EDITORIAL

Getting fit for allogeneic hematopoietic cell transplantation

Bone Marrow Transplantation (2014) 49, 1249–1250; doi:10.1038/bmt.2014.160; published online 28 July 2014

TBI-based myeloablative allogeneic hematopoietic cell transplantation (alloHCT) represents a life-saving therapy for patients with high risk hematologic diseases such as ALL. Unfortunately, despite the efficacy of this procedure relative to non-transplant therapies in this disease, TBI-based alloHCT is associated with a substantial risk of alloHCT-related morbidity and mortality. This risk is influenced by the physiological ability of a patient to withstand highly intensive therapy and the potential complications that ensue as a result of this treatment. In a recent registry-based analysis of myeloablative alloHCT for ALL, TRM increased with age, such that, in the most recent period of analysis (2002–2007), 19% of children, 31% of adolescents and young adults, and 41% of older adults died as a result of TRM.¹ The risk of TRM, in turn, contributes to the risk/benefit analysis of transplant in relationship to non-transplant therapy for a given indication. For example, in the large Medical Research Council/Eastern Cooperative Oncology Group ALL study, the investigators found a difference in survival between the donor and no donor groups in standard risk but not in higher-risk patients, where risk was defined by age > 35, presenting white blood count, and presence or absence of the Philadelphia chromosome. The survival differences between the risk groups appeared to be related to the higher TRM (36%) in the high-risk group.²

An accurate prediction of TRM might help to determine which patients could benefit more from lower-intensity conditioning approaches, or even from non-transplant approaches, than from myeloablative alloHCT. However, TRM remains difficult to predict. Physiological fitness likely contributes, as demonstrated by the relationship of TRM with age, and by the relationship of TRM with comorbid illness. The Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) was developed by Sorror *et al.*³ and was found to predict OS and TRM following myeloablative alloHCT in several different disease states. However, the HCT-CI is at best an indirect measurement of fitness. Additionally, as with other indices such as the Pretransplant Assessment of Mortality Score,⁴ the European Group for Blood and Marrow Transplantation risk score⁵ and the Disease Risk Index,⁶ there is room for improvement in the predictive accuracy of these indices for outcomes. In older adults, investigators are beginning to look at measurements of performance and function, such as the Comprehensive Geriatric Assessment (CGA),⁷ though the CGA may be less relevant for younger adults considering TBI-based conditioning.

With this as the context, the manuscript in this edition of *Bone Marrow Transplantation* by Kelsey *et al.*⁸ presents interesting data regarding the feasibility and potential usefulness of a pre-transplant direct measurement of patient fitness, cardiopulmonary exercise testing (CPET). Performance-based testing such as CPET and 6 min Walk Distance (6MWD) have been studied by the investigators in other cancer settings, such as non-small-cell lung cancer, in which peak oxygen uptake (VO₂peak) and 6MWD were strong predictors of all-cause mortality.⁹ Might CPET or 6MWD have similar utility in risk prediction for patients undergoing myeloablative alloHCT?

In their study, the investigators evaluated the feasibility and safety of symptom-limited CPET and 6MWD in patients preparing to undergo TBI-based alloHCT. CPET with 12-lead ECG monitoring

was conducted using an electronically braked cycle ergometer with breath-by-breath expired gas analysis. Participants cycled at a specified workload, which was then increased incrementally until volitional exhaustion or symptom limitation was achieved. Participants also underwent 6MWD in a measured corridor according to established guidelines. In all, 21 patients were enrolled onto the study. All patients successfully completed all testing measures, with no serious adverse events observed. All patients subsequently underwent planned TBI-based alloHCT. The authors concluded that this testing was feasible and safe, an important finding that has been suggested in a prior report.¹⁰

The investigators found that participants in their study had mean VO₂peak values that were ~30% below age- and sex-predicted sedentary values, and mean 6MWD values were 20% below those predicted for age and gender. Patients coming to alloHCT have been weakened and deconditioned by the effects of their underlying diseases and by months of multi-agent chemotherapy. These data confirm the physiological vulnerability of this population relative to non-cancer individuals, and help to provide understanding about why this patient population is susceptible to the toxicities of intensive therapies like TBI-based allogeneic transplantation. The investigators then went on to look at the association of performance-based testing measurements with post-transplant outcomes. Interestingly, in this small population, the univariate predictors of OS only included CPET-derived maximal variables (VO₂peak), submaximal variables (ventilatory threshold (VT) and oxygen uptake efficiency slope) and ECOG performance status, but no other variables including age, left ventricular ejection fraction, forced expiratory volume in 1s and diffusion capacity for carbon monoxide. VT is an effort-independent variable that estimates the onset of metabolic acidosis. CPET-derived maximal and submaximal variables also predicted post-alloHCT pulmonary toxicity, but no other variables did, including age and pre-transplant pulmonary function testing. CPET-derived VT was the only variable that predicted TRM (HR 0.72, 95% CI 0.54–0.95, *P* = 0.02). These data are consistent with a previous publication that found an association between pre-alloHCT VO₂peak and post-transplant survival.¹⁰

What are the implications of these findings? The authors note that CPET was performed within a 'high-risk' window between finishing conventional chemotherapy and starting conditioning with TBI, in a vulnerable population. It is encouraging that no serious adverse events were observed, which confirms other findings in cancer and non-cancer populations, and suggests that this type of testing can be performed safely in patients preparing to undergo alloHCT. The authors note important limitations to these findings, including the small and heterogeneous nature of their population and the potential for selection bias in this study. Trained personnel and specialized equipment are required to perform CPET, and it is not clear that all locations would have the ability to perform these tests. On the other hand, a limited amount of equipment can be used to administer multiple tests, and the training required for test administration is not extensive. In the setting of a highly specialized practice like allogeneic SCT, it is conceivable that transplant centers could feasibly develop the capacity to perform routine pre-transplant CPET. However, larger studies in more homogeneous populations and at several different centers will be needed to confirm the general feasibility of the approach as well as the relationships that the authors observed between CPET testing and outcomes.

If the findings are confirmed in subsequent studies, however, there are important potential implications of this work. First, performance-based testing may offer the opportunity to improve upon traditional risk-prediction measures prior to alloHCT. Performance-based testing directly measures physiological fitness, and thus intuitively seems to be a logical way to measure an individual's ability to tolerate intensive treatment. Even in the reduced intensity conditioning setting, post-transplant complications such as GVHD and infection quickly sap physiological reserve and may have greater effects in individuals in worse shape prior to transplantation. Interestingly, among the variables that the authors studied, the one variable that was associated with transplant-related mortality, VT, is a variable that is perhaps most closely associated with intensities of normal activities of living. It may be that these types of variables represent a more accurate and granular depiction of performance status than traditional clinician scoring systems such as ECOG Performance Status, which are subject to bias and which do not adequately discriminate among individuals who do not have significantly impaired functional status. Additional research in this area could investigate complementary variables that might also reflect pre-transplant performance status in order to further refine assessment of pre-transplant fitness and prognostication of post-transplant outcomes. For example, wearable accelerometers have been developed, in the form of wristbands or belt clips, that passively measure the amount and intensity of usual daily physical activity. Such data could add to CPET to create more comprehensive pre-transplant fitness assessments.

Second, unlike other pre-transplant predictive models that include a majority of unmodifiable variables, pre-transplant fitness represents a potentially modifiable target. As the authors note, structured aerobic exercise training has been shown to improve cardiopulmonary function, and is feasible in both transplant and non-transplant cancer populations. To date, the optimal timing and intensity of aerobic exercise training in transplant patients is not known. Intensive interval-based exercise training is feasible in other chronically ill and deconditioned patient populations, including individuals with coronary disease and chronic obstructive pulmonary disease, and suggests that intervention intensity in the alloHCT patient population may not be a major limitation.¹¹ Indeed, some of the transplant exercise studies that have shown the most beneficial effects have been conducted with fairly intensive interventions in the peri-transplant period, such as combined strength and aerobic training during and following transplantation.¹² A less-studied approach, however, has been to time pre-transplant exercise interventions prior to transplantation as exercise 'prehabilitation,' since many of the previous studies have been performed during or soon after transplantation. A pre-transplant 'prehabilitative' approach logically follows from the data of Kelsey *et al.*, as this method could be evaluated with pre- and post-CPET testing to measure the efficacy of the intervention upon physiological fitness before transplant has occurred. Such a study could then include collection of post-transplant clinical and patient-reported outcomes to assess the impact of prehabilitation relative to usual pre-transplant care. In this way, CPET-related data could be used to identify prehabilitative 'targets' in order to improve the transplant candidacy of less-conditioned individuals. As the science of TRM prediction becomes more refined, we will need to decide what threshold for TRM risk is considered

'acceptable' to proceed with transplantation, and what to offer to individuals who are unable to achieve this threshold. In this regard, viable non-transplant strategies for unfit individuals are urgently needed.

Clearly, there is much work to be done in the area of pre-transplant risk prediction, and larger, multi-center, confirmatory studies are needed to properly evaluate the role of CPET variables in this modeling. However, this is an important area for further study, and potentially represents an important shift in the way that practitioners in the field might evaluate and manage patients prior to alloHCT. Kelsey *et al.* have opened an exciting new chapter in pre-transplant risk assessment with significant long-term potential to improve patient outcomes.

CONFLICT OF INTEREST

The author declares no conflict of interest.

WA Wood

Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA
E-mail: wawood@med.unc.edu

REFERENCES

- 1 Wood WA, Lee SJ, Brazauskas R, Wang Z, Aljurf MD, Ballen KK *et al.* Survival improvements in adolescents and young adults after myeloablative allogeneic transplantation for acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 2014; **20**: 829–836.
- 2 Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK *et al.* In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008; **111**: 1827–1833.
- 3 Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG *et al.* Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; **106**: 2912–2919.
- 4 Parimon T, Au DH, Martin PJ, Chien JW. A risk score for mortality after allogeneic hematopoietic cell transplantation. *Ann Intern Med* 2006; **144**: 407–414.
- 5 Gratwohl A. The EBMT risk score. *Bone Marrow Transplant* 2012; **47**: 749–756.
- 6 Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME *et al.* Validation and refinement of the disease risk index for allogeneic stem cell transplantation: a study from the CIBMTR. *Blood* 2014; **123**: 3664–3671.
- 7 Muffy 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**: 1373–1379.
- 8 Kelsey CR, Scott JM, Lane A, Schwitzer E, West MJ, Thomas S *et al.* Cardio-pulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study. *Bone Marrow Transplant* 2014; **49**: 1330–1336.
- 9 Jones LW, Watson D, Herndon JE, Eves ND, Haithcock BE, Loewen G *et al.* Peak oxygen consumption and long-term all-cause mortality in non-small cell lung cancer. *Cancer* 2010; **116**: 4825–4832.
- 10 Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA *et al.* Cardio-pulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. *Bone Marrow Transplant* 2013; **48**: 1342–1349.
- 11 Moholdt T, Bekken Vold M, Grimsø J, Slordahl SA, Wisloff U. Home-based aerobic interval training improves peak oxygen uptake equal to residential cardiac rehabilitation: a randomized, controlled trial. *PLoS ONE* 2012; **7**: e41199.
- 12 Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N *et al.* Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood* 2011; **117**: 2604–2613.