Older Age But Not Donor Health Impairs Allogeneic Granulocyte Colony-Stimulating Factor (G-CSF) Peripheral Blood Stem Cell Mobilization

Elie. Richa,1 Mona Papari,1 JoAnn Allen,2 Guadalupe Martinez,2 Amittha Wickrema,2 John Anastasi,1 Koen Van Besien,2 Andrew Artz2

We evaluated stem cell mobilization in 195 consecutive sibling donors who underwent a uniform mobilization regimen of granulocyte colony-stimulating factor (G-CSF) at 10 μg/kg/day divided into twice daily dosing. On day 5, peripheral blood (PB) CD34 cells/μL were measured immediately prior to peripheral blood stem cell (PBSC) apheresis. Failed mobilization was defined as <20 CD34 cells/μL on day 5. The median age was 52 years and 73 (37%) were 55 years or greater. Comorbid conditions by the Charlson Comorbidity Index (CCI) occurred in 13%, but only 3% had Karnofsky performance status (PS) <100%. Eight (4%) failed mobilization, defined as <20 CD34 cells/μL on day 5. Older age was associated with fewer CD34 cells/μL (P = 0.002). In addition, 6/73 (8.2%) older donors failed mobilization compared to 2/122 (1.6%) younger donors (P = 0.054). Comorbidity, sex, race, and donor weight did not influence mobilization. Although low PS was very uncommon, it was associated with reduced mobilization (P = 0.021), but not mobilization failure. A small fraction of older donors mobilize poorly, and this is not explained by standard measures of comorbidity or PS.


KEY WORDS: Elderly, Allogeneic transplant, Stem cell, Progenitor cell, Mobilization

INTRODUCTION

Increasingly, allogeneic hematopoietic cell transplantation (HCT) has been applied to older patients. A natural consequence of transplanting older recipients is the need to consider older siblings as donors, who may have concomitant chronic health conditions related to aging. The ready availability and safety of granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cell (PBSC) collection [1-3] further promotes collection of older and possibly less healthy donors. PBSC have surpassed bone marrow (BM) as the primary graft source, and are often preferred among older adults [4,5]. Volunteer unrelated donors are a suboptimal alternative for most because of either the delay in procuring donors or the inability to find donors for others.

Higher PBSC CD34 yields per recipient weight are linked to faster hematopoietic engraftment and better transplant outcome [6,7], and an adequate PBSC apheresis yield of CD34 cells is commonly accepted as successful mobilization. Most, but not all studies, have suggested older age reduces PBSC apheresis yields [8-15]. The post-G-CSF preapheresis peripheral blood (PB) CD34 count reliably predicts collection yields [2], and when considering donor mobilization ability, has the advantage of not being influenced by apheresis factors that affect PBSC yields. Some [12,16], but not all [17], studies suggest older age reduces post-G-CSF preapheresis CD34 counts. Prior studies on the impact of donor age on CD34 yields or preapheresis CD34 counts have been confounded by different mobilization regimens, cytokine dose and type, and a paucity of older donors in many studies. Whether health conditions more frequently encountered among older donors predispose to poor mobilization related to older age also remains unexplored.

We took advantage of our cohort of uniformly mobilized sibling donors that represented a wide age range, to address the influence of older age on PBSC mobilization and to test whether donor health might account for age-related changes in mobilization.
METHODS

Donors

We obtained institutional review board (IRB) approval to retrospectively review the records of PBSC sibling donors mobilized at the University of Chicago Medical Center from January 2001 until April 2008. All donors were evaluated by the adult allogeneic transplant program. Rare donors underwent 2 mobilizations, often in case of disease recurrence in the recipient. In such cases only the first mobilization was considered. The standard evaluation included a history, physical examination, and laboratory testing. We extracted comorbidity, performance status, race, and weight from the medical record. Comorbidity was tabulated using the Charlson Comorbidity Index (CCI) [18,19] and performance status (PS) recorded by the Karnofsky Performance Status Scale.

Mobilization Regimen

Donors were mobilized with a uniform regimen of G-CSF (filgrastim; Amgen, Thousand Oaks, CA) at 10 \(\mu\)g/kg/day given twice daily as a subcutaneous injection of 5 \(\mu\)g/kg. Doses were rounded to vial sizes of 300 \(\mu\)g or 480 \(\mu\)g. The precise G-CSF dose administered was not available, but different vial sizes were used when needed for the same patient to obtain the goal of 10 \(\mu\)g/kg/day. On day 5, a PB sample was analyzed for CD34 content prior to G-CSF for day 5. Leukapheresis was initiated without awaiting PB CD34 results, knowing that day 5 is the peak CD34/\(\mu\)L [12]. CD34 cells were enumerated by a fluorescence-activated cell sorter (FACS). To quantify poor PBPC mobilization, we defined mobilization failure as <20 CD34 cells/\(\mu\)L in the PB on day 5 consistent with prior publications [12,16]. However, this did not preclude leukapheresis. Leukapheresis aimed for a target of \(\geq 5 \times 10^6\) CD34 cells per kg of recipient weight. Various machines were used. The majority of PBSC collections used a Cobe Spectra. Other machines used for collection included Fresenius AS 104 and Baxter CS 3000. The processing volume and number of collections varied.

Mobilization Failure

Statistical analysis

Descriptive statistics were first performed. We then focused on post G-CSF preapheresis PB CD34 counts/\(\mu\)L as a continuous variable. Because CD34 was not normally distributed when interrogated by the 1 sample Kolmogorov-Smirnov test, the effect of predictor variables was primarily tested by the Mann-Whitney test and \(P\) values generated. The Kruskal-Wallis rank test allowed comparisons of more than 2 groups. Significance tests and the appropriate 2-tailed \(P\) values were derived from Fishers Exact test for proportions. Statistical analysis was performed with Stata/SE 10.0 (StataCorp LP, College Station, TX).

RESULTS

Donor Characteristics

Table 1 summarizes baseline donor characteristics. The median age was 52 years, ranging from 17 to 71 years. Donors 55 years and older accounted for 37% of subjects. Eighty percent were White and 9% were African American (AA). The median donor weight was 86.3 kg, with adults \(\geq 55\) years being slightly heavier than younger donors (\(P = .025\)).

Comorbid Conditions and PS

Among the 182 patients evaluable for comorbidity, 24 donors had a total of 28 comorbid conditions by the CCI. Diabetes represented the majority of the comorbid conditions (n = 15, 54%), followed by cardiac (n = 4) and pulmonary (n = 4) abnormalities. Adults \(\geq 55\) years had more comorbid conditions (16/68, 23.5%) compared to younger adults (8/114, 7.0%) (\(P = .003\)). Only 6 of 173 evaluable subjects had a PS <100%; these 6 subjects all had PS rated as 80% to 90%. A PS <100% was more frequent among older

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value [range]</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>52, 49, [17-71]</td>
<td>122 (63)</td>
</tr>
<tr>
<td>(\geq 55)</td>
<td></td>
<td>122 (63)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>105 (54)</td>
<td>105 (54)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>142 (80)</td>
<td>142 (80)</td>
</tr>
<tr>
<td>African-American</td>
<td>16 (9)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (7)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Not available</td>
<td>17 (9)</td>
<td>17 (9)</td>
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<tr>
<td>Karnofsky Performance Status</td>
<td></td>
<td></td>
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<tr>
<td>(\geq 100)</td>
<td>158 (81)</td>
<td>158 (81)</td>
</tr>
<tr>
<td>(\geq 80)</td>
<td>173 (89)</td>
<td>173 (89)</td>
</tr>
<tr>
<td>(\geq 50)</td>
<td>195 (100)</td>
<td>195 (100)</td>
</tr>
<tr>
<td>(\leq 20)</td>
<td>8 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>(\leq 30)</td>
<td>16 (8)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Total CD34 yield (\times 10^9)/kg</td>
<td>6.56</td>
<td>6.56</td>
</tr>
<tr>
<td>Median, per donor weight</td>
<td>6.56</td>
<td>6.56</td>
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<tr>
<td>Median, per recipient weight</td>
<td>6.8</td>
<td>6.8</td>
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b.i.d. indicates twice daily; G-CSF, granulocyte colony-stimulating factor; PB, peripheral blood.

*Rounded to vial size of 300 \(\mu\)g or 480 \(\mu\)g.
adults (5/68, 7.4%) than for younger adults (1/111, 0.9%) \((P = .03)\).

**Mobilization**

The median and mean post-G-CSF preapheresis day 5 CD34 cells were 73.7 cells/μL and 88.2/μL, respectively. Failure of mobilization, defined as CD34 < 20/μL, occurred in 8/195 donors (4.1%). Twice as many (8.2%) had <30 CD34/μL. The median apheresis yield was 6.6 \(\times 10^6\) CD34 cells per donor weight and 6.8 \(\times 10^6\) CD34 cells per recipient weight. More than 1 day of collection was required in 49.2% of donors. Seven of 175 (4%) had yields <2.0 \(\times 10^6\) CD34 cells/kg in recipient weight and 47/175 (26.8%) had fewer than 5 \(\times 10^6\) CD34 cells/kg in recipient weight. Confirming the utility of day 5 preapheresis CD34 < 20/μL as a predictor, 3 of the 8 donors with <20/μL CD34 collected <2.0 \(\times 10^6\) CD34/kg in recipient weight and none reached 5 \(\times 10^6\) CD34/kg recipient weight.

**Predictors of Mobilization**

Age heavily influenced mobilization. Figure 1 depicts CD34 counts by age, showing reduced average CD34 counts with advancing age. Table 2 quantifies the effect of each decade of age on CD34/μL.

![Figure 1. Impact of Donor Age on Progenitor Cell Mobilization.](image)

<table>
<thead>
<tr>
<th>Table 2. G-CSF Progenitor Cell Mobilization by Donor Age</th>
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<tr>
<td><strong>Day 5 Preapheresis PB CD34 cells/μL</strong></td>
</tr>
<tr>
<td>Age Decade, Years</td>
</tr>
<tr>
<td>&lt;30</td>
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<tr>
<td>30-39</td>
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<tr>
<td>40-49</td>
</tr>
<tr>
<td>50-59</td>
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<tr>
<td>≥60</td>
</tr>
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G-CSF indicates granulocyte colony-stimulating factor; PB, peripheral blood.

\(P = .004\) and on mobilization failure. Table 3 describes the influence of clinical predictors on CD34 counts as a continuous variable and on mobilization failure defined as CD34 < 20/μL. Adults 55 years and older had significantly lower CD34 counts \((P = .002)\) and were more likely to experience mobilization failure \((P = .03)\). Among the 16 AA donors, the mean CD34 count of 102.5/μL did not statistically differ from the 84.7/μL found among Whites \((P = .12)\). None of the AA donors failed to mobilize.

Sex, comorbidity, and donor weight did not have an impact on CD34 counts or the incidence of mobilization failure. Interestingly, none of the 8 donors who failed mobilization had comorbid conditions by the CCI. The mean CD34 count for those with PS of 100% was 89.2/μL compared to 50.5/μL for the 6 donors with impaired PS. Thus, lower PS was associated with lower PB CD34 \((P = .021)\). Only 1 of the 8 poor mobilizers had a PS <100%, and, therefore, PS was not a predictor for mobilization failure. Although impaired PS was uncommon, we sought to exclude lower PS accounting for the age-related reduction in mobilization. In a stratified analysis, older age continued to predict for lower CD34 counts among those with a PS of 100% \((P < .001)\). Among the 16 donors without PS recorded, the mean CD34 was 91.3/μL, similar to those with a PS of 100%, arguing against a bias in this subgroup.

Older age was associated with a greater chance of requiring more than 1 day of collection \((P = .017)\).
DISCUSSION

HLA-compatible sibling donors have traditionally been considered the optimal hematopoietic stem cell (HSC) donor because of their immediate availability and superior outcomes compared to unrelated donors. As the median age of allogeneic HCT recipients has risen, questions regarding the desirability of collecting older sibling donors have emerged. Debate has focused to what extent if any older age reduces PBSC apheresis yields [8-15] and/or post-G-CSF preapheresis CD34 counts [12,16,17].

We confirmed the impact of age on G-CSF PBSC mobilization and report on the prevalence and influence of donor health on mobilization. We selected 2001 as a start date, because this is when we introduced a reduced intensity conditioning (RIC) regimen, facilitating transplantation of older adults. A uniform mobilization regimen and standard measurement of day 5 preapheresis CD34 enabled us to study donor factors affecting mobilization independent of apheresis variables such as volume of blood processed, collection machines, and collection efficiency.

We found a mean CD34 of 88/µL, similar to the mean of 84/µL reported by Vasu and colleagues [16] among donors to whom they gave 10 µg/kg/day of G-CSF. In addition, the 4.1% (8/195) incidence of mobilization failure, defined as <20/µL [12,16], was exactly the same among the 639 donors described by Vasu. The median CD34 of 74/µL was slightly higher than reported by de Lavallade et al. [17], who reported a median of 59.5/µL, but their study employed a slightly lower average G-CSF dose of 8.9 µg/kg/day. The data confirm preapheresis CD34 as a reproducible measure of mobilization capacity. We recommend future studies assessing biologic features of mobilization include post-G-CSF preapheresis CD34 results to isolate donor factors from collection variables.

Our data show a strong association of older donor age of 55 years or more (P = .002), and of age by decade (P = .004) with reduced mobilization. In addition, the incidence of mobilization failures was 8.2% among adults 55 years and older compared to 1.6% among younger donors (P = .054). Our data confirm the impact of age on mobilization reported by Vasu et al. [16]. By contrast, de Lavallade and colleagues [17] did not find that donors 55 years and over had reduced mobilization. The discordant results are not easily explained, but may relate in part to having only 44 older donors in their cohort compared to our cohort of 73 older donors.

No studies have assessed why older donors do not mobilize as well. Intuitively, one may suspect that chronic health conditions, which occur more often among older adults, might impair mobilization. As expected, older donors did harbor more comorbid conditions (24%) relative to younger adults (7%) as assessed by the charlson comorbidity index (P = .003). Only 6 donors had a Karnofsky performance status (PS) <100%, although PS limitations were generally restricted to older adults 5/68 (7.4%) (P = .03 for difference with younger donors). Perhaps surprisingly, the presence of comorbidity had no association with CD34/µL (P = .41) and none of the 8 donors who failed to mobilize had comorbid conditions. Impaired PS was associated with lower CD34, but not mobilization failure. Older age strongly predicted lower mobilization when only analyzing donors with normal PS. To our knowledge, only 1 report has evaluated comorbidity among allogeneic donors [9]. Both older age and comorbid conditions were more common among those with poor PBSC yields. No further analysis was performed, and the authors concluded older age impairs PBSC yields.

Our data provide important baseline data about health status of sibling donors in the modern era, and should facilitate planning future studies related to donor health impairments. Unrelated donor registries have fairly rigid guidelines for donation including age <60 years (www.psbc.org/programs/marrow_guidelines.htm) and permanent deferral if receiving a medication for diabetes [20]. Not surprisingly, in the national marrow donor registry, only 9% of PBSC donors were 51 to 60 years of age [3]. In contrast, 54% of our donors were over 50 years of age, 14.6% 60 years and older, and 8% had diabetes. The unrelated donor guidelines would have excluded a considerable fraction of our donors. It has been suggested to screen older sibling donors for comorbidity [21], although the acceptable age and comorbidity conditions for related donors are determined by donor centers. Although highly controversial, it remains unproven that older donor age worsens recipient outcomes [22-25]. Our data suggest that centers should not exclude sibling donors on the basis of age or certain comorbid conditions, simply for fear of poor mobilization. Further study on the impact of older age and comorbid conditions on donor adverse events and recipient outcomes such as hematopoietic engraftment, immune reconstitution, and survival are sorely needed.

Several additional limitations are worth noting. Most importantly, the CCI [18], although a highly validated and widely used tool, only captures common comorbid conditions recorded in the history. More comprehensive measures of comorbid conditions, including medications and alcohol that might hinder hematopoietic function, warrant study. The HCT-comorbidity index has been applied to transplant recipients, but most of the comorbidity conditions are related to objective tests not indicated in donors (eg, pulmonary function tests) and/or conditions recorded by the CCI [26]. We believe more sensitive measures of functional status hold the most promise. Although very few patients had a PS <100%, there was
a tendency for such subjects to not mobilize as well. Simple and more discriminative measures of functional status such as walk speed or grip strength should be explored [27-29]. Aside from limitations in the instruments themselves, it is likely that some HLA-compatible donors were excluded for comorbidity, age, and/or functional limitations either at the time of donor evaluation or were not even HLA-typed.

The precise defects that impair mobilization or result in mobilization failure remain of both practical and biologic interest. Age-related deficiencies in HSCs number seem unlikely, considering preclinical data showing older mice mobilize HSCs and progenitor cells more efficiently after G-CSF than younger mice [30]. Moreover, older mice generally have similar or greater numbers of HSCs relative to younger mice [31]. We concur with Vasu and colleagues [16], who speculated that genetic variation may influence stem cell mobilization. We further postulate that the interaction of genetic predisposition and advancing age culminates in mobilization failure. Although HSC quantity may be adequate with aging, understress, functional impairments in aged HSCs can be identified, possibly resulting from DNA damage [32]. Clinical results further support a genetic contribution to mobilization. Remobilization of the same donors leads to strikingly similar yields, whereas interindividual variation in mobilization is quite wide [33,34]. In addition, mobilization appears to differ by race. Vasu and colleagues [16] described significantly greater preapheresis CD34 of 104 for AA compared to 79 for Whites. In our data, the mean preapheresis CD34 count of 102.5 among AAs was considerably greater than that of 84.7 for Whites; however, the difference was not significant, owing to a small number of AA donors. This racial difference might even explain the lower CD34 counts found in a recent study of Italian donors [17].

In conclusion, older age impairs G-CSF PBSC mobilization, but older adults usually mobilize adequately. The presence of comorbidity does not predict for worse mobilization, but the few donors with impaired PS may not mobilize as well.

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