Comparison of Patient Age Groups in Transplantation for Myelodysplastic Syndrome
The Medicare Coverage With Evidence Development Study

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IMPORTANCE In 2010, the US Centers for Medicare & Medicaid Services (CMS) indicated that data regarding efficacy of allogeneic hematopoietic stem cell transplantation (HCT) in the CMS beneficiary population with myelodysplastic syndrome (MDS) were currently insufficient, but that coverage would be provided for patients enrolled in a clinical study that met its criteria for Coverage with Evidence Development (CED).

OBJECTIVE The Center for International Bone Marrow Transplant Research (CIBMTR) submitted a study concept comparing the outcomes of patients aged 55 to 64 years vs aged 65 years or older who met those criteria, effectively providing coverage by CMS for HCT for MDS.

DESIGN, SETTING, AND PARTICIPANTS Data on patients aged 65 years or older were prospectively collected and their outcomes compared with patients aged 55 to 64 years. Patients were enrolled in the study from December 15, 2010, to May 14, 2014. The results reported herein were analyzed as of September 4, 2017, with a median follow-up of 47 months. The study was conducted by the CIBMTR. It comprises a voluntary working group of more than 420 centers worldwide that contribute detailed data on allogeneic and autologous HCT and cellular therapies.

INTERVENTIONS Patients with MDS received HCT according to institutional guidelines and preferences.

MAIN OUTCOMES AND MEASURES The primary outcome was overall survival (OS); secondary outcomes included nonrelapse mortality (NRM), relapse-free survival, and acute and chronic graft vs host disease.

RESULTS During the study period, 688 patients aged 65 years or older underwent HCT for MDS and were compared with 592 patients aged 55 to 64 years. Other than age, there were no differences in patient and disease characteristics between the groups. On univariate analysis, the 3-year NRM rate was 28% vs 25% for the 65 years or older group vs those aged 55 to 64 years, respectively. The 3-year OS was 37% vs 42% for the 65 years or older group vs the 55 to 64 years age group, respectively. On multivariable analysis after adjusting for excess risk of mortality in the older group, age group had no significant association with OS (HR, 1.09; 95% CI, 0.94-1.27; P = .23) or NRM (HR, 1.19; 95% CI, 0.93-1.52; P = .16).

CONCLUSIONS AND RELEVANCE Older patients with MDS undergoing HCT have similar OS compared with younger patients. Based on current data, we would recommend coverage of HCT for MDS by the CMS.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01166009

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Melodysplastic syndromes (MDS) are a group of clonal hematological disorders characterized by progressive cytopenias and leukemic transformation. More than 15,000 patients are diagnosed with MDS annually in the United States, and 80% of those patients are older than 65 years. The median age at diagnosis is 70 years in western countries and incidence increases with age. The incidence rate is 0.22/100,000 in those younger than 49 years, 4.8/100,000 between the ages of 50 and 70 years, and 22.8/100,000 in those older than 70 years.

The only available therapy with the potential to cure MDS is allogeneic hematopoietic stem cell transplantation (HCT). It is the treatment of choice for younger patients with high-risk MDS. Prior to the introduction of reduced intensity conditioning (RIC) regimens, regimen-related morbidity and mortality limited the utility of HCT in older patients. Although RIC regimens allow HCT to be offered more safely to older patients, HCT is underused in the older population. This was evident in a study by the Center for International Bone Marrow Transplant Research (CIBMTR), where only 10% of patients with acute myelogenous leukemia (AML) or MDS who underwent HCT were older than 65 years. In that study, age had no significant impact on outcome in multivariable analysis in a cohort of patients between 40 and 70 years. The 100-day mortality rate was about 20% and the 2-year probability of survival was approximately 40%.

There are multiple reasons that older patients do not undergo transplantation. They may have comorbidities that compromise their ability to tolerate HCT. Some oncologists are reluctant to refer older patients for HCT, even if there are no clinical contraindications, because of perceived worse outcomes. Some transplant centers have arbitrary upper age limits for HCT candidates. Third-party payers do not cover HCT for MDS in older patients until there is transformation to acute leukemia. Finally, given the known morbidity and mortality associated with MDS, many older patients are apprehensive to undergo HCT. Previously, coverage of HCT for MDS by the US Centers for Medicare & Medicaid Services (CMS) was approved providing coverage for HCT through CMS’s CED program.

Key Points

Question Is age associated with survival in the US Centers for Medicare & Medicaid Services (CMS) beneficiary population with myelodysplastic syndrome (MDS) who undergo allogeneic hematopoietic stem cell transplantation (HCT)?

Findings In this prospective observational study that included 1280 patients with MDS undergoing HCT, age alone was not associated with survival.

Meaning Based on these findings, we would recommend coverage of HCT for MDS by the CMS.

Methods

Data Source

The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. It comprises a voluntary working group of more than 420 centers worldwide that contribute detailed data on allogeneic and autologous HCT and cellular therapies. Participating centers are required to report all transplants consecutively; compliance is monitored by research staff, and patients are followed longitudinally. Computerized checks for discrepancies, physicians’ review of submitted data, and on-site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable US federal regulations pertaining to the protection of human research participants. The research protocol applicable to patients described in this study has had continuous institutional review board oversight from the Center for International Blood and Marrow Transplant Research, and is listed on ClinicalTrials.gov. The trial protocol is available in Supplement 1. All participants signed informed consent for research. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR’s capacity as a Public Health Authority under the HIPAA Privacy Rule. This study followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guidelines.

Written informed consent was obtained by the centers to collect and report data to the CIBMTR and for patients to participate in the CMS CED observational study. After signing informed consent, data for patients with Medicare coverage were prospectively collected using the standard CIBMTR forms. Race was reported as designated by the transplant center. Race was defined by either the investigator or participant depending on each institution’s standard operating procedures. Patient characteristics and outcomes were compared to a randomly selected group of patients aged 55 to 64 years with MDS undergoing allogeneic HCT and reported to CIBMTR. All patients aged 65 years or older or younger than 65 years with Medicare who gave consent for research were included in the study. Patients aged 55 to 64 years were selected based on a randomization algorithm where 50% of all patients with MDS undergoing allogeneic HCT in the United States and reported to CIBMTR were selected (Figure 1).
This study had 2 phases. The first phase was a safety phase with a 100-day mortality end point. The first phase had a target accrual of 240 patients aged 65 years or older for the 100-day mortality primary end point. Sample sizes were based on an inferiority test of the hypothesis that the 100-day mortality rate in the aged 65 years or older cohort was higher than 20%, which is the approximate 100-day mortality rate in a 55- to 64-year-old cohort. The study was designed to have approximately 80% power to detect a 6.5% or greater increase in 100-day mortality rates in the aged 65 years or older cohort. There was no difference in the 100-day mortality for patients aged 65 years or older compared with those aged 55 to 64 years when assessed in the first cohort of 240 patients.

After demonstrating that the 100-day mortality for the aged 65 years or older group was similar to the aged 55 to 64 years group, accrual to the second phase of the study continued. The aim of the second phase was to determine the prognostic value of additional patient and disease factors on outcomes of HCT in patients aged 65 years and older. Based on the distribution of age (65-69 years vs 70 years or older), performance score, HCT Comorbidity Index (HCT-CI), revised international prognostic scoring system (R-IPSS), and disease status in the first 180 patients, approximately 700 patients aged 65 years and older were required to complete an analysis of prognostic factors.

Probabilities of acute and chronic GVHD, NRM, and relapse were calculated by using the cumulative incidence estimator. Relapse or progression of the primary disease was treated as a competing risk for NRM and vice versa, and death was a competing event for GVHD. Overall survival and RFS were estimated using the Kaplan-Meier method. Log transformation was used to generate 95% CIs. Proportional hazards models were used to estimate the hazard ratio (HR) for each outcome associated with the aged 65 years or older cohort compared with the aged 55 to 64 years group. The proportional hazards assumption was assessed for all variables using graphical methods or time-dependent covariates. The age group variable was forced into all models, and stepwise model building was used to identify additional covariates for inclusion in the regression model. Aside from age group, the following factors were considered for adjustment: sex, Karnofsky performance status at HCT, race/ethnicity, HCT-CI score at HCT, IPSS-Rat Dx, disease status prior to preparative regimen, secondary MDS, time from Dx to Tx, prior transplant, blasts in BM prior to preparative regimen, therapy given before diagnosis and preparative regimen, graft type, donor type/HLA matching, unrelated donor age, donor-recipient sex match, donor-recipient CMV match, conditioning regimen intensity, GVHD prophylaxis, and use of ATG/Campath. Interactions between the main effect and other variables were assessed, but none were found significant. Subsets of the aged 65 years or older population (70 years or older vs aged 65-69 years) were also compared in the multivariable models but were not significantly different for any outcomes. Adjusted OS and DFS were estimated using a stratified Cox model, adjusting for the significant variables in the final multivariable models.

We also assessed the contribution of age older than 65 years to mortality after transplant while accounting for the increased mortality risk in the general population for older individuals. To do this, we fit a Cox proportional hazards model for the excess hazard for death, defined as the difference between the observed hazard of the cohort and the hazard of the general population accounting for age and sex. Population mortality was obtained from the US life tables. We adjusted for the same risk factors as in the overall mortality and nonrelapse model, and focused on the effect of age older than 65 years in this model, summarized as an HR for excess mortality risk. The model was estimated using the Estevemethod, implemented in the function rsadd in the packagereusr in R statistical software (R Foundation). All P values are 2-sided. Analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Inc.).

Results

Patients

From December 2010 to May 2014, 688 patients aged 65 years or older were enrolled in the study and their outcomes were
Comparison of Patient Age Groups in Transplantation for Myelodysplastic Syndrome

Table 1. Patient-, Disease-, and Transplant-Related Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age ≥65, y</th>
<th>Age 55-64, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>688</td>
<td>592</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>68 (65-79)</td>
<td>61 (55-64)</td>
</tr>
<tr>
<td>Female</td>
<td>212 (31)</td>
<td>221 (37)</td>
</tr>
<tr>
<td>Karnofsky score ≥80 prior to preparative regimen</td>
<td>618 (90)</td>
<td>526 (89)</td>
</tr>
<tr>
<td>Recipient race: white, non-Hispanic</td>
<td>624 (91)</td>
<td>536 (89)</td>
</tr>
<tr>
<td>HCT-CI</td>
<td>0</td>
<td>119 (20)</td>
</tr>
<tr>
<td>1-2</td>
<td>187 (27)</td>
<td>159 (27)</td>
</tr>
<tr>
<td>3</td>
<td>127 (18)</td>
<td>129 (22)</td>
</tr>
<tr>
<td>≥4</td>
<td>218 (32)</td>
<td>185 (31)</td>
</tr>
<tr>
<td>Disease status prior to preparative regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never treated</td>
<td>45 (7)</td>
<td>55 (9)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>68 (10)</td>
<td>73 (12)</td>
</tr>
<tr>
<td>Hematologic improvement</td>
<td>120 (17)</td>
<td>90 (15)</td>
</tr>
<tr>
<td>No response/stable disease</td>
<td>372 (54)</td>
<td>308 (52)</td>
</tr>
<tr>
<td>Progression to HI/relapse from CR</td>
<td>51 (7)</td>
<td>37 (6)</td>
</tr>
<tr>
<td>Not assessed/missing</td>
<td>32 (5)</td>
<td>29 (5)</td>
</tr>
<tr>
<td>R-IPSS at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>48 (7)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Low</td>
<td>115 (17)</td>
<td>90 (15)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>161 (23)</td>
<td>144 (24)</td>
</tr>
<tr>
<td>High</td>
<td>101 (15)</td>
<td>101 (17)</td>
</tr>
<tr>
<td>Very high</td>
<td>75 (11)</td>
<td>84 (14)</td>
</tr>
<tr>
<td>Missing</td>
<td>188 (27)</td>
<td>144 (24)</td>
</tr>
<tr>
<td>Blasts in BM prior to preparative regimen, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>443 (64)</td>
<td>406 (69)</td>
</tr>
<tr>
<td>5-10</td>
<td>134 (19)</td>
<td>93 (16)</td>
</tr>
<tr>
<td>11-20</td>
<td>75 (11)</td>
<td>45 (8)</td>
</tr>
<tr>
<td>Missing</td>
<td>36 (5)</td>
<td>48 (8)</td>
</tr>
<tr>
<td>Preparative regimen intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloablative</td>
<td>197 (29)</td>
<td>288 (49)</td>
</tr>
<tr>
<td>Reduced intensity conditioning</td>
<td>491 (71)</td>
<td>304 (51)</td>
</tr>
</tbody>
</table>

Abbreviations: BM, bone marrow; CR, complete remission; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; HI, hematologic improvement; MDS, myelodysplastic syndrome; R-IPSS, Revised International Prognostic Scoring System.

compared with 592 randomly selected patients aged 55 to 64 years treated during the same time period (eFigure 1 in Supplement 2). There was no difference in the outcome of the randomly selected sample of patients included in this study compared with the rest of the patients aged 55 to 64 years treated during the same time period. With a data cutoff date of September 4, 2017, the median follow-up was 47 months (range, 13-73 months) for the 1280 patients. In the aged 65 years or older group, 76%, 22%, and 2% were age 65 to 69 years, 70 to 74 years, and older than 74 years old, respectively. Otherwise, patient and disease characteristics were similar in both groups. Patient characteristics in this cohort were similar to prior studies reported by the CIBMTR.17,18 Patient, disease, and treatment characteristics are detailed in Table 1 (eTable 1 in Supplement 2).

Figure 2. Overall Survival by Age

Overall Survival

On univariate analysis, there was no statistically significant difference in the probability of OS at 100 days, 1 day, and 3 years. There was a trend for better 3-year adjusted probability of OS for patients aged 55 to 64 years (42%) vs those aged 65 years or older (37%); however, it did not reach statistical significance (P = .06) (eTable 2 in Supplement 2) (Figure 2).

Multivariable analysis for OS identified high/very high R-IPSS, blasts in bone marrow (bBM) greater than 11% prior to HCT, non–age-adjusted HCT-CI of 4 or greater, and GVHD prophylaxis with calcineurin inhibitor plus methotrexate were independently associated with inferior outcome (Table 2). Age group 65 years or older vs those aged 55 to 64 years had no statistically significant association with hazard ratio [HR], 1.09; 95% CI, 0.94-1.27; P = .23) or without (HR, 1.13; 95% CI, 0.98-1.3; P = .08) adjustment for excess population-based risk of mortality in the older group (Table 2).

We further analyzed OS for patients aged 70 years or older vs 55 to 64 years (eTable 3 in Supplement 2). On univariate analysis, the 3-year OS was 30%, 39%, and 42% (P = .02), respectively. On multivariable analysis, there was a trend for better OS for the aged 55 to 64 years group vs 70 years or older group (HR, 1.29; 95% CI, 1.05-1.60; P = .02); however, this was not statistically significant after adjusting for multiple comparisons. This demonstrates that allo-HCT can be reasonably considered in patients aged 70 years or older; however, only 14 (2%) patients in this study were older than 75.

Relapse-Free Survival

The adjusted RFS at 3 years was 27% vs 35% for the group aged 65 years or older vs those aged 55 to 64 years (P = .005) (eTable 2 and eFigure 2 in Supplement 2). On multivariable analysis, age group 65 years or older vs those 55 to 64 years had no significant association with RFS (HR, 1.14; CI, 0.99-1.31; P = .07) (Table 3). Overall, R-IPSS high/very high, in vivo T-cell depletion, bBM greater than 11% prior to transplant, conditioning regimen (non-fludarabine/busulfan myeloablative [MA], RIC fludarabine/cyclophosphamide/total body irradiation [TBI]), not in CR before transplant, and HCT-CI of 4 or greater were associated with worse RFS on MVA (Table 3).
Nonrelapse Mortality
There was no statistical difference in NRM between the age groups (eTable 2 in Supplement 2). At 3 years, NRM was 28% vs 25% for the 65 years or older vs the 55 to 64 years age group. On multivariable analysis, age group 65 years or older, non–fludarabine/busulfan MA conditioning regimen, unrelated donor/cord blood, HCT-CI of 4 or greater, and disease status not in CR before transplant were independently associated with increased risk of NRM (eTable 3 in Supplement 2).

However, after adjusting for excess risk of NRM in the older population, there was no statistically significant difference in NRM between the aged 65 years or older group and the aged 55 to 64 years group NRM (HR, 1.19; 95% CI, 0.93-1.52; P = .16).

Acute GVHD
There was no difference between groups in rates of grades II to IV acute GVHD (aGVHD) (eTable 2 in Supplement 2). At 100 days, the incidence of grades II to IV aGVHD was 38% in both groups.

By multivariable analysis, age group had no significant association with aGVHD. Findings indicate that MA regimens other than fludarabine/busulfan, unrelated donor, HCT-CI of 4 or greater, and female sex were independently associated with increased risk of aGVHD (eTable 4 in Supplement 2).

Chronic GVHD
On univariate analysis, there was no statistical difference in chronic GVHD (cGVHD) between the age groups (eTable 2 in Supplement 2). At 1 year, the incidence of cGVHD was 44% and 47% in the aged 65 years or older and the 55 to 64 years groups, respectively.

On multivariable analysis, in vivo T-cell depletion, T depletion, BM graft source, conditioning regimen (fludarabine/busulfan RIC and other RIC), and HLA-identical sibling were associated with lower risk of cGVHD (eTable 5 in Supplement 2).

In addition, on multivariable analysis, center characteristics such as volume of allogeneic transplants, total transplant volume, and years of operation had no effect on any outcome listed above.

Discussion
Although the safety and efficacy of RIC has been established for more than a decade, older patients with hematologic malignant diseases are not routinely offered allo-HCT. In a recent large intergroup trial for patients with high-risk MDS with a median age of 70 (range, 28-93) years, only 13% of patients proceeded to HCT. Sekeres et al. conducted a cross-sectional survey between June 2005 to January 2007 of 101 physicians responsible for treating 4154 patients with MDS. The median age of the patients was 71 (range, 65-80) years, 55% were men, and less than 5% of patients were evaluated for allo-HCT. Older patients may not have routine access to allo-HCT for multiple reasons previously discussed. Since approval of the CED, the number of transplants in patients with MDS older than 65 years has quadrupled from 96 in 2010 to 361 in 2014 (eFigure 2 in Supplement 2), providing access through the CED mechanism. Clearly, insurance coverage was a factor limiting access to HCT in this population.

Results of this study showed that there was no difference in OS, RFS, NRM, aGVHD, or cGVHD in patients older than 55 years. These results are similar to the retrospective study by Shaffer et al. In that study, the median age of patients was 56 (range, 18-77) years and 42% of patients had intermediate- or high-risk MDS. Using a maximum likelihood method, the optimal cut points for age prognostic categories were 18 to 29, 30 to 49, and older than 50 years, which indicates that patients older than 50 years were uniformly experiencing the same rate of survival, corroborating the findings in our study.
Not unexpectedly, an HCT-CI® score of 4 or higher was independently associated with worse outcome for OS, DFS, NRM, and aGVHD. These results indicate that chronologic age alone, which is likely a surrogate for other risk factors associated with aging, may not be an appropriate selection factor for HCT. Physiologic age and functional status, as measured by the HCT-CI, are more relevant indicators of fitness for HCT. Other factors defining patients’ functional status such as geriatric assessments have been shown to be independently associated with outcomes in older patients receiving allo-HCT. This study and ours demonstrate that functional status is more predictive of outcome than age alone. The newly developed BMT-CTN study—the CHARM study—is meant to develop and validate a risk score for NRM for older patients receiving allo-HCT.

On multivariable analysis, NRM was significantly higher in the aged 65 years or older group compared with patients aged 55 to 64 years. The absolute difference in NRM between the aged 55 to 64 years and the aged 65 years or older group was 2%, 1%, 1%, and 3% at 100 days, 6 months, 1 year, and 3 years, respectively. As time from HCT increased, the difference in NRM between the aged 65 years or older and the aged 55 to 64 years group increased. This finding suggests that the excess NRM seen at year 3 may be owing to a general higher risk of dying in the older population. After applying an excess risk of mortality model to account for the standardized increased death rate in the older population, there was no significant difference in NRM between the groups. This confirmed that the excess NRM is more likely owing to age-related trends in mortality than related to HCT.

Several other important practical findings were evident. There was no difference in OS or relapse risk for patients with less than 5% blasts or 5% to 10% blasts, suggesting that achieving a blast percentage less than 11% may be an appropriate goal of pre-HCT treatment. In addition, there was no difference in OS based on conditioning regimen intensity.

**Limitations**

There are several limitations to our study. First, because our study only included patients who were referred for, and were able to receive HCT, these results may not be generalizable to all older patients with MDS. Second, there was no systematic collection of geriatric assessments, which may help identify older patients who can tolerate HCT. Third, we did not collect information about quality of life among these recipients. Finally, molecular data were not collected, but may be helpful to further predict which patients with MDS are most likely to benefit from allo-HCT.

**Conclusions**

Findings of this study suggest that chronologic age alone should not be used as a determinant for transplant consideration. Availability of insurance coverage affects access to HCT. Outcomes in patients older than 65 years are only marginally different from those in younger patients. Based on current data, we would recommend coverage of HCT for MDS by CMS.

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Table 3. Relapse-Free Survival Multivariable Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Age, y</td>
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<td></td>
</tr>
<tr>
<td>≥65</td>
<td>586</td>
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<tr>
<td>≥65</td>
<td>682</td>
<td>1.14 (0.99-1.31)</td>
<td>.07</td>
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<tr>
<td>R-IPSS</td>
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<tr>
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<td>78</td>
<td>1 [Reference]</td>
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</tr>
<tr>
<td>Low</td>
<td>204</td>
<td>1.24 (0.90-1.71)</td>
<td>.20</td>
</tr>
<tr>
<td>Intermediate</td>
<td>302</td>
<td>1.16 (0.85-1.58)</td>
<td>.36</td>
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<tr>
<td>High</td>
<td>201</td>
<td>1.60 (1.16-2.22)</td>
<td>.005</td>
</tr>
<tr>
<td>Very high</td>
<td>159</td>
<td>1.75 (1.25-2.46)</td>
<td>.001</td>
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<td>Missing</td>
<td>324</td>
<td>1.32 (0.97-1.8)</td>
<td>.08</td>
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<td>In vivo T-cell depletion</td>
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<tr>
<td>No alemtuzumab/ATG</td>
<td>833</td>
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<td>ATG</td>
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<td>1.22 (1.06-1.41)</td>
<td>.007</td>
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<td>Alemtuzumab</td>
<td>43</td>
<td>1.38 (0.95-2.02)</td>
<td>.09</td>
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<td>Blasts in BM prior to preparative regimen</td>
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<tr>
<td>&lt;5%</td>
<td>843</td>
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<td>5%-10%</td>
<td>226</td>
<td>0.97 (0.81-1.16)</td>
<td>.74</td>
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<tr>
<td>≥11%</td>
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<td>1.32 (1.05-1.66)</td>
<td>.02</td>
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<tr>
<td>Missing</td>
<td>80</td>
<td>1.36 (1.03-1.79)</td>
<td>.03</td>
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<tr>
<td>Conditioning regimen</td>
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<tr>
<td>Fludarabine + busulfan +/− others MA</td>
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<td>1 [Reference]</td>
<td></td>
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<tr>
<td>Other myeloablative</td>
<td>134</td>
<td>1.33 (1.04-1.69)</td>
<td>.02</td>
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<tr>
<td>Fludarabine + busulfan RIC</td>
<td>281</td>
<td>1.14 (0.94-1.37)</td>
<td>.18</td>
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<td>Fludarabine + melphalan RIC</td>
<td>214</td>
<td>0.79 (0.64-0.99)</td>
<td>.04</td>
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<tr>
<td>Fludarabine + TBI + Cy RIC</td>
<td>85</td>
<td>1.40 (1.06-1.86)</td>
<td>.02</td>
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<td>Other TBI based RIC</td>
<td>136</td>
<td>1.17 (0.92-1.49)</td>
<td>.19</td>
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<td>Other RIC</td>
<td>73</td>
<td>1.42 (1.07-1.88)</td>
<td>.02</td>
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<td>Status prior to preparative regimen</td>
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<tr>
<td>Complete remission</td>
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<tr>
<td>Hematological improvement</td>
<td>210</td>
<td>1.32 (1.01-1.72)</td>
<td>.04</td>
</tr>
<tr>
<td>No response/stable disease</td>
<td>673</td>
<td>1.52 (1.20-1.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Progression/relapse</td>
<td>87</td>
<td>1.43 (1.01-2.01)</td>
<td>.04</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>100</td>
<td>1.30 (0.94-1.79)</td>
<td>.11</td>
</tr>
<tr>
<td>Missing</td>
<td>57</td>
<td>1.08 (0.73-1.6)</td>
<td>.68</td>
</tr>
<tr>
<td>HCT-CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>271</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>343</td>
<td>1.15 (0.95-1.4)</td>
<td>.16</td>
</tr>
<tr>
<td>3</td>
<td>254</td>
<td>1.21 (0.99-1.49)</td>
<td>.07</td>
</tr>
<tr>
<td>≥4</td>
<td>400</td>
<td>1.36 (1.14-1.66)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; MA, myeloablative; Cy, cyclophosphamide; HCT-CI, Hematopoietic Stem Cell Transplantation Comorbidity Index; RIC, reduced intensity conditioning; R-IPSS, Revised International Prognostic Scoring System; TBI, total body irradiation.
Institute for Health and Equity, Medical College of Wisconsin (Logan); Center for International Bone Marrow Transplant Research, Medical College of Wisconsin, Milwaukee (Chen, Saber, Horowitz, Rizzo); Dana-Farber Cancer Institute, Boston, Massachusetts (Cutler); Fred Hutchinson Cancer Research Center, Seattle, Washington (Deeg); Washington University School of Medicine in St Louis, St Louis, Missouri (Jacoby); Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, Texas (Champlin); Moffitt Cancer Center, University of South Florida, Tampa (Nishihori); National Marrow Donor Program, Minneapolis, Minnesota (Confer, Farnia); Lu Dapeo Hospitals, Beijing (Gajewski); Oregon Society of Medical Oncology, Portland (Gajewski); Stanford University School of Medicine, Stanford, California (Greenberg); University of Minnesota, Minneapolis (Warlick, Weisdorf).

Author Contributions: Dr Atallah and Ms Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Atallah, Logan, Cutler, Deeg, Champlin, Confer, Gajewski, Farnia, Greenberg, Weisdorf, Horowitz, Rizzo. Acquisition, analysis, or interpretation of data: Atallah, Logan, Chen, Jacoby, Champlin, Nishihori, Gajewski, Warlick, Weisdorf, Saber, Horowitz, Rizzo. Drafting of the manuscript: Atallah, Chen, Gajewski, Saber, Rizzo.

Critical revision of the manuscript for important intellectual content: Atallah, Logan, Chen, Jacoby, Champlin, Nishihori, Gajewski, Warlick, Weisdorf, Saber, Horowitz, Rizzo. Obtained funding: Atallah, Horowitz, Rizzo. Administrative, technical, or material support: Atallah, Champlin, Gajewski, Farnia, Horowitz, Rizzo. Study supervision: Atallah, Gajewski, Horowitz, Rizzo.

Conflict of Interest Disclosures: Dr Logan reported grants from the National Institutes of Health (NIH) during the conduct of the study. Dr Jacoby reported personal fees from Celgene, grants and personal fees from Jazz, grants and personal fees from Amgen, and personal fees from Novo Nordisk outside the submitted work. Dr Nishihori reported personal fees from Novartis outside the submitted work. Dr Farnia reported personal fees from Nortint Consulting during the conduct of the study, personal fees from Nortint Consulting outside the submitted work. Dr Weisdorf reported grants from Incyte and personal fees from Pharmacyscience outside the submitted work. Dr Horowitz reported grants from NIH, grants from Health Resources and Services Administration, personal fees from Accutain Pharmaceuticals, Adaptive Immunotherapies, Amgen, Anthene, bluebird bio, Bristol-Myers Squibb, Celgene, Chimerix, CSL Behring, CytoSen Therapeutics, Daichi Sankyo, Gamida Cell, GlaxoSmithKline, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Kite/Gilead, Magenta Therapeutics, Medoblast, Miltenyi, Omeros, Oncimmune, Pfizer, Pharmacyscience, Regeneron, Sanofi Genzyme, Seattle Genetics, Shire, and Takeda Oncology during the conduct of the study; grants from Amgen outside the submitted work. Dr Rizzo reported grants from National Cancer Institute, grants from the National Heart, Lung, and Blood Institute, grants from the National Institute of Allergy and Infectious Diseases, and the Health Resources and Services Administration during the conduct of the study; grants from Office of Naval Research, Actinium Pharmaceuticals, Adaptive Biotechnologies, Amgen Inc, Anthem Inc, Astellas Pharma US, Atara Biotherapeutics, Be the Match Foundation, bluebird bio, Bristol-Myers Squibb, Boston Children's Hospital, Celgene Corp, Children's Hospital of Los Angeles, Chimerix, CSL Behring, CytoSen Therapeutics, Dana-Farber Cancer Institute, Daichi Sankyo Co Ltd, Fred Hutchinson Cancer Research Center, Gamida-Cell Ltd, Gilead Sciences, Inc, GlaxoSmithKline, Histogenetics, Inc, Immunuc, Incyte Corporation, Janssen Biotech, Inc, Janssen Pharmaceuticals, Inc, Janssen Scientific Affairs, LLC, Jazz Pharmaceuticals, Inc, Karius, Inc, Karyopharm Therapeutics, Inc, Kite, a Gilead Company, Magenta Therapeutics, Medac GmbH, Medwire, Merck & Company, Inc, Mesoblast, Mesoscope Diagnostics, Inc, Millennium, the Takeda Oncology Co, Miltenyi Biotec, Inc, Mundipharma EDO, National Marrow Donor Program, Novartis Oncology, Novartis Pharmaceuticals Corporation, Omeros Corporation, Oncimmune, Inc, grants from PCORI, grants from Pfizer, Inc, grants from Pharmacyscience, LLC, Pirchage AG, Regeneron Pharmaceuticals, Inc, REGIMUNE Corp, Sanofi Genzyme, Seattle Genetics, Shire, Sobi, Inc, Spectrum Pharmaceuticals, Inc, St. Baldwin's Foundation, Swedish Orphan Biovitrum, Takeda Oncology, University of Minnesota, University of Pittsburgh, University of Texas-MD Anderson, University of Wisconsin - Madison, and Viraco Eurofins outside the submitted work. No other disclosures were reported.

Funding/Support: The Center for International Bone Marrow Transplant Research is supported primarily by Public Health Service grant/ cooperative agreement SU24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NAID); a grant/cooperative agreement 1U24HL138660 from NHLBI and NCI; a contract HHS152017000606C with Health Resources and Services Administration (HRSA); Grants N0014-17-12388, N0014-17-2850 and N0014-18-12045 from the Office of Naval Research HHS812017000606C; and grants from Adaptive Biotechnologies; Amgen, Inc; anonymous donation to the Medical College of Wisconsin; Astellas Pharma US, Atara Biotherapeutics, Inc; Be the Match Foundation; bluebird bio, Inc; Bristol-Myers Squibb Oncology; Celgene Corporation; Chimerix, Inc; CytoSen Therapeutics, Inc; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd, Gilead Sciences, Inc, Histogenetics, Inc; Immunuc, Incyte Corporation; Janssen Scientific Affairs, LLC, Jazz Pharmaceuticals, Inc, Karius, Inc, Karyopharm Therapeutics, Inc, Kite Pharma, Inc, Medac, GmbH; Medwire; The Medical College of Wisconsin; Merck & Co, Inc; Mesoblast; Mesoscope Diagnostics, Inc, Millennium, the Takeda Oncology Co; Miltenyi Biotec, Inc, Mundipharma EDO; National Marrow Donor Program; Novartis Pharmaceuticals Corporation; PCori; Pfizer, Inc, Pharmacyscience, LLC; Pirchage AG; Sanofi Genzyme; Seattle Genetics; Shire; Spectrum Pharmaceuticals, Inc; St. Baldwin's Foundation; Swedish Orphan Biovitrum, Takeda Oncology; and University of Minnesota.

Role of the Funder/Sponsor: The Center for International Bone Marrow Transplant Research had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA), or any other agency of the US Government.

REFERENCES
Comparison of Patient Age Groups in Transplantation for Myelodysplastic Syndrome

Young Enough to Undergo Allogeneic Transplantation for Myelodysplastic Syndromes? Considering the Results of the Medicare Coverage With Evidence Development Study

Georg-Nikolaus Franke, MD; Anne Sophie Kubasch, MD; Uwe Platzbecker, MD

The median age of patients with myelodysplastic syndromes (MDS) at diagnosis is more than 70 years, and allogeneic hematopoietic stem-cell transplantation (allo-HCT) remains the only potentially curative therapy.1 The introduction of reduced-intensity conditioning regimens has substantially extended the use of allo-HCT to patients aged 65 years or older, but only a small minority of patients in this age group are undergoing this procedure at present. In fact, in a retrospective European Group for Blood and Marrow Transplantation analysis, only 16 patients older than 70 years underwent allo-HCT between 2000 and 2004; however, numbers increased to 181 patients between 2011 and 2013.2 The increase was a result of improved selection criteria for these patients.

In a pivotal study presented in this issue of JAMA Oncology, Atallah et al3 prospectively collected the data of 688 patients who had MDS, were 65 years or older, and underwent allo-HCT and compared the outcome to that of a random selection of 592 patients with MDS who were aged 55 to 64 years.2 Except for age, there were no differences in patient and disease characteristics between the 2 groups. On multivariate analysis, the 3-year nonrelapse mortality rate and overall survival rate were not significantly different between the 2 age groups when the increased mortality risk in the general population for older individuals was taken into account. The strongest factors associated with overall survival after allo-HCT were not age but hematopoietic cell transplantation–specific comorbidity index scores of 4 or more, International Prognostic Scoring System–Revised scores, a pretransplant bone marrow blast count greater than 11%, and prophylaxis for graft-versus-host disease using calcineurin inhibitor and methotrexate. The conduct of this trial massively affected the number of patients 65 years or older who underwent transplant (a 4-fold increase, per the Center for International Blood and Marrow Transplant Research) because reimbursement was covered by Medicare for patients included in the trial.2

Considering the potential complications of treatment with allo-HCT, a stringent selection process of eligible patients with MDS is inevitable, including the identification of patient-level and disease-level factors associated with outcomes. Several retrospective studies have shown the benefit of allo-HCT compared with standard-of-care approaches in the elderly population as well,3-4 provided that a stringent selection process is applied.5 In a prospective donor vs no-donor comparison, Robin et al6 showed that a group of patients with higher-risk cases of MDS who received transplants had a better overall survival rate than patients without a donor. In addition to conventional prognostic scoring systems, such as the International Prognostic Scoring System and International Prognostic Scoring System–Revised, performance status, bone marrow blast count prior to transplantation, hematopoietic cell transplantation–specific comorbidity index scores, choice of conditioning regimen, and prophylaxis for graft-versus-host disease, but not biological age, are important variables that determine the outcome of the individual patient.7 The trials by Atallah et al3 confirmed many findings of the previous studies in a large cohort of patients, most importantly that age itself is not significantly associated with...