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Geriatric syndromes in two-year, progression-free survivors among older recipients of allogeneic hematopoietic cell transplantation

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TO THE EDITOR

Allogeneic hematopoietic cell transplantation (allo-HCT) is increasingly utilized in older patients with advanced hematologic malignancies because of advances in reduced-intensity conditioning regimens, improved supportive care, and better selection of appropriate

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RJL, BKG, AS, AAJ and SAG designed the research. RJL, REB and SAG analyzed the data. RJL, TAE, MAM, GLS, MS, IP, CC, AAT, NCF, MSE and LYSS collected and managed essential data. JWY, RT, BCS, CSS, DMP, BG, MAP, EBP, PBD, AAJ, JNB, and SAG provided patients and collected data. RJL wrote the paper and all authors edited and approved the manuscript.

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candidates.[1] Little is known, however, about how allo-HCT affects the function, cognition, and quality of life of older recipients.[2,3] Given the emphasis on functional and cognitive independence among older adults and their vulnerabilities to stress-induced frailty,[4] it is critical to examine the trajectory of functional decline and the development of geriatric syndromes among long-term survivors of older allo-HCT recipients. We previously described the substantial burden and adverse impact of geriatric syndromes such as delirium and fall in the early post-HCT period among recipients of allo-HCT at older age (≥60 years).[5] We now report the incidence and impact of geriatric syndromes in 2-year, progression-free survivors among this cohort, as well as their long-term survival outcomes.

This retrospective cohort analysis included patients aged 60 years or older who underwent first allo-HCT for a hematologic malignancy between 2001 and 2016 at our institution. One-hundred-ninety-nine survived for 2 years without relapse/disease progression. A waiver of authorization was obtained from the Institutional Review and Privacy Board. Pre-HCT evaluation, HCT care including anti-microbial prophylaxis, and disease monitoring followed standard institutional guidelines. Functional impairment (FI) was defined as documented onset of functional dependence, mechanical fall, use of a wheel chair or walker, or admission to a skilled nursing facility (≥2 weeks). Cognitive or psychiatric impairment were defined as the onset of either clinical cognitive decline or new or worsening psychiatric illness, respectively, through review of the electronic medical record.[5] Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. The cumulative incidence was (relapse/disease progression). Cumulative incidences of non-relapse mortality (NRM) and geriatric syndromes were estimated using the cumulative incidence method for competing risks (relapse/disease progression and secondary malignancy). For OS, the Cox proportional hazard regression model was used to assess univariable and multivariable associations with clinical, transplant, and geriatric characteristics. Proportional sub-distribution hazards regression models for competing risks were used to assess associations with NRM and FI. All statistical analyses were performed in software R v3.6.2.

Of 199 patients among 472 who met eligibility criteria, 111 (46% of 241 patients) received ex vivo CliniMACS CD34+ selected grafts (Miltenyl Biotech, Bergisch Gladbach, Germany); and 88 (38% of 231 patients) received conventional graft-versus-host disease (GVHD) prophylaxis.[5] Patients who received post-transplant cyclophosphamide as GVHD prophylaxis were excluded. Approximately two-thirds of patients in our cohort received a myeloablative conditioning regimen and more than two-thirds were in the high/very high HCT-Comorbidity Index (HCT-CI)/Age category (Supplemental Table 1).[6] Most patients received a peripheral blood stem cell grafts, and 14% had a mismatched unrelated donor. At a median follow-up of 5.7 years for survivors, the 3-year OS and PFS rates from the 2-year landmark were 86% (95% CI, 80 – 91) and 83% (95% CI, 78 – 89), respectively (Supplemental Figure 1). The 3-year cumulative incidences of relapse/disease progression and NRM were 7% (95% CI, 3 – 11) and 10% (95% CI, 5 – 14), respectively (Supplemental Figure 1). Thirty-three patients died, including 8 from relapse/disease progression; 6 each from secondary neoplasm, organ failure, and infections; 4 from chronic GVHD; and 3 others.

Among geriatric syndromes examined, the 3-year cumulative incidence of new FI from the 2-year landmark was 20% (95% CI, 15–27, Figure 1A). The 3-year cumulative incidences of cognitive or psychiatric impairments were 5% (95% CI, 3–10) and 6% (95% CI, 3–11), respectively. The cumulative incidences of other geriatric syndromes such as hearing and visual impairment, urinary incontinence, and chronic pain/opioid use were low (<3%, data not shown). Patients who received a CD34+ selected grafts had a lower incidence of new FI compared to those who received conventional GVHD prophylaxis (Gray's test P=0.012, Figure 1B), with unadjusted hazard ratio (HR) of 0.49 (95% CI 0.28–0.86, P=0.014). In addition, acute grade 2–4 GVHD was associated with an increased incidence of new FI (unadjusted HR=2.05, 95% CI 1.13–3.69, P=0.018); while extensive chronic GVHD was borderline significant (unadjusted HR=2.5, 95% CI 0.99 – 6.32, P=0.054). No other variables were significant including donor types, comorbidities, or individual immunosuppressant in conventional GVHD prophylaxis.

As a time-dependent covariate in a multivariate analysis, new FI after the 2-year landmark was associated with significantly increased NRM (HR=11.1, 95% CI 4.8–25.8, P<0.001) and inferior OS (HR=4.96, 95% CI 2.32–10.6, P<0.001) (Table 1). In addition, high comorbidity burden (high/very high HCT-CI/Age index) was also significantly associated with increased NRM (hazard ratio [HR]=4.36, 95% CI 1.22 – 15.6, P=0.024) and significantly inferior OS (HR=2.99, 95% CI 1.12–7.98, P=0.028) (Table 1). No other clinical, transplant, or geriatric characteristics was associated with NRM or OS in the multivariable analysis.

We described here for the first time the baseline incidence of new onset geriatric syndromes among 2-year, progression-free survivors of allo-HCT recipients who underwent HCT at an older age (≥60 years). We found that within 3-years from the 2-year landmark, the cumulative incidence of new FI was 20%, higher than what has been reported for the general population and younger allo-HCT survivors.[7,8] In contrast, we detected much lower incidences of cognitive or psychiatric impairment among our cohort than what has been reported.[7,9] Several potential reasons may account for these differences. First, this is a retrospective, single institution study that likely has underreporting bias. Second, we lacked clinician-assessed geriatric functions. Third, we did not investigate the impact of post-transplant cyclophosphamide on geriatric impairments due to small sample size. Finally, our final cohort has a high proportion of patients with lower-risk disease which may not be representative of the HCT population.[5]

Despite these limitations, our results suggest that long-term survival is compromised for patients who developed new FI, and the magnitude of the effect is much stronger than that of multi-morbidity. This increased mortality is likely mediated through decline in physical functioning, an early marker of frailty among community dwelling older people [7]; and increased symptom burden and reduced quality of life.[10] Alternatively, FI may be associated with immune senescence and increase the risk of subsequent infection, and thereby increase mortality.[11] Our findings support the proposition that functional status and comorbidity are independent predictors of health status among older people.[12]

Interestingly, in our study, the development of new FI appeared to be related to GVHD prophylaxis and to acute and chronic GVHD, although multicollinearity among these variables prevented multivariable analysis. Mechanistically, the pleotropic effect of GVHD and steroid treatment may substantially impact older patients' functional status.[13,14] Additionally, even treated acute GVHD may lead to subtle accumulation of functional deficits in older adults, contributing to frailty.[15] Our finding here of lower risk of new FI among patients who received ex vivo CD34+ selected grafts supports this notion. Prospective studies are in progress to study the impact of steroid treatment on body composition and functional outcomes.

In summary, our findings illustrate the high incidence and subsequent adverse effects of FI among older allo-HCT survivors, which is not addressed in the current HCT survivorship guideline; we believe that the impact of GVHD on FI merits additional investigation. Our study lays the foundation for future studies to improve outcomes in long-term survivors among older allo-HCT recipients and may aid HCT physicians in discussing expectations with older patients considering allo-HCT. Strategies such as intensified post-HCT monitoring program and scheduled diet and exercise intervention may be explored in older allo-HCT survivors, as has been done for older solid tumor patients [16]. Finally, long-term FI should be considered as an important secondary outcome when comparing HCT approaches for older patients with hematologic malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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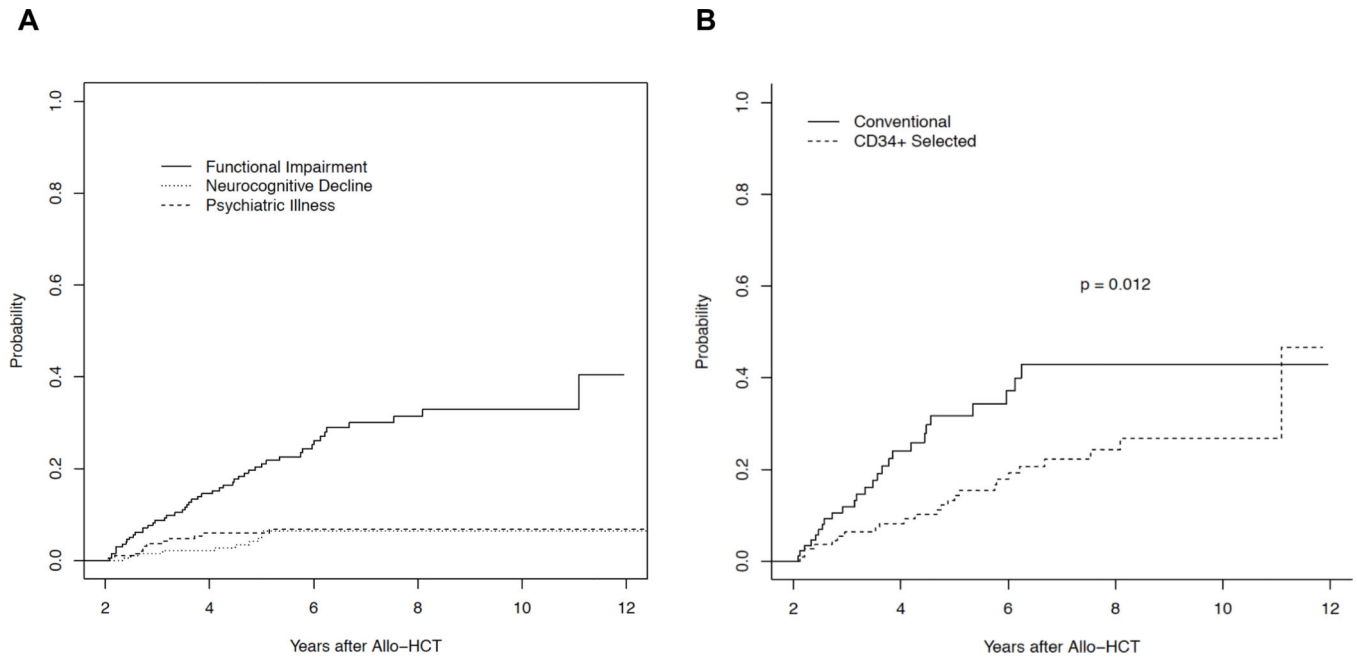

Figure 1.

(A) Cumulative incidences of new functional impairment (FI, solid line); neurocognitive decline (dotted line); and psychiatric impairment (interrupted line)

(B) Cumulative incidence of new FI for 2-year survivors of older allo-HCT recipients on either CD34+ selected platform (dotted line) or conventional GVHD prophylaxis (solid line)

Table 1.

Multivariable analyses of overall survival and non-relapse mortality.

	Overall Survival		Non-relapse Mortality	
Variables	**HR (95% CI)**	**P value**	**HR (95% CI)**	***P* value**
HCT-CI/Age		**0.028**		**0.024**
Low/Intermediate	Reference		Reference	
High/Very high	2.99 (1.12–7.98)		4.36 (1.22–15.6)	
Disease		-		0.11
Myeloid	-		Reference	
Lymphoid	-		0.43 (0.15–1.22)	
Donor		0.074		-
Matched	Reference		-	
Mismatched	2.01 (0.93–4.32)		-	
Functional impairment		**<0.001**		**<0.001**
No	Reference		Reference	
Yes	4.96 (2.32–10.6)		11.1 (4.80–25.8)	

Abbreviations: HR, hazard ratio; CI, confidence interval; HCT-CI, hematopoietic cell transplant-comorbidity index.