resolution of their symptoms and discontinued immunosuppressive medications after a median of 2.5 years from diagnosis of chronic GVHD. Both the incidence of chronic GVHD and its resolution among older patients were comparable with those among younger patients treated with high-dose HCT.27- 29 These findings, together with the normal to near-normal performance status of surviving patients, should help

allay reluctance in entering older patients with hematologic cancers in nonmyeloablative HCT protocols. Last, lack of an HLA-identical sibling should no longer be a limitation, given that HLA-matched unrelated grafts give comparable outcomes.

Current efforts are focused on reducing morbidity and mortality rates by addressing the principal problems: acute GVHD and relapse. Chronic GVHD conveys definite, powerful graft-vs-tumor effects,30 while acute GVHD does not appear to convey such effects but contributes significantly to mortality.30 Biomarkers for severe acute GVHD might enable prompt and more powerful therapy.31 Also, preliminary retrospective data suggest that grafts from donors taking statins might not cause grades III-IV acute GVHD, thereby averting their associated mortality.32 Therefore, statins might become part of future GVHD prevention strategies. As for recurrent malignancies, most relapses occur during the first year after transplantation, when graft-vs-tumor effects have as yet not been fully developed. These early relapses are being addressed by reducing tumor burden through tandem autologous HCT followed by allogeneic HCT for multiple myeloma and advanced lymphoma33 or the addition of disease-specific agents. These disease-specific manipulations, while not curative on their own, are meant to help bridge the immunocompromised post-HCT period until graft-vs-tumor effects develop. Furthermore, minimal residual disease monitoring using multiparameter flow cytometry and molecular techniques,34,35 combined with preemptive therapies36 with or without subsequent donor lymphocyte infusion, will be useful to avert disease progression.

Hematologic malignancies are mainly diseases of the elderly population. For example, while the average general annual incidence of AML is approximately 3.43 per 100 000, it increases progressively with age, to a peak of 55.1 per 100 000 in those 65 or older.3 Yet only 12% of patients treated with HCT between 2004 and 2008 were older than 60 years,37 and only 26% of patients with AML who were seen in consultation for HCT ultimately received it.38 This clearly highlights the reluctance of physicians to offer allogeneic HCT to elderly patients. To our knowledge, there is no literature on the reasons behind the low rate of referral of older patients to transplantation or on how nonmyeloablative HCT outcomes compare with those after conventional therapies. To answer both of these questions, we are initiating a multicenter longitudinal observational study designed to provide patient follow-up from the time of diagnosis.

In summary, among patients aged 60 to 75 years and diagnosed with advanced hematologic malignancies, treatment with nonmyeloablative conditioning followed by allogeneic HCT resulted in 5-year overall survival and progression-free survival of 35% and 32%, respectively. Moreover, half of those older patients were never hospitalized, and two-thirds of survivors experienced eventual resolution of their chronic GVHD with return to normal or near-normal physical function. Comorbid conditions and risks for disease relapse, but not increasing age, were associated with worse outcomes.

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Figures

Figure 1. Nonrelapse Mortality in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older

A, Cumulative incidence of nonrelapse mortality of 27% at 5 years among 372 patients 60 years or older treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .81, likelihood ratio statistics from Cox regression model) detected in cumulative incidences of nonrelapse mortality among patients 60 through 64, 65 through 69, and 70 years or older.

Figure 2. Disease Progression or Relapse in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older

A, Rate of disease progression or relapse of 41% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .38, likelihood ratio statistics from Cox regression model) detected in rates of disease progression or relapse among patients 60 through 64, 65 through 69, and 70 years or older.

Figure 3. Overall Survival in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older

Vertical lines indicate censored events. A, Kaplan-Meier estimate of overall survival of 35% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .18, likelihood ratio statistics from Cox regression model) detected in rates of overall survival among patients 60 through 64, 65 through 69, and 70 years or older.

Tables

Table Graphic Jump LocationTable 1. Patient Characteristics

Table Graphic Jump LocationTable 2. Cox Regression Models for Assessment of Risk Factors for NRM, Relapse or Progression, Overall Survival, and Progression-Free Survival Among 372 Patients 60 Years and Older Treated With Nonmyeloablative Conditioning Followed by Allogeneic Hematopoietic Cell Transplantationa