PERSPECTIVE

Pretransplantation Assessments and Symptom Profiles: Predicting Transplantation-Related Toxicity and Improving Patient-Centered Outcomes

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With the advent of reduced-intensity conditioning regimens and improvements in supportive care, hematopoietic cell transplantation (HCT) has become increasingly available to older adults and medically vulnerable populations with hematologic diseases. However, adverse outcomes including long-term treatment-related distress, disability (frailty), and death remain important concerns in this population. In other areas of oncology, comprehensive geriatric assessments have been used to stratify patients for treatment-related risk, and patient-reported outcomes (PROs) have helped in understanding treatment-related toxicity from a patient perspective. However, these powerful tools have not yet become widely used in HCT. Here, we review the theories and available data that support the development of pretreatment functional assessments and longitudinal PRO sampling in HCT. We discuss the potential for these techniques to improve transplantation outcomes through risk stratification, interventional studies, and predictive models that incorporate genetic and biomarker data. Predicting and understanding long-term transplantation-related toxicity through functional assessments and PROs will be critical to calculating the risk/benefit ratio of aggressive therapies in older patient populations, and we contend that functional assessments and PRO sampling should become standard parts of the routine evaluation of HCT patients.

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DISTRESS, DISABILITY, AND DEATH IN OLDER HCT RECIPIENTS

Over 30,000 autologous transplants and 25,000 allogeneic transplantations were performed worldwide in 2009, representing >50% increase in allogeneic and a >20% increase in autologous transplantation volume over the last 10 years [1]. Improvements in supportive care and development of reduced-intensity conditioning (RIC) regimens have enabled growth in transplantations for patients over the age of 60 [2,3]; from 2004 to 2008, 34% of autologous transplantation recipients and 12% of allogeneic transplantation recipients were older than 60, with a majority of autologous recipients (65%) and over one-third of allogeneic recipients older than 50 during this time period.

A substantial body of literature, mostly in the myeloablative setting, documents threats to health-related quality of life (HRQOL) posed by transplantation and related complications [4-9]. Many patients experience significant HRQOL impairments in the early posttransplantation period, with most reporting that quality of life is back to baseline by 4 years following transplantation. Nonetheless, >25% of patients report long-term emotional distress and impaired life satisfaction after allogeneic transplantation [4,5]. It is likely that these HRQOL impairments are mediated by short- and long-term toxicities of transplantation, including effects of the conditioning regimen, acute and chronic graft-versus-host disease (aGVHD, cGVHD), infection, and organ dysfunction. It is not clear whether expected long-term HRQOL following RIC conditioning is substantially different than after myeloablative conditioning, and in general, the topic of HRQOL following RIC transplantation [10,11] is relatively understudied.

There are several reasons to study long-term HRQOL and functional impairments in older patients conditioned with RIC regimens. First, rates of aGVHD and cGVHD remain significant despite RIC

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conditioning, and both aGVHD and cGVHD have been consistently associated with HRQOL impairments [12,13]. Second, older adults are more likely to have baseline comorbid medical illnesses [14]. Studies using standardized transplantation comorbidity scales have demonstrated higher treatment-related mortality (TRM) rates in patients with higher comorbidity scores [15], consistently so after myeloablative regimens and, in several studies, after reduced-intensity regimens as well [16,17]. Presumably, these findings reflect complications of transplantation-related toxicities in vulnerable individuals. Thus, older adults may be at higher risk for HRQOL and functional impairments through this mechanism.

"Frailty" [18] is a syndrome marked by loss of physiologic reserve, strength, and function, with an increased likelihood of subsequent functional decline and mortality. Elements that comprise the frailty syndrome include weight loss, exhaustion, weakness, slow walking speed, and decreased physical activity. Outside of hematopoietic cell transplantation (HCT), the frailty syndrome has been associated with aging and chronic comorbid illness. Given the expected toxicities (aGVHD and others) of various HCT conditioning regimens (even RIC regimens), transplantation in older individuals carries a risk of inducing frailty; as more older patients are undergoing HCT, the absolute number of frail transplantation recipients are going to increase. However, the incidence and prevalence of frailty in transplantation survivors is understudied. An indirect estimate of this comes from self-report of physical functioning by HCT survivors; in one study, 22% of HCT survivors reported ongoing major physical limitations at 3 years following transplantation [8]. There is an important need within HCT to understand how many patients experience transplantation-related frailty, and which patients are most at risk. A variety of interventions have the potential to reduce incident frailty among older people with and without cancer such as exercise, pharmacotherapeutics, and systems of care; studies are ongoing. Such interventions hold similar promise for the prevention or treatment of post-transplantation frailty.

Finally, many (although not all) studies have shown lower TRM rates after RIC compared with myeloablative regimens. A recent large registry study demonstrated 1-year nonrelapse mortality (NRM) rates of 25% to 35% for patients over the age of 60 who received RIC HCT for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) in first complete remission [2]. In a retrospective institutional review of patients over the age of 70 who received autologous transplantations for lymphoma, investigators found a 1-year NRM rate of 35% [19], substantially higher than standard estimates of TRM for this procedure. Although NRM is prevalent in older patients undergoing HCT and thus an important outcome to predict, only patients who survive and do not succumb to relapse-related death will be eligible for long-term disability and distress. In the registry study, 2-year overall survival (OS) estimates for patients ≥65 with AML and MDS were 36% and 38% respectively, underlining the important contribution of relapse to overall mortality. Nonetheless, the modest rates of long-term survivorship among older HCT recipients highlight the importance of understanding the prevalence of functional impairment among those who are alive, so that we can more properly estimate the true proportion of "excellent" long-term outcomes among older adults undergoing HCT.

COMPREHENSIVE GERIATRIC ASSESSMENTS AND PATIENT-REPORTED OUTCOMES IN CLINICAL ONCOLOGY

In other areas of oncology, measurements of physiological vulnerability and patient-reported toxicity are used routinely in research and treatment settings. For example, a Comprehensive Geriatric Assessment (CGA) is a frailty assessment tool used routinely in geriatric practice that captures patient- and physician-provided information across domains that include functional status, comorbidity, cognitive status, psychological state, social support, nutritional status, and medication review [20-22]. The CGA predicts treatment-related toxicities and OS for older individuals and identifies new problems during follow-up care, including those in cancer [23-27]. Hurria and colleagues [28] demonstrated the feasibility of implementing CGA in cancer cooperative group clinical trials. CGAs have not yet been incorporated into HCT-related research or practice.

Concurrently, patient-reported outcomes (PROs) have emerged as an important way to understand and monitor the patient experience with cancer treatment over time. PROs are defined by the US Food and Drug Administration as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." PROs are a reliable, valid, and quantifiable way of monitoring symptoms, quality of life, psychological concerns, satisfaction with care, and treatment adherence. A classic PRO used routinely in cancer care is the Review of Systems; there are numerous validated well-recognized research instruments (eg, FACT-G, MDASI, HADS) that can be administered electronically or with pen and paper. Routine PRO assessment provides a mechanism to monitor treatment toxicity output by directly querying the patient and is more accurate than traditional clinician symptom assessment [29,30]. PROs can also be used to guide clinical decision making, such as chemotherapy dosing [31], nursing interventions, and

identification and response to sensitive subjects [32]. Many centers are now routinely collecting PRO data as part of research protocols or routine care [33-35].

Several recent studies have shown the practical utility of PRO collection in oncologic care. In a study by Cleeland et al. [36], postsurgical patients reported symptoms by interactive voice response technology, and this triggered alerts to providers. The investigators found that most clinicians responded to the alerts, and that there was an 11% decrease in severe symptom events in the alert group. In another study by Berry et al. [37], clinicians were able to integrate PRO data into their existing workflows and were more likely to discuss issues flagged by the PRO system.

Despite the potential for longitudinal collection of PRO data to improve routine oncologic care, commentators have rightly observed that this type of data collection might be better suited for nursing rather than clinician workflow at the current time [38]. However, as PRO data are shown to lead to measurable improvements in clinical care, and as it is linked to critical issues such as drug safety [30], this may change. When collected frequently enough, PRO data have the potential to complement laboratory assessments and clinical exams in providing a mechanism for continuously monitoring treatment-related toxicity, disease status (eg, recurrence, relapse), patient functioning, and longitudinal patient experience. As these data become more objective and reliable in appearance and function, they are likely to become more relevant to researchers and practicing clinicians. Despite the advances and routine application of PRO data in clinical oncology, however, the practice of frequent PRO sampling is still in its very early stages in HCT.

Pretransplantation Assessments in HCT

Transplantation clinicians have generally resisted the routine use of CGAs in part because even "older" transplantation recipients are still younger than the geriatric population and also because of the widely held belief that frail patients are not considered for transplantation. However, individuals up to the age of 80 are now evaluated for autologous HCT, and patients in their 70s are routinely assessed for reduced-intensity allogeneic transplantations. Additionally, less robust candidates are now considered for transplantation; in one recent analysis, 81% of patients over the age of 50 met "prefrail" criteria and 24% met criteria for frailty, by the 5-point Fried criteria before transplantation [39]. In this 146 patient prospective study, frailty was not associated with NRM, aGVHD, or OS ($P = .32$), but higher frailty scores were associated with advanced pre-HCT disease and higher rates of subsequent relapse. These findings suggest that greater amounts of treatment for advanced disease before HCT might induce a frailty phenotype, and it could be theorized that individuals with this phenotype are at higher risk for long-term disability and distress. The lack of association between pre-HCT frailty and other outcomes in this study was somewhat surprising, although the use of more nuanced measures of performance status and the incorporation of outcomes other than death would be worth exploring. Given the association between frailty and death from any cause, and the continued risks for late toxicities and deaths years after transplantation, an accurate assessment of not only pre-HCT frailty but also post-HCT frailty is also important.

Comorbidity, a domain within the CGA, has demonstrated predictive power for treatment-related toxicity and OS following transplantation [15]. One of the most commonly used comorbidity scales in transplantation, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [15], aggregates 15 different comorbidities to provide a score that can stratify patients into lower or higher risk for NRM. In the original Sorror study involving 1,055 consecutive patients conditioned with ablative and nonablative regimens, HCT-CI scores of 0 were associated with 2-year NRM and OS estimates of 14% and 71%, respectively, whereas scores of 3 or more were associated with 2-year NRM and OS estimates of 41% and 34%. The HCT-CI has subsequently been found to predict NRM and OS in different diseases, graft sources, and conditioning regimen intensities [40-49].

There has been relatively less work in prospectively evaluating functional status in HCT recipients beyond standardized comorbidity assessment. One commonly used measurement of performance status, the Karnofsky Performance Scale (KPS), has demonstrated utility in predicting NRM after transplantation [16,50]. In one study of 408 patients receiving nonmyeloablative allogeneic transplantations at four different centers, investigators showed that KPS $<80\%$ was associated with higher NRM ($P = .04$), higher incidence of ≥ 3 toxicities ($P = .01$), and higher mortality ($P = .01$). In multivariate analysis, KPS remained associated with mortality, but only the HCT-CI scores were still significantly associated with NRM. In a smaller single-institution study of 105 consecutive patients receiving reduced-intensity conditioning with fludarabine, melphalan, and alemtuzumab, performance status also influenced TRM ($P = .03$) and OS ($P = .0056$). Separately from overall functional status, researchers have shown differences in performance on specific physical function tests between cancer and noncancer patients [51], but these have not yet been evaluated or reported prospectively as part of a pretransplantation evaluation.

Physiologic and biologic tests measuring fitness have the potential to enhance discriminatory power predicting appropriateness for HCT beyond simple measures like HCT-CI, KPS, or even global frailty assessements. Examples include 6-minute walk testing [52], DXA scanning [53], cardiopulmonary VO_2

max testing [54], and robust strength/mobility assessments beyond grip strength. Molecular tests of physiologic aging, such as telomere length or p16INK4a expression levels [55] may eventually prove to have similar utility. Combinations of these tests with standardized comorbidity and performance status scoring may allow for the construction of a routine pretransplantation assessment that will be as useful for transplantation recipients as a CGA is for older individuals with cancer. Standardized cognitive, psychologic, social, and nutritional status assessments are also likely to contribute meaningfully to the pretransplantation assessment.

Symptom Profiles in HCT

PROs [56] following HCT are influenced by treatment-related toxicity, disease status, comorbidities, psychologic functioning, and other contributors to the overall patient experience. The term "symptom profile" (or "symptom burden" [57]) refers to an aggregate of patient-reported symptoms (eg, mucositis, nausea, insomnia, fatigue, anxiety, depression) derived from repetitive, daily to weekly assessments after a physiologic stressor such as HCT. Most patients undergoing allogeneic or autologous stem cell transplantation experience multiple physical, affective, and/or cognitive symptoms. Symptoms affect HRQOL [6,58], and specific symptoms (such as depression) [59] have been shown to predict eventual morbidity and mortality after transplantation.

Symptom profiles can be expressed in several ways, such as the number and/or severity of all or an interrelated subset (cluster) of symptoms, a symptom area under the curve [60] throughout a period of time, or symptom changes over time. The relatively new technique of symptom profiling promises to yield comprehensive patient-reported datasets that will be instructive in ways that traditional, infrequent HRQOL assessments are not. Daily to weekly symptom assessments reflect underlying pathophysiology, representing a patient-reported data stream that complements clinician- and laboratory-acquired information to monitor health. The theoretical usefulness of this technique is at least two-fold. Increases in patient-reported symptoms above baseline reflect an individual's "tolerance" to treatment and long-term ability to absorb further physiologic stress. Second, symptom assessments can help to identify changes over time that herald the onset of clinical events. They have both prognostic and predictive value.

To date, researchers in this area have conducted a handful of studies in HCT that are beginning to validate this approach. For example, Anderson et al. [61] administered the MDASI-BMT to patients with multiple myeloma (n = 66) or non-Hodgkin lymphoma (n = 34) undergoing autologous stem cell transplantation. Patients provided symptom reports before transplantation, at conditioning, at nadir, twice a week for 30 days thereafter, and weekly for up to 1 year. Symptoms peaked at WBC nadir, 7 to 10 days posttransplantation, and then declined to baseline levels within several weeks. Symptom burden curves differed by disease and by conditioning regimen. Together, these observations implied that the symptom burden was dependent on the type of physiologic stressor (consistent with its role as a toxicity output), and that symptom peaks corresponded with underlying pathophysiology (consistent with the ability of the symptom burden to capture changes over time). In another autologous transplantation study, researchers performed a limited longitudinal assessment of symptoms and six cytokines during and after HCT in 18 patients with multiple myeloma or non-Hodgkin lymphoma, this time finding a relationship between IL-6 and symptom severity [62].

In an allogeneic HCT symptom burden study, Wang et al. [63] administered the MDASI to 30 patients with AML or MDS undergoing allo-HCT. Assessments were conducted at baseline, during conditioning, on the day of allo-HSCT, and twice a week for 30 days thereafter. Levels of the most severe symptoms increased significantly from baseline to WBC nadir and then decreased. Cytokine levels were also sampled in the early posttransplantation period in this study, and IL-6 and sTNFRI predicted the intensity of the most severe early posttransplantation symptoms. Interestingly, the nature of the symptom burden appeared to parallel cytokine-induced "sickness behavior" observed in mouse models. This study again showed the feasibility of relating early posttransplantation symptom changes to underlying pathophysiology, as measured through biomarker changes.

Finally, in a retrospective analysis of symptom reporting in 125 allo-HCT patients, Williams et al. [64] found that the difference in symptom burden between patients with and without aGVHD was not significant from the day of transplantation through D22, but was significant between D22 and D90. This study demonstrated the feasibility of capturing the symptom burden farther out from transplantation and again showed the relationship of symptoms to changes in disease status. Unfortunately, in this study, the symptoms were assessed too infrequently to determine whether symptoms preceded or were coincident with aGVHD onset.

Routine PRO assessment in the HCT clinic is straightforward, especially as electronic data capture solutions become ubiquitous [35]. Studies in diverse populations have found that technology-based methods of PRO data capture are well received by patients, if not preferred over paper-based instruments [65,66]. A meta-analysis of 65 studies showed that computer- and paper-administered PROs are equivalent data collection methodologies, with small mean differences that were neither statistically or clinically

significant [67]. In cancer settings, regular, repeated PRO collection and feedback to oncologists facilitates physician-patient communication and has a positive impact on HRQOL and emotional functioning [68]. When the electronic PRO system delivers a survey instrument that can simultaneously function as a clinical review of systems and a validated tool for assessing symptoms and quality of life (eg, the Patient Care Monitor 2.0 [69]), then a unique clinical environment is established that allows the simultaneous capture of research-quality clinical data [35]. The PRO data can be reported to clinicians at point of care to contribute to in-clinic HCT patient monitoring. These data can be subsequently linked to other datasets and analyzed in order to understand the needs of the HCT population, develop predictive models, and monitor quality of care provided.

Using Pretransplantation Assessments and Symptom Profiles to Improve Outcomes in HCT

The techniques of pretransplantation assessment and longitudinal symptom profiles are well positioned to move into HCT to improve outcomes in physiologically vulnerable populations. For example, a pretransplantation assessment should be developed and validated in order to determine recipient fitness before transplantation and distinguishing the best management plan. In turn, the pretransplantation assessment should then be linked with early posttransplantation symptom profiles to identify individuals at lower or higher risk of longer-term transplantation-related distress, disability, or death. Once these predictive models are constructed and refined, interventions should be developed and the impact of the interventions monitored. For example, high-risk patients can be targeted for supportive care interventions [70-75] such as exercise or physical therapy training, health coaching, home monitoring, or enhanced clinical services with goals of preventing poor long-term outcomes among older patients receiving RIC transplants.

Similarly, the primary adverse outcomes in older transplantation recipients should be reconceptualized to include transplantation-related frailty in addition to transplantation-related mortality. New composite endpoints in older transplantation recipients can be conceptualized—and tested for patient-centric meaning—such as progression-free survival with functional independence. Older individuals place a high priority on functional independence as a principal determinant of HRQOL, and relevant outcome measures are justified. Longitudinal PRO data will be critical to understanding the trajectory of transplantation-related morbidity and mortality. Profiling patient experiences in this way will allow for comparative effectiveness studies that involve competing treatment options of varying intensities. Comparative effectiveness studies include not only primary treatment outcomes (ie, survival and disease control) but also the "burden of therapy" borne by patients. In addition to adverse event and cost data, longitudinal symptom profiling will add to these analyses by including a patient-reported point of view about the treatment experience.

Additionally, longitudinal symptom profiles in HCT recipients must be linked to genetic and biomarker data to enhance mechanistic understanding of early transplantation-related toxicity. In turn, these models should be used to construct rational dosing or therapeutic interventions to improve symptoms and the overall patient experience. For example, genetic polymorphisms in melphalan metabolism should be linked to variation in symptom profiles in myeloma patients; these data would then be used to interpret and predict therapeutic response and toxicity at the population and individual patient level, likely leading to personalized modifications to melphalan dosing. As another example, if additional symptom profile data validate the correlation between IL-6 levels and symptom peaks, then a molecule such as the anti-IL-6 antibody could be used to address symptoms in the early posttransplantation period.

Symptom profiles should be linked to biomarker data to predict risk for intermediate clinical events. Several recent studies have looked at biomarkers predictive for or coincident with aGVHD onset; examples of biomarkers implicated in subsequent aGVHD onset include CRP [76], CCL8 [77], IL-6 [78,79], IL-7 [80], IL-17 [81], and proteomic patterns [82,83]. Acute GVHD is also associated with characteristic clinical prodromal symptoms (malaise, anorexia, fatigue) as well as specific symptom clusters (rash, diarrhea [84], nausea, and others) that herald onset. Frequent symptom assessments could identify changes in symptom profiles that, when combined with biomarkers of interest, might produce sufficient predictive power for aGVHD to warrant consideration of early intervention trials. Although symptom-biomarker combinations are not likely to be sufficient to predict outcome and avoid overtreatment of individuals not destined to develop aGVHD, the morbidity and mortality of delayed treatment of conditions like this might justify this risk. If this type of symptom-biomarker modeling proves useful for early intervention trials in aGVHD, similar approaches might be used for other posttransplantation complications.

The time is right for pretransplantation assessments and longitudinal symptom profiling to be used in HCT in much the same way that CGAs and PROs are currently being used in non-HCT settings. A growing body of evidence demonstrates that CGAs predict treatment-related risk and identify vulnerable populations for intervention in noncancer settings. These are instruments already in routine use by geriatricians, and the transplantation community would benefit from similar application. Likewise, routine collection

of PRO data is already leading to interventional trials and overall improvements in the patient experience in other cancer settings [35,85]. Because the feasibility of this approach has been shown in HCT, longitudinal PRO sampling is truly ready to move into usual care for the transplantation population.

With sophistication, it is realistic to imagine complex multivariable predictive models that incorporate CGAs, longitudinal PRO data, biomarkers, and other clinical parameters to determine individuals at risk for near and late effects of HCT and evolving disease recurrence, as well as signal events before they become clinically apparent. More complex is the issue of integrating these sophisticated models with individual patient data at point of care. HCT clinicians already have a dizzying array of responsibilities, and new software will be needed to incorporate patient level information and support clinical decision making.

There are many reasons to support the integration of functional assessments and symptom profiles into HCT. We call for the routine use of these techniques and investment in research in this area so that we can limit treatment-related distress, disability, and death in the patients whom we serve.

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REFERENCES

1. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2010. 2010.
2. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010; 28:1878-1887.
3. Diaconescu R, Flowers CR, Storer B, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood*. 2004;104:1550-1558.
4. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. *Blood*. 2009;114:7-19.
5. Andrykowski MA, Bishop MM, Hahn EA, et al. Long-term health-related quality of life, growth, and spiritual well-being after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2005; 23:599-608.
6. Bevans M. Health-related quality of life following allogeneic hematopoietic stem cell transplantation. *Hematology*. 2010; 2010:248-254.
7. Lee SJ, Fairclough D, Parsons SK, et al. Recovery after stem-cell transplantation for hematologic diseases. *J Clinical Oncol*. 2001; 19:242-252.
8. Syrjala KL, Langer SL, Abrams JR, et al. Recovery and long-term function after hematopoietic cell transplantation for leukemia or lymphoma. *JAMA*. 2004;291:2335-2343.
9. Wong FL, Francisco L, Togawa K, et al. Long-term recovery after hematopoietic cell transplantation: predictors of quality-of-life concerns. *Blood*. 2010;115:2508-2519.
10. Bevans MF, Marden S, Leidy NK, et al. Health-related quality of life in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;38:101-109.
11. Diez-Campelo M, Perez-Simon JA, Gonzalez-Porras JR, et al. Quality of life assessment in patients undergoing reduced intensity conditioning allogeneic as compared to autologous transplantation: results of a prospective study. *Bone Marrow Transplant*. 2004;34:729-738.
12. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2006;108:2867-2873.
13. Pallua S, Giesinger J, Oberguggenberger A, et al. Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant*. 2010;45:1534-1539.
14. Extermann M. Measuring comorbidity in older cancer patients. *Eur J Cancer*. 2000;36:453-471.
15. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912-2919.
16. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer*. 2008;112:1992-2001.
17. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J Clin Oncol*. 2008;26: 4912-4920.
18. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. 2011;27:1-15.
19. Andorsky DJ, Cohen M, Naeim A, Pinter-Brown L. Outcomes of auto-SCT for lymphoma in subjects aged 70 years and over. *Bone Marrow Transplant*. 2011;46:1219-1225.
20. Brunello A, Sandri R, Extermann M. Multidimensional geriatric evaluation for older cancer patients as a clinical and research tool. *Cancer Treat Rev*. 2009;35:487-492.
21. Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol/Hematol*. 2005;55: 241-252.
22. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol*. 2007;25:1824-1831.
23. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann Oncol*. 2005;16:1795-1800.
24. Pope D, Ramesh H, Gennari R, et al. Pre-operative assessment of cancer in the elderly (PACE): a comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery. *Surg Oncol*. 2006;15:189-197.
25. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol*. 2002;20:494-502.
26. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma

patients who benefit from aggressive therapy. *Cancer*. 2009;115: 4547-4553.
27. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer*. 2005; 104:1998-2005.
28. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a Geriatric Assessment in Cooperative Group Clinical Cancer Trials: CALGB 360401. *J Clin Oncol*. 2011;29:1290-1296.
29. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. *Am J Manage Care*. 2008;14:530-539.
30. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med*. 2010;362:865-869.
31. Basch E, Artz D, Dulko D, et al. Patient online self-reporting of toxicity symptoms during chemotherapy. *J Clin Oncol*. 2005;23: 3552-3561.
32. Basch E, Abernethy AP. Supporting clinical practice decisions with real-time patient-reported outcomes. *J Clin Oncol*. 2011; 29:954-956.
33. Snyder CF, Jensen R, Courtin SO, Wu AW. PatientViewpoint: a website for patient-reported outcomes assessment. *Qual Life Res*. 2009;18:793-800.
34. Basch E, Artz D, Iasonos A, et al. Evaluation of an online platform for cancer patient self-reporting of chemotherapy toxicities. *J Am Med Informatics Assoc*. 2007;14:264-268.
35. Abernethy AP, Herndon JE 2nd, Wheeler JL, et al. Improving health care efficiency and quality using tablet personal computers to collect research-quality, patient-reported data. *Health Serv Res*. 2008;43:1975-1991.
36. Cleeland CS, Wang XS, Shi Q, et al. Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol*. 2011;29:994-1000.
37. Berry DL, Blumenstein BA, Halpenny B, et al. Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. *J Clin Oncol*. 2011;29:1029-1035.
38. Basch E, Abernethy AP. Commentary: encouraging clinicians to incorporate longitudinal patient-reported symptoms in routine clinical practice. *J Oncol Pract*. 2011;7:23-25.
39. Artz A, Swanson K, Kocherginsky M, et al. Features of frailty are surprisingly common in adults 50 years and older undergoing allogeneic hematopoietic cell transplantation (HCT) in the modern era. *Biol Blood Marrow Transplant*. 2011;17:S302.
40. Barba P, Pinana JL, Martino R, et al. Comparison of two pretransplant predictive models and a flexible HCT-CI using different cut off points to determine low-, intermediate-, and high-risk groups: the flexible HCT-CI Is the best predictor of NRM and OS in a population of patients undergoing allo-RIC. *Biol Blood Marrow Transplant*. 2010;16:413-420.
41. Farina L, Bruno B, Patriarca F, et al. The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia*. 2009;23:1131-1138.
42. Labonte L, Iqbal T, Zaidi MA, et al. Utility of comorbidity assessment in predicting transplantation-related toxicity following autologous hematopoietic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14:1039-1044.
43. Majhail NS, Brunstein CG, McAvoy S, et al. Does the hematopoietic cell transplantation specific comorbidity index predict transplant outcomes? A validation study in a large cohort of umbilical cord blood and matched related donor transplants. *Biol Blood Marrow Transplant*. 2008;14:985-992.
44. Pollack SM, Steinberg SM, Odom J, Dean RM, Fowler DH, Bishop MR. Assessment of the hematopoietic cell transplantation comorbidity index in non-Hodgkin lymphoma patients receiving reduced-intensity allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:223-230.
45. Smith AR, Majhail NS, MacMillan ML, et al. Hematopoietic cell transplantation comorbidity index predicts transplantation outcomes in pediatric patients. *Blood*. 2011;117:2728-2734.
46. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2007;25:4246-4254.
47. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood*. 2008;111:446-452.
48. Terwey TH, Hemmati PG, Martus P, et al. A modified EBMT risk score and the hematopoietic cell transplantation-specific comorbidity index for pre-transplant risk assessment in adult acute lymphoblastic leukemia. *Haematologica*. 2010;95:810-818.
49. Zipperer E, Pelz D, Nachtkamp K, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. *Haematologica*. 2009;94:729-732.
50. Artz AS, Pollyea DA, Kocherginsky M, et al. Performance status and comorbidity predict transplant-related mortality after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2006;12:954-964.
51. Simmonds MJ. Physical function in patients with cancer: psychometric characteristics and clinical usefulness of a physical performance test battery. *J Pain Symptom Manage*. 2002;24: 404-414.
52. Laboratories ACoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166: 111-117.
53. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33:997-1006.
54. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol*. 2008;9:757-765.
55. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*. 2009;8:439-448.
56. Lohr KN, Zebrack BJ. Using patient-reported outcomes in clinical practice: challenges and opportunities. *Qual Life Res*. 2009; 18:99-107.
57. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Instit Monogr*. 2007;37:16-21.
58. Bevans MF, Mitchell SA, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). *Support Care Cancer*. 2008;16:1243-1254.
59. Prieto JM, Atala J, Blanch J, et al. Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation. *J Clin Oncol*. 2005;23:6063-6071.
60. Mendoza T, Rosenthal D, Wang X, Mobley G, Cleeland C. Measuring the symptom buren of head and neck cancer patients undergoing concurrent chemotherapy and radiation therapy using an area under the curve. *J Clin Oncol*. 2009;27(15S):1.
61. Anderson KO, Giralt SA, Mendoza TR, et al. Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplant*. 2007;39:759-766.
62. Wang XS. Mixed effects modeling of the relationship of cytokines and symptom severity in patients during the first 30 days autologous BMT. *Int Soc Qual Life Res*. 2004.
63. Wang XS, Shi Q, Williams LA, et al. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer*. 2008;113: 2102-2109.
64. Williams LA. Measuring the symptom burden of allogeneic hematopoietic stem cell transplantation in patients with and without acute graft versus host disease. *Biol Blood Marrow Transplant*. 2009;15(S2):20-21.

65. Velikova G, Wright EP, Smith AB, et al. Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *J Clin Oncol*. 1999;17:998-1007.
66. Abernethy AP, Herndon JE 2nd, Wheeler JL, et al. Feasibility and acceptability to patients of a longitudinal system for evaluating cancer-related symptoms and quality of life: pilot study of an e/Tablet data-collection system in academic oncology. *J Pain Symptom Manage*. 2009;37:1027-1038.
67. Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value Health*. 2008;11:322-333.
68. Velikova G, Booth L, Smith AB, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol*. 2004;22:714-724.
69. Abernethy AP, Zafar SY, Uronis H, et al. Validation of the Patient Care Monitor (Version 2.0): a review of system assessment instrument for cancer patients. *J Pain Symptom Manage*. 2010;40: 545-558.
70. Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45:355-362.
71. Carlson LE, Smith D, Russell J, Fibich C, Whittaker T. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. *Bone Marrow Transplant*. 2006;37:945-954.
72. DeFor TE, Burns LJ, Gold EM, Weisdorf DJ. A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. *Biol Blood Marrow Transplant*. 2007;13:948-955.
73. Dimeo F, Fetscher S, Lange W, Mertelsmann R, Keul J. Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood*. 1997;90:3390-3394.
74. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplant*. 2009;43:725-737.
75. Jarden M, Nelausen K, Hovgaard D, Boesen E, Adamsen L. The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. *J Pain Symptom Manage*. 2009;38:174-190.
76. Fuji S, Kim SW, Fukuda T, et al. Preengraftment serum C-reactive protein (CRP) value may predict acute graft-versus-host disease and nonrelapse mortality after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2008;14:510-517.
77. Hori T, Naishiro Y, Sohma H, et al. CCL8 is a potential molecular candidate for the diagnosis of graft-versus-host disease. *Blood*. 2008;111:4403-4412.
78. Tawara I, Koyama M, Liu C, et al. Interleukin-6 modulates graft-versus-host responses after experimental allogeneic bone marrow transplantation. *Clin Cancer Res*. 2011;17:77-88.
79. Pihusch M, Pihusch R, Fraunberger P, et al. Evaluation of C-reactive protein, interleukin-6, and procalcitonin levels in allogeneic hematopoietic stem cell recipients. *Eur J Haematol*. 2006;76:93-101.
80. Dean RM, Fry T, Mackall C, et al. Association of serum interleukin-7 levels with the development of acute graft-versus-host disease. *J Clin. Oncol*. 2008;26:5735-5741.
81. Kappel LW, Goldberg GL, King CG, et al. IL-17 contributes to CD4-mediated graft-versus-host disease. *Blood*. 2009;113: 945-952.
82. Weissinger EM, Schiffer E, Hertenstein B, et al. Proteomic patterns predict acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Blood*. 2007;109: 5511-5519.
83. Paczesny S, Krijanovski OI, Braun TM, et al. A biomarker panel for acute graft-versus-host disease. *Blood*. 2009;113:273-278.
84. Liu D, Yan C, Xu L, et al. Diarrhea during the conditioning regimen is correlated with the occurrence of severe acute graft-versus-host disease through systemic release of inflammatory cytokines. *Biol Blood Marrow Transplant*. 2010;16:1567-1575.
85. Abernethy AP, Ahmad A, Zafar SY, Wheeler JL, Reese JB, Lyerly HK. Electronic patient-reported data capture as a foundation of rapid learning cancer care. *Med Care*. 2010;48(6 suppl): S32-S38.