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Comorbidity Burden in Patients with Chronic Graft Versus Host Disease

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Abstract

Chronic graft-versus-host disease (cGVHD) is associated with mortality, disability and impaired quality of life. Understanding the role of comorbidity in patients with cGVHD is important both for prognostication and potentially for tailoring treatments based on mortality risks. In a prospective cohort study of patients with cGVHD (n=239), we examined the performance of two comorbidity scales, the Functional Comorbidity Index (FCI) and the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI). Both scales detected a higher number of comorbidities at cGVHD cohort enrollment than pre-HCT ($p<0.001$). Higher HCT-CI scores at the time of cGVHD cohort enrollment were associated with higher non-relapse mortality (HR 1.21:1.04–1.42,p=0.01). For overall mortality, we detected an interaction with platelet count. Higher HCT-CI scores at enrollment were associated with an increased risk of overall mortality when the platelet count was less than or equal to 100,000/μl (HR 2.01: 1.20–3.35, p=0.01), but not when it was greater than 100,000/μl (HR 1.05: 0.90–1.22, p=0.53). Comorbidity scoring may help better predict survival outcomes in patients with cGVHD. Further studies to understand vulnerability unrelated to cGVHD activity in this patient population are needed.

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Authorship

DW, PJM, CC, JP, JP, MA, SA, MJ and SJL contributed clinical data; XC and BS performed statistical analysis and drafted the manuscript; WW and SJL designed research and drafted the manuscript; and all authors contributed to analysis and interpretation of data and critical review of the manuscript.

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Keywords

Chronic graft-versus-host disease; comorbidities; outcomes; allogeneic hematopoietic cell transplantation

Introduction

Chronic graft-versus-host disease (cGVHD) is associated with significant morbidity and mortality.[1,2] In addition to being a leading cause of late treatment-related deaths among allogeneic recipients, cGVHD is associated with deficits in quality of life that parallel systemic autoimmune diseases. The Chronic Graft versus Host Disease Consortium was established to test the 2005 NIH working group definitions for cGVHD severity,[3] and to determine other prognostic measures that predict overall and disease-free survival, non-relapse mortality, and functional impairment among patients with cGVHD.[4] Early data from the Consortium have demonstrated prognostic utility of the NIH global cGVHD severity score at enrollment,[5] and the poor prognosis of the "overlap" subtype of cGVHD when both acute and cGVHD manifestations are present concurrently.[6] The prevalence of comorbid illness in patients with cGVHD, and the influence of comorbidity burden upon subsequent functional and survival outcomes, have been examined in only a single previous study of 100 patients.[7]

Previous studies have evaluated the role of co-morbidities present at the time of transplantation and shown that greater comorbidity burden is associated with higher rates of non-relapse mortality and inferior overall survival compared to patients who have fewer comorbidities. The Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) is an example of a standardized way of measuring comorbidities in a population of hematopoietic cell transplant (HCT) candidates.[8] This scale measures a mixture of pre-existing diagnoses and organ dysfunction at the time of HCT, assigning weights to different comorbidities to derive a composite score. This scale has demonstrated prognostic importance among patients receiving transplants for AML and MDS[9] including in RIC settings,[10] for CLL,[11] and for NHL and MM.[12,13] However, it has not been applied to patients in the post-transplant setting. The Functional Comorbidity Index (FCI) is a comorbidity scale that was developed in a population of patients with spine disease and controls,[14] with physical function rather than mortality as an outcome. This index has also been found to predict future physical function in a population of patients with adult respiratory distress syndrome [15] and has been used to assess HCT patients with cGVHD.[7]

The prognostic value of the HCT-CI has not yet been examined in the setting of chronic GVHD. Chronic GVHD imposes unique physiological and functional vulnerabilities through the effects of the disease itself and the toxicities of the immunosuppressive treatments used to manage cGVHD. Knowledge of the contribution that factors such as comorbidity make to the interpretation of survival outcomes in cGVHD has the potential to strengthen study design and interpretation. This knowledge may also inform risk assessment and survival prognostication for newly diagnosed cGVHD patients, which may have direct utility in the clinic. Thus, we determined whether a measure of comorbidity could provide prognostic information independent of cGVHD characteristics. There are currently no validated scales for measuring comorbidity in patients with chronic GVHD, so we used the HCT-CI and FCI to determine comorbidities at the time of enrollment into the cGVHD consortium and tested their associations with overall mortality and non-relapse mortality. Finally, we aimed to evaluate whether these scales supplemented information provided by the NIH cGVHD Global Severity Scale.

Methods

The cGVHD Consortium began patient accrual in 2007 and has prospectively followed recipients with cGVHD in a multicenter, observational study. Because previously published data[18] have demonstrated discrepancies in the way that the elements of the HCT-CI are captured between sites, this analysis was restricted to participants from Fred Hutchinson Cancer Research Center (FHCRC) where two clinicians performed all the chart reviews in order to ensure uniformity of comorbidity scoring. The protocol was approved by the Institutional Review Board at Fred Hutchinson Cancer Research Center, and all subjects provided informed consent in accordance with the Declaration of Helsinki. Enrolled patients were allogeneic HCT recipients age 2 or older with cGVHD, diagnosed by the NIH consensus criteria, requiring systemic immunosuppressive therapy. The cohort includes patients with either classic cGVHD or overlap syndrome. Cases were classified as incident (enrollment < 3 months after cGVHD diagnosis) or prevalent (enrollment 3 or more months after cGVHD diagnosis but < 3 years after HCT). At enrollment and every 6 months thereafter, physicians and patients report standardized information on cGVHD organ involvement and symptoms. Incident cases had an additional assessment time point 3 months after enrollment. Chronic GVHD global severity (mild, moderate severe) was determined from individual organ scoring provided by clinicians using the NIH consensus scoring.

Comorbidity Grading

A complete list of comorbidities was systematically abstracted from medical records for all patients at transplant and at the time of cGVHD cohort enrollment based on comprehensive history and physical exam documentation and available test results. Extracted data included comorbidities found in the FCI and the HCT-CI. These definitions adhered to the respective FCI and HCT-CI comorbidity definitions with a few exceptions (e.g. pulmonary dysfunction was assessed by recent PFTs, as in the HCT-CI definition, although the FCI definition uses a patient history of ARDS, COPD or emphysema).

An FCI score was calculated for each patient based on work by Groll et al.[14] The FCI measures 18 different comorbidities, though this instrument was developed in part to predict physical function rather than mortality, and has not been studied extensively within the transplant setting. In this scale, which includes several comorbidities distinct from the HCT-CI (such as osteoporosis, visual and hearing impairment, and degenerative disc disease), each comorbidity is assigned a score of 1 and comorbidities are summed to determine a total score (theoretical range 0–18).

An HCT-CI was calculated for each patient based on work by Sorror et. al.[7] The HCT-CI is a scale that includes 17 comorbidities and was developed to be used at the time of transplantation. Comorbidities include prior diagnoses (e.g. prior solid malignancy, cardiac disease), current diagnoses (e.g. active infection, diabetes, obesity, depression) and ongoing organ dysfunction (e.g. renal, pulmonary, hepatic). Each comorbidity, if present, is assigned a weighted score from 1 to 3, and some comorbidities are assigned different scores according to severity (e.g. moderate pulmonary dysfunction is assigned a 2 and severe pulmonary dysfunction is assigned a 3). The weighted comorbidities are summed to determine a total score (theoretical range 0–26).

Statistical Methods

Descriptive characteristics of the cohort are reported. The weights and aggregation algorithms recommended by the scales' developers were applied to yield an FCI and an HCT-CI score at two time points: at the time of transplantation and at the time of enrollment

into the cohort. Paired t-tests were used to determine whether scores changed between the two time points. NIH cGVHD global severity scoring at the time of enrollment was calculated from information reported on the case report forms completed by providers. The association of the proportion of involved patients for each comorbidity item between pre-transplant and enrollment was evaluated by McNemar's test.[16] Logistic regression models were used to test associations between individual comorbidities and HCT-CI quartiles.

For the purposes of model construction, cutpoints were used according to previously reported prognostic importance (platelet count < 100,000/μl vs ≥ 100,000/μl; Karnofsky performance score < 80 vs ≥ 80; age at transplantation ≥ 50 vs < 50; months between transplant and enrollment < 12 vs ≥ 12). Both incident and prevalent cases were included. The HCT-CI was included in the models with published weights as a continuous variable.

The criteria for scoring liver or lung disease as a comorbidity in the HCT-CI overlap with organ-specific scoring criteria for these manifestations on the NIH cGVHD severity scale. Both the HCT-CI and the NIH cGVHD severity scale define the presence and severity of pulmonary dysfunction by abnormalities of the FEV1 or DLCO, though the cut-points are different between scales and the NIH scale incorporates the Lung Function Score (a composite of these two variables). For liver, both the HCT-CI and the NIH cGVHD severity scale define moderate and severe liver dysfunction by abnormalities of the bilirubin or transaminases, though again the cut-points are different between the two scales. Because of the overlap between the HCT-CI and the NIH scale for pulmonary and liver dysfunction, we also tested a version of the HCT-CI that excluded lung and liver dysfunction in calculating the HCT-CI score.

Univariate and multivariate Cox regression models were constructed to examine associations between the comorbidity indices at the time of cohort enrollment and subsequent survival, adjusting for all known and available risk factors. Models were constructed with and without the NIH global severity score in order to determine the relative prognostic importance of the comorbidity scales vs. the NIH global severity score. Overall survival (OS) was calculated from the time of enrollment, with patients censored at the date last known alive. Non-relapse mortality (NRM) was defined as death prior to relapse, with relapse treated as a competing event. The C statistic was calculated for the co-morbidity scores as a measure of their predictive ability for the outcomes of interest. The C statistic varies from 0.5–1.0, with 0.5 indicating no predictive ability and higher numbers indicating better prediction. Statistical analyses were conducted using SAS software, Version 9.2 (SAS Institute).

Results

Population characteristics

Baseline characteristics of the 239 patients included in this analysis are displayed in Table 1a (transplant characteristics) and Table 1b (additional variables at the time enrollment into the cGVHD cohort). Most recipients had a history of prior acute I-IV GVHD (74%). Global cGVHD severity by NIH criteria was mild or less in 8%, moderate in 54%, and severe in 38% of recipients. Median follow-up of survivors was 32 months (range 0.6–55.0).

Prevalence of co-morbidities according to the FCI

Table 2 demonstrates the complete Functional Comorbidity Index (FCI) and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), at the assessment points. Three comorbidities in the FCI (peripheral vascular disease, visual impairment, and hearing impairment) were not seen at the time of transplantation in any recipients. At the time of transplantation, comorbidities in the FCI seen in more than 10% of recipients included

pulmonary disease (61%), upper gastrointestinal disease (31%), obesity (25%) and depression (22%). At the time of cohort enrollment, 13 comorbidities in the FCI increased in prevalence. Among these, pulmonary disease (69%), osteopenia/osteoporosis (47%), upper gastrointestinal disease (52%), depression (24%), and diabetes (17%) were seen in more than 10% of recipients. The proportions of patients with osteopenia/osteoporosis (p <0.001), lung dysfunction (p =0.02), neurological disease (p=0.007), diabetes (p <0.001), and upper gastrointestinal disease (p <0.001) were significantly higher at enrollment than at the time of transplantation, and the proportion of patients with obesity (p <0.001) was significantly lower at enrollment than at the time of transplantation. The mean FCI score at the time of transplantation was 1.8 (range 0–8) and increased to 2.7 (range 0–7) at the time of cohort enrollment (p<0.001).

Prevalence of co-morbidities according to the HCT-CI

Prevalent comorbidities in the HCT-CI at the time of transplantation included moderate pulmonary dysfunction (41%), psychiatric disturbance (25%), severe pulmonary dysfunction (20%), prior solid tumor (13%), and obesity (11%) (Table 2). Eight comorbidities in the HCT-CI were observed in less than 5% of patients. At the time of enrollment, seven comorbidities were seen in 10% or more of patients: severe pulmonary dysfunction (38%, nearly doubling from 20% at the time of transplantation), psychiatric disturbance (29%), moderate pulmonary dysfunction (31%), mild hepatic dysfunction (23%), diabetes (17%), infection (13%) and prior solid malignancy (13%). The proportions of patients with diabetes (p<0.001), mild hepatic dysfunction (p<0.001), infection (p=0.007), and severe pulmonary dysfunction (p<0.001) were significantly higher at cGVHD cohort enrollment than at the time of transplantation, and the proportions of patients with obesity (p=0.008), and moderate pulmonary dysfunction (p=0.03) were significantly lower at enrollment than at the time of transplantation. The mean HCT-CI weighted score at the time of transplantation was 2.6 (range 0–8) and increased to 3.7 (range 0–12) at the time of cohort enrollment (p<0.001).

Table 3 depicts comorbidities in the HCT-CI at the time of cGVHD cohort enrollment, listed by quartiles of overall HCT-CI scores (0–2, 3, 4–5, and ≥6). The prevalence and number of comorbidities increased progressively across the score quartiles. For example, in the lowest quartile, one comorbidity (moderate pulmonary dysfunction) was seen in more than 20% of patients, whereas in the highest quartile, 8 comorbidities were seen in more than 20% of patients, including one (severe pulmonary dysfunction) that was identified in more than half of patients. The proportion of patients with specific comorbidities increased progressively across HCT-CI quartiles, including cardiac (p=0.001), inflammatory bowel disease (p=0.04), diabetes (p=0.001), psychiatric disturbance (p<0.001), mild hepatic dysfunction (p=0.02), infection (p=0.001), moderate/severe renal (p<0.001), severe pulmonary (p<0.001), prior solid tumor (p<0.001), and moderate/severe hepatic (p<0.001). Table 4 shows the prevalence of specific comorbidities in patients with a platelet count of ≥ or < 100,000 at the time of cohort enrollment. There was a significantly higher prevalence of infection in patients with a platelet count < 100,000 than in patients with a platelet count ≥100,000 at the time of enrollment (29% vs 10%, p=0.001).

Overall survival

The FCI at the time of cGVHD cohort enrollment was not predictive of overall survival in univariate or multivariate analysis (data not shown). Table 5 shows that higher HCT-CI scores at the time of cGVHD cohort enrollment were predictive for an increased risk of overall mortality (HR 1.16: 1.02–1.31, p=0.02) as a continuous variable in the multivariate model. Enrollment in the cGVHD cohort within the first year after transplant was an adverse prognostic factor (HR 2.38: 1.08–5.24, p=0.03), and lower Karnofsky performance score (<80) at enrollment was also predictive of subsequent higher risk of overall mortality (HR

2.32: 1.17–4.59, p=0.02). No other variables were statistically significant in the multivariate analysis. No interaction effect between HCT-CI and case type was observed (p=0.99), but a statistically significant interaction of the HCT-CI with platelet count was observed (p=0.003), such that higher HCT-CI scores were associated with an increased risk of overall mortality when the platelet count was less than 100,000/μl (HR 2.01: 1.20–3.35, p=0.01), but not when it was greater than 100,000/μl (HR 1.05: 0.90–1.22, p=0.53). After excluding NIH global severity score in the model, higher HCT-CI scores were still associated with an increased risk of overall mortality (HR 1.16: 1.03–1.31, p=0.02).

Non-relapse mortality

The FCI at the time of cGVHD cohort enrollment was not predictive of NRM in univariate or multivariate analysis (data not shown). Table 6 shows that higher HCT-CI scores at enrollment were predictive for an increased risk of non-relapse mortality (HR 1.21: 1.04–1.42, p=0.01) in the multivariate model. No interaction effect was observed between HCT-CI and case type (p=0.69), nor between HCT-CI and platelet count (p=0.12). After controlling for HCT-CI at the time of transplantation, higher HCT-CI change scores from the time of transplantation to cohort enrollment were still associated with an increased risk of NRM (HR: 1.22: 1.00–1.49, p=0.05).

Common elements in the HCT-CI and NIH cGVHD global severity scoring

The NIH global severity score includes liver and lung dysfunction, which together substantially determine the maximum global severity score based on a previous Consortium analysis.[5] The HCT-CI also includes pulmonary and hepatic dysfunction, with both given weights up to 3. Because the NIH global severity score predicts mortality, we sought to determine whether these scales overlapped significantly with one another, and whether liver and lung dysfunction were responsible for the prognostic importance of the HCT-CI. We found that overlap existed between the HCT-CI and the NIH cGVHD severity scales at enrollment in the scoring of liver (correlation=0.61) and lung (correlation=0.61) dysfunction. We constructed a multivariate model that excluded the NIH severity score, and found that the significance of the HCT-CI was not enhanced (HR 1.16, p=0.02), suggesting that the HCT-CI is an independent predictor. We calculated a version of the HCT-CI that excluded consideration of pulmonary and liver comorbidities. While this version of the HCT-CI was significant in univariate analysis (HR 1.19, p=0.02), it was not significant in a covariate-adjusted model (HR 1.15, p=0.12). It is possible that the lack of significance of this version of the HCT-CI in the multivariate model may reflect lack of prevalence of the remaining comorbidities to provide sufficient power for this analysis. We also constructed a model that included pulmonary and liver comorbidity scores individually, without the HCT-CI, while controlling for other prognostic factors. In this model, neither pulmonary nor liver dysfunction was statistically associated with an increased risk of mortality (p=0.17 and p=0.19, respectively). These results suggest that the influence of the HCT-CI on mortality outcomes is not predominantly accounted for by pulmonary and liver dysfunction. In its complete form, the HCT-CI showed fair predictive ability for overall survival (c-statistic 0.63) and non-relapse mortality (c-statistic 0.68) in our cGVHD population.

Discussion

We examined the performance of two approaches to comorbidity assessment in patients with cGVHD. We found that one, the HCT-CI, predicted the risk of mortality when platelet counts were less than 100,000/μl but not when the platelet count was over 100,000/μl while another, the FCI, was not associated with the risk of mortality. These results suggest that understanding comorbidity burden is important in patients with cGVHD because it has independent prognostic significance even after adjustment for cGVHD variables but that the

choice of co-morbidity measurement tool matters. We acknowledge that the prognostic significance of the HCT-CI is modest, and thus may not in its current construction be the most ideal measure of comorbidity in this patient population. Additionally, the finding of significance in patients with platelets less than but not more than 100,000 does not have intuitively obvious meaning, though the difference in prevalence of infection in these two groups may suggest one possible explanation.

The HCT-CI was developed and validated for use at the time of transplantation and has not been examined previously in cGVHD, a condition for which there are no currently validated comorbidity scales. In our study of people with cGVHD, an HCT-CI captured at the time of enrollment into the cGVHD cohort predicted the risk of subsequent mortality. Whether comorbidity burden increases equally in patients with or without cGVHD is not currently known, and should be examined in future studies to determine the proportion of comorbidity burden increase that can be attributed to cGVHD.

The HCT-CI places particular weight on substantial, objectively measured pulmonary dysfunction, a variable that has been identified as prognostically relevant in hematopoietic cell transplantation[17] but can also reflect cGVHD and is part of the calculation of cGVHD global severity. Liver dysfunction is also part of the global NIH severity score. Our analyses support the relevance of the HCT-CI independent of the NIH severity score, and suggest that the totality of the index, and not just commonly abnormal variables such as pulmonary and liver dysfunction, is prognostically relevant for patients with cGVHD.

Several caveats should be considered in generalizing our study findings. Children, ethnic and racial minorities are under-represented. Patients with mild cGVHD requiring topical therapy only were not enrolled in the cohort. The HCT-CI, as previously noted, was not developed nor validated for a patient population with cGVHD. Additionally, HCT-CI scoring is complicated, laborious, based on specific laboratory tests for some organs, prone to inter-observer variability, and requires training to ensure accuracy.[18] In our study, two clinicians did all the chart review to generate the HCT-CI scores. Currently, efforts are underway to ensure uniformity and consistency of HCT-CI scoring across institutions, which will allow a multicenter effort investigating the relationship of the comorbidities with outcomes after cGVHD.

Moving forward, we urge further investigations that could lead to a mechanistic understanding of physiologic vulnerability in patients with cGVHD. Though the original HCT-CI appears to be prognostically significant in a cGVHD population, the measure was not developed for use in this population and the prognostic strength of this measure in patients with cGVHD is modest. It is likely that additional work to develop and validate a new “cGVHD-CI” will provide greater prognostic information for the cGVHD population.

One could also explore other measures of dysfunction for prognostic relevance that are not captured in traditional comorbidity scales. Examples of these include longitudinal patient-reported outcomes (PROs),[19] direct functional assessments such as cardiopulmonary exercise testing,[20] or molecular markers of toxicity and aging[21] that might help to measure vulnerability[22] in this patient population. The knowledge derived from improved assessment of comorbidity can be applied in at least three ways. First, the inclusion of comorbidity scores can help isolate the effects of cGVHD and its treatment on morbidity and mortality, separate from the effects of concurrent conditions, thus improving the interpretation of findings in both observational studies and therapeutic trials. Second, comorbidity assessment can help tailor cGVHD therapies in order to avoid giving overly toxic therapies to patients who are unable to tolerate them. Lastly, knowledge of comorbidities may also help in constructing and targeting supportive care regimens to improve overall outcomes.

For now, we recommend further studies of comorbidity scoring at the time of cGVHD onset or at enrollment into a clinical trial in order to improve the prediction of outcomes in this patient population. We also recommend continued study of whether supportive care interventions or different cGVHD treatment approaches in low versus high comorbidity scoring patients might influence outcomes. We hope that studies of this kind will lead to improved overall survival in this vulnerable patient population.

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References

1. Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood. 2002; 100:406–414. [PubMed: 12091329]
2. Pidala J, Kurland B, Chai X, Majhail N, Weisdorf DJ, Pavletic S, et al. Patient reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD consortium. Blood. 2011; 117:4651–4657. [PubMed: 21355084]
3. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biology of Blood and Marrow Transplantation. 2005; 11:945–956. [PubMed: 16338616]
4. Chronic GVHD Consortium. Rationale and design of the Chronic GVHD Cohort Study: improving outcomes assessment in chronic GVHD. Biology of Blood and Marrow Transplantation. 2011; 17:1114–1120. [PubMed: 21664473]
5. Arai S, Jagasia M, Storer B, Chai X, Pidala J, Cutler C, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH consensus criteria. Blood. 2011; 118:4242–4249. [PubMed: 21791424]
6. Pidala J, Vogelsang G, Martin P, Chai X, Storer B, Pavletic S, et al. Overlap subtype of chronic graft-versus-host disease is associated with an adverse prognosis, functional impairment, and inferior patient-reported outcomes: a Chronic Graft-versus-Host Disease Consortium study. Haematologica. 2012; 97:451–458. [PubMed: 22058206]
7. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC, et al. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). Bone Marrow Transplantation. 2010; 45:762–769. [PubMed: 19784078]
8. 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 SCT. Blood. 2005; 106:2912–2919. [PubMed: 15994282]
9. Sorror ML, Sandmaier BM, Storer BE, Maris MB, Baron F, Maloney DG, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. Journal of Clinical Oncology. 2007; 25:4246–4254. [PubMed: 17724349]
10. Lim ZY, Ingram W, Brand R, Ho A, Kenyon M, Devereux S, et al. Impact of pretransplant comorbidities on alemtuzumab-based reduced-intensity conditioning allogeneic hematopoietic SCT for patients with high-risk myelodysplastic syndrome and AML. Bone Marrow Transplantation. 2010; 45:633–639. [PubMed: 19767782]
11. 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. [PubMed: 17916744]

12. Farina L, Bruno B, Patriarca F, Spina F, Sorasio R, Morelli M, 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. [PubMed: 19194465]
13. 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. Biology of Blood and Marrow Transplantation. 2009; 15:223–230. [PubMed: 19167682]
14. Groll DL, Heyland DK, Caeser M, Wright JG. Assessment of long-term physical function in acute respiratory distress syndrome (ARDS) patients: comparison of the Charlson Comorbidity Index and the Functional Comorbidity Index. Am J Phys Med Rehabil. 2006; 85:574–581. [PubMed: 16788388]
15. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. Journal of Clinical Epidemiology. 2005; 58:595–602. [PubMed: 15878473]
16. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika. 1947; 12:153–157. [PubMed: 20254758]
17. Parimon T, Madtes DK, Au DH, Clark JG, Chien JW. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. Am J Respir Crit Care Med. 2005; 172:384–390. [PubMed: 15894602]
18. Sorror ML. Comorbidities and outcomes: advancing the field comes at a price. Biology of Blood and Marrow Transplantation. 2011; 17:1721–1723. [PubMed: 22030092]
19. Lohr KN, Zebrack BJ. Using patient-reported outcomes in clinical practice: challenges and opportunities. Quality of Life Research. 2009; 18:99–107. [PubMed: 19034690]
20. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncology. 2008; 9:757–765. [PubMed: 18672211]
21. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, et al. Expression of p16INK4a in peripheral blood T-cells is a biomarker of human aging. Aging Cell. 2009; 8:439–448. [PubMed: 19485966]
22. Wood WA, Abernethy AP, Giralt S. Pretransplantation assessments and symptom profiles: predicting transplantation-related toxicity and improving patient-centered outcomes. Biology of Blood and Marrow Transplantation. 2012; 18:497–504. [PubMed: 22015992]

Table 1

a. Baseline patient characteristics

Characteristic	
Age at transplantation, median years (range)	51.8 (2.7–78.9)
Gender, n (%)	
Female	107 (45)
Male	132 (55)
White, non-Hispanic, n (%)	207 (87)
Case type, n (%)	
Incident	144 (60)
Prevalent	95 (40)
Diagnosis, n (%)	
Acute leukemia (AML/ALL)	106 (44)
Chronic leukemia (CML/CLL)	30 (13)
MDS	50 (21)
NHL/HD	29 (12)
MM	12 (5)
AA	4 (2)
Other	8 (3)
Disease stage, n (%)*	
Early	90 (38)
Intermediate	85 (36)
Advanced	61 (26)
Donor, n (%)	
HLA-matched related	82 (34)
HLA-matched URD	114 (48)
HLA-mismatched	43 (18)
Donor sex, n (%)	
Female into male	62 (26)
Other	177 (74)
Graft source, n (%)	
Mobilized blood	216 (90)
Bone marrow	19 (8)
Cord blood	4 (2)
Conditioning regimen, n (%)	
Myeloablative	141 (59)
Not myeloablative	98 (41)

b. Additional patient characteristics at time of cGVHD cohort enrollment

Characteristic	
Age at enrollment, median y (range)	53.0 (11.0–79.0)
Time from transplant to enrollment, median months (range)	11.9 (3.0–294.2)

b. Additional patient characteristics at time of cGVHD cohort enrollment

Characteristic	
Time from transplant to cGVHD onset, median months (range)	7.3 (1.2–291)
Time from cGVHD onset to enrollment, median months (range)	1.6 (0.0–27.1)
Karnofsky performance status at enrollment, n (%)	
80+	118 (49)
<80	71 (30)
Missing	50 (21)
Platelet count at enrollment, 10^9/L, n (%)	
<100	45 (19)
≥100	192 (81)
Prior acute GVHD, n(%)	
Yes	178 (74)
No	61 (26)
NIH cGVHD severity score, n (%)	
Mild or less	17 (8)
Moderate	130 (54)
Severe	92 (38)
Overlap vs classic cGVHD, n(%)	
Classic	46 (19)
Overlap	193 (81)

* Missing data for 3 patients

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HD, Hodgkin lymphoma; MM, multiple myeloma; AA, aplastic anemia; HLA, human leukocyte antigen; and URD, unrelated donor.

Table 2

Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) and Functional Comorbidity Index (FCI) prevalence of item-level comorbidities at transplant and enrollment (N=239)

Organ system	**HCT-CI comorbidity (weight)**	**n (%) pts pre-HCT**	**N (%) pts cGVHD enrollment**	***P****	**FCI comorbidity**	**n (%) pts pre-HCT**	**N (%) pts cGVHD enrollment**	***P****
Musculo-skeletal	Rheumatologic (Lupus, mixed connective tissue disorders, rheumatoid arthritis, polymyalgia rheumatica, requiring treatment) (2)	7(3)	6(3)	0.32	Arthritis (rheumatoid and osteoarthritis)	11(5)	16(7)	0.10
	N/A				Osteoporosis	8(3)	112(47)	<0.001
	N/A				Degenerative disk disease (back disease, spinal stenosis, or severe chronic back pain)	2(1)	6(3)	0.10
Pulmonary	N/A				Asthma	10(4)	10(4)	1.00
	Severe Pulmonary (DLCO corrected for hemoglobin ≤65% of predicted, FEV1 ≤65% of predicted, dyspnea at rest or requiring oxygen therapy (3)	46(20)	92(38)	<0.001	COPD, ARDS, or Emphysema $^{\Psi}$	142(61)	166(69)	0.02
	Moderate Pulmonary (DLCO corrected for hemoglobin 66–80% of predicted, FEV1 66–80% of predicted, dyspnea on slight activity (2)	96(41)	74(31)	0.03	N/A			
Cardio-vascular	Cardiac (Coronary artery disease, congestive heart failure, myocardial infarction, ejection fraction ≤50%) (1)	15(6)	12(5)	0.18	Angina Congestive Heart Failure (or heart disease) Heart Attack (myocardial infarction)	10(4) 5(2) 3(1)	11(5) 2(1) 3(1)	0.32 0.18 1.00
	Heart Valve Disease (except asymptomatic mitral valve prolapse (3)	1(<1)	3(1)	0.32	N/A			
	Arrhythmia (Atrial fibrillation, atrial flutter, sick sinus syndrome, ventricular arrhythmia (1)	5(2)	10(4)	0.10	N/A			
	N/A				Peripheral Vascular Disease	0(0)	1(<1)	N/A
	Cerebrovascular Disease (Transient ischemic attacks, cerebrovascular ischemic or hemorrhagic stroke(1)	1(<1)	1(<1)	1.00	Stroke or TIA	1(<1)	1(<1)	1.00
Neurological	N/A				Neurological Disease (such as multiple sclerosis or Parkinson's)	10(4)	23(10)	0.007
	N/A				Visual Impairment (such as cataracts, glaucoma, macular degeneration)	0(0)	1(<1)	N/A

Organ system	HCT-CI comorbidity (weight)	n (%) pts pre-HCT	N (%) pts cGVHD enrollment	*P**	FCI comorbidity	n (%) pts pre-HCT	N (%) pts cGVHD enrollment	*P**
	N/A				Hearing Impairment (very hard of hearing, even with hearing aids)	0(0)	1(<1)	N/A
Psychiatric	Psychiatric Disturbance (depression or anxiety requiring psychiatric consult or treatment (1)	59 (25)	70 (29)	0.14	Depression Anxiety or Panic Disorders	51(22) 14(6)	57(24) 21(9)	0.47 0.18
Endocrine	Diabetes (treated with oral hypoglycemic drugs) (1)	23(10)	41(17)	<0.001	Diabetes Types I and II	23(10)	41(17)	<0.001
	Obesity (BMI > 35) (1)	25(11)	14(6)	0.008	Obesity and/or BMI > 30	59(25)	39(17)	<0.001
Gastro-intestinal	Peptic Ulcer (confirmed by endoscopy and requiring treatment) (2)	4(2)	3(1)	0.56	Upper Gastrointestinal Disease (ulcer, hernia, reflux)	73(31)	124(52)	<0.001
Renal	Inflammatory Bowel Disease (Crohn's disease, ulcerative colitis) (1)	4(2)	4(2)	1.00	N/A			
	Hepatic, mild (Chronic hepatitis, bilirubin >ULN - 1.5×ULN, AST/ALT > ULN – 2.5×ULN) (1)	18(8)	54(23)	<0.001	N/A			
	Hepatic, moderate/severe (Liver cirrhosis, bilirubin >1.5xULN, AST/ALT > 2.5×ULN) (1)	0(0)	25(10)	N/A	N/A			
	Moderate/severe renal (Serum creatinine > 2, on dialysis, prior renal transplantation) (2)	0(0)	9(4)	N/A	N/A			
Infection	Infection (requiring antimicrobial treatment before, during and after day 0) (1)	15(6)	32(13)	0.007	N/A			
Prior Solid Malignancy	Prior Solid Tumor (treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer) (3)	31(13)	31(13)	1.00	N/A			
Overall Score (pre-HCT)		Mean 2.6 (range 0–8)				Mean 1.8 (range 0–8)		
Overall Score (cGVHD enrollment)			Mean 3.7 (range 0–12)				Mean 2.7 (range 0–7)	

*from McNemar's test

ΨCOPD, ARDS and emphysema not collected – based on HCT-CL categories of either moderate or severe pulmonary strategies

Bone Marrow Transplant. Author manuscript; available in PMC 2014 May 01.

Table 3

Comorbidities at enrollment from most to least prevalent, by HCT-CI score quartile; only comorbidites with ≥10% prevalence within the respective quartile are listed

HCT-CI Score 0–2 (N=70)	%*	HCT-CI Score 3 (N=53)	%	HCT-CI Score 4–5 (N=63)	%	HCT-CI Score ≥6 (N=53)	%
Moderate pulm.	31	Moderate pulm.	42	Severe pulm	62	Severe pulm	68
Psychiatric	13	Severe pulm.	32	Psychiatric	43	Prior solid tumor	42
Mild hepatic	11	Psychiatric	25	Mild hepatic	41	Psychiatric	40
		Mild hepatic	17	Diabetes	29	Mod./sev. hepatic	34
				Moderate pulm.	22	Moderate pulm.	30
				Infection	16	Infection	25
				Prior solid tumor	11	Diabetes	25
				Obesity	11	Mild hepatic	21
						Mod./sev. renal	13
						Cardiac	11

*Percent of patients affected within respective quartile

Table 4

Distribution of comorbidities by patients with a platelet count ≥ or < 100,000 at the time of enrollment

Comorbidity	Platelets < 100K (N=45)	Platelets ≥100K (N=192)	p-value
Arrhythmia	3 (7%)	7 (4%)	0.36
Cardiac	1 (2%)	11 (6%)	0.33
Inflammatory bowel disease	2 (4%)	2 (1%)	0.11
Diabetes	8 (18%)	33 (17%)	0.92
Cerebrovascular disease	0 (0%)	1 (1%)	0.63
Psychiatric	13 (29%)	55 (29%)	0.97
Mild hepatic	11 (24%)	43 (22%)	0.77
Obesity	1 (2%)	13 (7%)	0.25
Infection	13 (29%)	19 (10%)	0.001
Rheumatologic	1 (2%)	5 (3%)	0.88
Ulcer	1 (2%)	2 (1%)	0.52
Moderate/severe renal	3 (7%)	6 (3%)	0.26
Moderate pulmonary	14 (31%)	60 (31%)	0.99
Severe pulmonary	18 (40%)	73 (38%)	0.81
Prior solid malignancy	7 (16%)	24 (13%)	0.58
Heart valve disease	2 (4%)	1 (1%)	0.03
Moderate/severe hepatic	5 (11%)	20 (10%)	0.89

Table 5

Multivariate analysis of risk factors for overall mortality at the time of enrollment

		p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
HCT-CI*		0.02	1.16	1.02	1.31
Case type	**Incident**	0.21	0.61	0.28	1.33
	Prevalent		1.00		
Months from HCT to enrollment	**< 12**	0.03	2.38	1.08	5.24
	≥ 12		1.00		
Platelet count at enrollment	< 100K	0.06	1.95	0.97	3.92
	≥ 100K		1.00		
Karnofsky score at enrollment	**< 80**	0.02	2.32	1.17	4.59
	Missing	0.75	1.16	0.47	2.89
	≥ 80		1.00		
Patient age at transplant	**≥ 50**	0.28	0.70	0.37	1.34
	< 50		1.00		
Donor match	**Matched unrelated**	0.40	0.73	0.34	1.55
	Mismatched	0.78	1.12	0.50	2.50
	Matched related		1.00		
Donor patient gender	**Female into male**	0.36	0.70	0.33	1.51
	Other		1.00		
Transplant type	**Myeloablative**	0.21	0.66	0.35	1.26
	Non-myeloablative		1.00		
Prior acute GVHD	**Yes**	0.37	1.44	0.65	3.20
	No		1.00		
CGVHD type	**Overlap**	0.48	1.43	0.53	3.86
	Classic		1.00		
NIH global severity	**Severe**	0.66	1.16	0.60	2.23
	Less than severe		1.00		

* Interaction of HCT-CI with platelet count noted; for platelets < 100,000/μl and HCT-CI, HR 2.01 (1.20–3.35), p=0.01

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Table 6

Multivariate analysis of risk factors for non-relapse mortality at the time of enrollment

		p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
HCT-CI		0.01	1.21	1.04	1.42
Case type	**Incident**	0.07	0.42	0.16	1.07
	Prevalent		1.00		
Months from HCT to enrollment	**< 12**	0.14	2.05	0.78	5.37
	≥ 12		1.00		
Platelet count at enrollment	**< 100K**	0.03	2.51	1.08	5.85
	≥ 100K		1.00		
Karnofsky score at enrollment	**< 80**	0.03	2.72	1.11	6.63
	Missing	0.30	1.77	0.60	5.19
	≥ 80		1.00		
Patient age at transplant	**≥ 50**	0.16	0.57	0.26	1.25
	< 50		1.00		
Donor match	**Matched unrelated**	0.65	0.80	0.31	2.09
	Mismatched	0.75	0.84	0.28	2.48
	Matched related		1.00		
Donor patient gender	**Female into male**	0.26	0.56	0.20	1.53
	Other		1.00		
Transplant type	**Myeloablative**	0.08	0.49	0.22	1.09
	Non-myeloablative		1.00		
Prior acute GVHD	**Yes**	0.31	1.70	0.61	4.76
	No		1.00		
CGVHD type	**Overlap**	0.39	1.75	0.49	6.24
	Classic		1.00		
NIH global severity	**Severe**	0.88	1.07	0.45	2.53
	Less than severe		1.00		