EBMT

COMMENT

Physically "fit" for allogeneic stem cell transplant?

Reena V. Jayani[1]✉ and Rebecca L. Olin[2]

Bone Marrow Transplantation (2021) 56:2628–2629; https://doi.org/10.1038/s41409-021-01436-1

Current standards for evaluation of patient eligibility for hematopoietic cell transplant (HCT) include comorbidity assessment and provider-rated performance status. However, these assessments provide a relatively narrow view of a patient's health status. With the increasing number of older adults receiving allogeneic HCT, there is an increased awareness of the importance of frailty and functionality prior to allogeneic HCT [1]. Ten to 33% of older adults are found to be frail prior to undergoing HCT [2–4]. In studies inclusive of all adults or younger adults, frailty is seen in 36% and 26%, respectively, prior to HCT, demonstrating that frailty is not limited to older adults [4, 5]. Frail adults have been shown to have decreased overall survival (OS), increased non-relapse mortality (NRM), and increased toxicities posttransplant [2–4, 6]. A major component of frailty includes an evaluation of impairments in instrumental activities of daily living (IADLs), activities required for individuals to live independently in the community. Older adults who have impairments in IADLs prior to HCT have been shown have decreased OS posttransplant at single institution studies, although this was not seen in a multicenter retrospective study [3, 7, 8].

While independence in IADLs is often used as a marker of physical function, both objective and patient-reported measures of physical function may provide an additional perspective of a patient's health status. Patient-reported physical function prior to HCT has been shown to predict for OS and NRM [9, 10]. However, the impact of objective measures of physical function in prognostication is less clear. In one prior report by Jones et al., over 400 patients completed a 6 min Walk Test (6MWT) prior to HCT, and while this was a significant univariate predictor of clinical outcomes, it did not provide prognostic information beyond performance status and other markers [11]. Other objective measures of physical function studied specifically in older adult HCT recipients include gait speed and Timed Up and Go (TUG), both of which predict functional decline in community-dwelling older adults [12]. Gait speed has also shown to be important predictor of OS in this vulnerable population of HCT recipients, whereas there are mixed reports of the predictive ability of TUG on posttransplant survival [3, 5, 7, 13]. The optimal evaluation of physical function prior to HCT remains an area of uncertainty.

In this issue of the journal, Mishra et al. report on objective and patient-reported physical function in adult recipients of allogeneic HCT [14]. Objective measures of physical function included wrist actigraphy (a wearable device) and 6MWT; subjective patient-reported physical activity was measured by the International Physical Activity Questionnaire (IPAQ), which generates an estimate of the patients' metabolic equivalent of task units. In this pilot study of 47 patients with median age 60 (range 24–75), these measures were performed prior to HCT, and 6MWT and IPAQ were also performed at prespecified timepoints post-HCT. Measures of physical function were analyzed in association with post-HCT outcomes.

There are some important methodologic lessons to be learned from this study. First, measuring physical function pre-HCT was reasonably feasible. The completion rate of baseline testing is reported as 100% (47/47 patients), although of 50 patients enrolled, two were ineligible for HCT and one did not complete baseline testing so was excluded; as well, an additional 27 patients screen failed for the study due to inability to complete baseline testing prior to HCT. Measuring physical function was more challenging in the post-HCT period (completion rate of all timepoints 60% and 45% for IPAQ and 6MWT, respectively). No significant predictors of assessment completion were found, including by age or performance status. Second, measures of objective and patient-reported physical function had only limited correlation. By wrist actigraphy, the majority of patients' time pre-HCT was spent in light or moderate activity, with no patients demonstrating vigorous or very vigorous activity. However, by IPAQ, the majority of patients reported moderate activity, with 21% reporting vigorous activity. Thus, this study suggests that patients overestimate their level of physical activity, and in fact are actually quite sedentary pre-HCT. Future work in this field should continue to evaluate both objective and patient-reported measures of physical function, since these appear to provide different and potentially complementary information.

When looking at the ability of pre-HCT physical function measures to predict post-HCT outcomes, the authors found no association of either subjective or patient-reported measures with OS or NRM. With respect to patient-reported physical function, this finding is discordant with the current literature [9, 10], which is likely driven by the small cohort of this study and potentially the specific measures of physical function utilized. However, with respect to objective physical function, results of this study are consistent with a prior study examining the predictive ability of 6MWT, in which baseline 6MWT was not an independent predictor of survival [11]. Findings in the general adult HCT population may also vary from findings in studies focused in older adult or frail recipients of HCT. Additional measures of physical function may be needed to better understand pretransplant fitness in a younger population.

A notable positive finding in this study was the impact of early post-HCT objective physical function. Both a shorter 6MWT distance at day 30 post-HCT, as well as a greater decrease in

[1]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [2]Division of Hematology/Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA, USA. ✉email: Reena.V.Jayani@VUMC.org

Received: 19 July 2021 Revised: 23 July 2021 Accepted: 3 August 2021
Published online: 16 August 2021

6MWT distance from baseline to day 30, were associated with inferior OS. Careful interpretation of this finding is required, to avoid assuming that this association is causal. Inferior function post-HCT is likely correlated with inferior outcomes, but this may be confounded by factors that affect both, such as pre-HCT reserve or resilience, toxicity during HCT, early GVHD, or other factors. Post-HCT physical function may therefore be best viewed as a summary measure of several factors that can identify patients at high risk for poor outcome, and potentially allow provision of additional resources for these patients (if shown to be beneficial). More work is needed to understand whether day 30 post-HCT physical function can be viewed specifically as a target outcome, where interventions to improve it may also be associated with improved OS.

Targeting physical function might be best achieved using exercise. However, a multicenter study assessing the impact of a self-directed exercise program did not demonstrate either improved survival or increased patient-reported physical activity [15], so more work is also needed to understand how best to improve physical function. We look forward to future work characterizing the utility of physical function, both self-reported and objectively measured, as a prognostic marker as well as a target for alternative types of exercise programs. Given the impact of the COVID-19 pandemic on social isolation and the resultant increased use of technology, we predict that wearable monitors and app-based reporting of physical activity will be the way of the future in this field.

REFERENCES

1. D'Souza A, Fretham C, Lee SJ, Arora M, Brunner J, Chhabra S, et al. Current use of and trends in hematopoietic cell transplantation in the United States. Biol Blood Marrow Transpl. 2020;26:e177–82.
2. Sung A, Koll T, Gier SH, Lew M, Free MM, Bohannon L, et al. Fried's frailty phenotype predicts overall survival for older hematopoietic cell transplantation recipients. Transpl Cell Ther. 2021;27:S53–S4.
3. Muffly LS, Kocherginsky M, Stock W, Chu Q, Bishop MR, Godley LA, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. Haematologica. 2014;99:1373–9.
4. Pamukcuoglu M, Bhatia S, Weisdorf DJ, DeFor TE, Ustun C, Nayar M, et al. Hematopoietic cell transplant-related toxicities and mortality in frail recipients. Blood Biol Marrow Transpl. 2019;25:2454–60.
5. Salas MQ, Atenafu EG, Bascom O, Wilson L, Lam W, Law AD, et al. Pilot prospective study of frailty and functionality in routine clinical assessment in allogeneic hematopoietic cell transplantation. Bone Marrow Transpl. 2021;56:60–9.
6. Polverelli N, Tura P, Battipaglia G, Malagola M, Bernardi S, Gandolfi L, et al. Multidimensional geriatric assessment for elderly hematological patients (≥60 years) submitted to allogeneic stem cell transplantation. A French–Italian 10-year experience on 228 patients. Bone Marrow Transpl. 2020;55:2224–33.
7. Huang LW, Sheng Y, Andreadis C, Logan AC, Mannis GN, Smith CC, et al. Functional status as measured by geriatric assessment predicts inferior survival in older allogeneic hematopoietic cell transplant recipients. Biol Blood Marrow Transpl. 2019;26:189–96.
8. Olin RL, Fretham C, Pasquini MC, Arora M, Bhatt VR, Derman B, et al. Geriatric assessment in older alloHCT recipients: association of functional and cognitive impairment with outcomes. Blood Adv. 2020;4:2810–20.
9. Jayani RV, Pidala J, Jim HSL, Whiting J, Mo Q, Mishra A. Association of patient-reported physical activity on allogeneic hematopoietic cell transplant outcomes. Clin Hematol Int. 2021;3:34–9.
10. Wood WA, Le-Rademacher J, Syrjala KL, Jim H, Jacobsen PB, Knight JM, et al. Patient-reported physical functioning predicts the success of hematopoietic cell transplantation (BMT CTN 0902). Cancer. 2016;122:91–8.
11. Jones LW, Devlin SM, Maloy MA, Wood WA, Tuohy S, Espiritu N, et al. Prognostic importance of pretransplant functional capacity after allogeneic hematopoietic cell transplantation. Oncologist. 2015;20:1290–7.
12. Viccaro LJ, Perera S, Studenski SA. Is timed up and go better than gait speed in predicting health, function, and falls in older adults? J Am Geriatr Soc. 2011;59:887–92.
13. Deschler B, Ihorst G, Schnitzler S, Bertz H, Finke J. Geriatric assessment and quality of life in older patients considered for allogeneic hematopoietic cell transplantation: a prospective risk factor and serial assessment analysis. Bone Marrow Transpl. 2018;53:565–75.
14. Mishra A, Pidala J, Thapa R, Betts BC, Fernandez H, Locke FL, et al. Objective and subjective physical function in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2021.
15. Jacobsen PB, Le-Rademacher J, Jim H, Syrjala K, Wingard JR, Logan B, et al. Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. Biol Blood Marrow Transpl. 2014;20:1530–6.

AUTHOR CONTRIBUTIONS

RVJ and RLO contributed to manuscript preparation, manuscript editing, and manuscript review.

COMPETING INTERESTS

RLO: site PI for Daiichi Sankyo, Astellas, Genentech, Pfizer, Cellectis; consulting/honoraria from Amgen, Abbvie, Astellas, Actinium.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to R.V.J.