The global severity of chronic graft-*versus*-host disease, determined by National Institutes of Health consensus criteria, is associated with overall survival and non-relapse mortality

Joseph Pidala,[1] Jongphil Kim,[2] Claudio Anasetti,[1] Taiga Nishihori,[1] Brian Betts,[1] Teresa Field,[1] and Janelle Perkins[1]

[1]Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, Fl; and [2]Biostatistics, Moffitt Cancer Center, Tampa, Fl, USA

ABSTRACT

Background
The 2005 National Institutes of Health Consensus Development Conference on chronic graft-*versus*-host disease proposed major changes in the classification and grading of severity of chronic graft-*versus*-host disease.

Design and Methods
We aimed to study the association of the proposed chronic graft-*versus*-host disease classification and global severity with transplantation outcomes among a consecutive series of patients who received pharmacokinetically-targeted doses of intravenous busulfan and fludarabine conditioning followed by transplantation of allogeneic peripheral blood stem cells.

Results
From a total cohort (n = 242) of patients surviving more than 100 days after hematopoietic stem cell transplantation, 181 (75% of those at risk) had some manifestations of graft-*versus*-host disease after day 100. Of these, at onset 13 (7%) had late acute graft-*versus*-host disease, 62 (34%) had classic chronic graft-*versus*-host disease, and 106 (59%) had the overlap subtype of chronic graft-*versus*-host disease. The global severity of the chronic graft-*versus*-host disease was mild in 25% of cases, moderate in 46%, and severe in 29%. Multivariable modeling demonstrated the independent association of global severity of chronic graft-*versus*-host disease with overall survival (moderate/severe *versus* mild; HR 2.9, 95% CI 1.8–4.7, $P<0.0001$) and non-relapse mortality (moderate *versus* mild; HR 3.86, 95% CI 1.17–12.73, $P=0.03$, and severe *versus* mild (HR 10.06, 95% CI 3.07–32.97, $P<0.001$). The type of onset of progressive chronic graft-*versus*-host disease and the platelet count at the time of diagnosis of the disease were significantly associated with overall survival. The occurrence and severity of chronic graft-*versus*-host disease was also significantly associated with primary disease relapse.

Conclusions
Patients with moderate to severe chronic graft-*versus*-host disease, as determined by National Institutes of Health Consensus criteria, have an inferior overall survival and worse non-relapse mortality. Clinical and research advances are needed to improve the outcomes of affected patients.

Key words: chronic graft-*versus*-host disease, NIH criteria, transplantation outcome, overall survival, non-relapse mortality.

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Corrispondence:
Joseph Pidala, MD, MS Blood and Marrow Transplantation
Moffitt Cancer Center 12902 Magnolia Drive, FOB 3308
Tampa, Fl 33612 USA.
Phone: international +1.813.7452556.
Fax: international +1.813.4498248.
E-mail: joseph.pidala@moffitt.org

Introduction

Chronic graft-*versus*-host disease (GVHD), an immune-mediated syndrome that can occur following allogeneic hematopoietic cell transplantation (HCT), is associated with late morbidity, mortality, functional impairment, prolonged duration of immune suppression, and inferior quality of life.[1-4] Following the 2005 National Institutes of Health (NIH) Consensus Development Project on Chronic GVHD, there have been major proposed changes in the diagnosis, classification, and grading of severity of chronic GVHD. Rather than focusing on the historical division of 100 days as the determinant of acute or chronic GVHD, the proposed NIH Consensus Criteria invoke diagnostic manifestations of the respective syndromes for classification. Thus, those manifestations occurring beyond day 100 that are diagnostic of chronic GVHD are considered classic chronic GVHD, those solely consistent with acute GVHD are defined as late acute GVHD, and the concurrent presentation of both chronic and acute manifestations is defined as an overlap subtype of chronic GVHD. Furthermore, a revised scheme for grading severity of GVHD assigns a severity score for each involved organ with attention to functional impairment, and provides a global summary score (mild/moderate/severe) based on the number of organs involved and the severity of the condition in these organs.[5] The original intent of this severity grading was classification for the conduct of clinical trials.

Since then, investigators have performed retrospective analyses in which post-day 100 GVHD manifestations have been re-classified GVHD based on the NIH Consensus Criteria and investigated the relevance of both the syndrome classification and severity grading with regards to HCT outcomes. Overall these retrospective analyses suggested that the proposed NIH classification is prognostically useful, but reached somewhat divergent conclusions about the impact of both the syndrome classification and the global severity grading. Several factors, including the small number of subjects affected by chronic GVHD and heterogeneous clinical variables (such as graft source and conditioning regimen) in these series, may have influenced the outcomes. We, therefore, performed an analysis of global severity of chronic GVHD, as determined by NIH Consensus Criteria, and transplantation outcomes among a consecutive series of patient undergoing allogeneic HCT after uniform conditioning with a regimen of intravenous (IV) pharmacokinetically targeted doses of busulfan and fludarabine with transplantation of peripheral blood stem cells. The major objectives of the analysis were to examine the association of: (i) GVHD characteristics including type of onset (*de novo*, quiescent, and progressive) and syndrome classification (late acute, classic, overlap), and (ii) the global severity of the GVHD, as determined using NIH criteria, and transplantation outcomes.

Design and Methods

Patients and classification of chronic graft-versus-host disease

A consecutive series of patients conditioned with intravenous pharmacokinetically targeted doses of busulfan and fludarabine at the Moffitt Cancer Center between July, 2004 and April, 2008 were identified by retrospective review to provide a minimum of 3 years of follow up. All patients gave consent to the study of transplant outcome data, and this analysis was performed under the provision of an IRB approved protocol at the University of South Florida. The patients' socio-demographic, disease, and transplantation data, gathered by standardized medical record abstraction in all cases, included: age, gender, race/ethnicity, Karnofsky performance status score at the time of HCT, HCT co-morbidity index (HCT-CI);[6] donor and recipient gender, cytomegalovirus serostatus matching, disease condition and remission status at the time of HCT, donor relation and HLA matching, $CD34^+$ cell dose, stem cell source, pharmacokinetic information on the conditioning regimen, agents used for GVHD prophylaxis, and use of antithymocyte globulin as additional prophylaxis against acute GVHD in those cases with mismatched unrelated donors.

The occurrence and severity of acute GVHD within 100 days after HCT were recorded. Consensus criteria were employed to grade the severity of the GVHD.[7] From day 100 onward, all surviving patients were systematically evaluated for manifestations of both acute and chronic GVHD. Late acute GVHD was graded weekly until resolution, and upon any recurrence of the syndrome. In the case of classic chronic GVHD and overlap subtype, severity was graded at minimum every 3 months until death or last contact. The syndrome was classified according to the proposed NIH Consensus Criteria. This retrospective classification was dynamic, respecting changes in type of chronic GVHD syndrome and changes in severity.

For those patients with solely late acute manifestations at onset, the syndrome was classified as persistent, recurrent, or new onset based on prior acute GVHD activity before day 100. Classic chronic GVHD was defined by diagnostic manifestations of chronic GVHD or distinctive manifestations confirmed by laboratory, radiographic, or biopsy information; no concurrent manifestations of acute GVHD were present in those cases considered classic chronic GVHD. The concurrent presentation of both chronic and acute manifestations defined the overlap subtype of chronic GVHD. For those with classic chronic GVHD or the overlap subtype, the onset of the syndrome was classified as *de novo*, quiescent, or progressive based on the history of prior acute GVHD; progressive onset indicated onset of chronic GVHD without resolution of prior existing acute GVHD. For patients with classic chronic GVHD and the overlap subtype, the severity criteria recommended by the NIH Consensus Conference were employed. The number of organs involved and the severity of the disease in these organs dictated the global summary score used to define the disease as mild, moderate, or severe. Mild disease indicates one or two organs involved each with a maximal score of 1. Moderate disease indicates three or more organs involved with a score of 2 in any individual organ, or lung involvement with a score of 1. Severe global GVHD is defined by a score of 3 in any organ, or a lung score of 2. At the time of onset of chronic GVHD or late acute GVHD, the following information was recorded: Karnofsky performance status, platelet count, and serum bilirubin and albumin levels.

Transplantation outcome data included, in all cases, time to neutrophil and platelet engraftment, serial measures of donor chimerism, primary relapse post-HCT, non-relapse death, cause of death, and dates of last contact for surviving patients.

Statistical methods

Descriptive statistics were used to summarize the patients' socio-demographic, transplantation, and GVHD characteristics. From the overall consecutive series of patients, only those alive beyond day 100 were considered. This 100-day landmark served as the starting point for all analyses. Non-relapse mortality was estimated with primary disease relapse as a competing risk.[8] The proportional sub-distribution hazard model approach of Fine and

Gray was used for the multivariate analysis of the outcome of non-response mortality.[9] The Kaplan-Meier method was utilized for estimation of overall survival. Stratified overall survival curves were compared with the log-rank statistic. A Cox proportional hazard model with time-dependent covariates was used for multivariable modeling, considering chronic GVHD involvement and severity as time-dependent covariates. In these analyses, we examined the relationship between the following variables of interest and outcome: GVHD syndrome (late acute, classic chronic, overlap); onset type (*de novo*, quiescent, progressive); NIH global severity score (mild, moderate, severe). Other baseline patients' socio-demographic, disease, and transplantation covariates were included in the multivariable model according to the results of the univariable analysis. The multivariable model was constructed using the backward elimination method with a cut-off *P* value of 0.25.

Results

Landmark cohort characteristics

From July, 2004 to April, 2008, a consecutive series of 275 patients received pharmacokinetically-targeted doses of IV busulfan and fludarabine and underwent allogeneic hematopoietic cell transplantation at the Moffitt Cancer Center. From this total, 242 patients survived for more than 100 days after HCT. All of the analyses reported here represent landmark analysis from 100 days post-HCT. Baseline socio-demographic, disease condition, and transplantation characteristics of this cohort are reported in Table 1. One patient received stem cells harvested from the bone marrow, while all the rest (n = 241) received peripheral blood stem cells mobilized by granulocyte colony-stimulating factor. The median age of the patients was 48 years (range, 21–69 years). The majority were transplanted for acute myeloid leukemia/myelodysplastic syndrome. Approximately half had unrelated donors. Sixty-nine percent had a HCT-CI of 3 or less, and the majority had Karnofsky performance status of 80% or more at transplantation. Patients received fludarabine 40 mg/m^2 daily for 4 days, followed each day by IV busulfan (BuFlu) pharmacokinetically targeted to an average daily area under the curve (AUC) of 3500 (n=15), 5300 (n=201), or 6000 (n=26) μmol*min/L per day, depending on the patients' age, comorbidities, and disease risk. Busulfan targeted to 3500 μmol*min/L per day was given to patients over the age of 65, over the age of 60 if comorbidities were present, and to patients with chronic lymphocytic leukemia. Patients receiving busulfan targeted to 6000 μmol*min/L per day were enrolled on a prospective study evaluating increasing AUC of busulfan. The rest of the patients were treated to our institutional standard of 5300 μmol*min/L per day. The maximal grade of acute GVHD that occurred within 100 days post-HCT was as follows: grade 1 (n=37, or 15%), grade 2 (n=145, or 60%), grade 3 (n=30, or 13%), and grade 4 (n=8, or 3%).

Characteristics of the graft-versus-host disease

From the total cohort of patients (n=242) surviving beyond the day 100 landmark, 181 (75% of those at risk) had some type of GVHD manifestation after day 100. Of these, at onset 13 (7%) had late acute GVHD, 62 (34%) had classic chronic GVHD, and 106 (59%) had overlap subtype of chronic GVHD. Of the 106 with overlap subtype, 32 (30%) had erythematous skin manifestations, 85 (80%) had gastrointestinal involvement, and 36 (34%) had liver involvement. Of these concurrent acute GVHD sites, 62 (58%) had one, 41 (39%) had two, and 3 (3%) had three organs involved. Of those with two or more of these sites involved, 16 (36%) had gastrointestinal and liver, 21 (48%) had skin and gastrointestinal, 4 (9%) had skin and liver, and 3 (7%) had skin, gastrointestinal, and liver manifestations. Chronic GVHD characteristics at the time of onset are reported in Table 2. Organ involvement and maximal severity of individual organ disease for the duration of chronic GVHD activity are reported in Table 3. No significant association was detected between year of chronic GVHD diagnosis and either chronic GVHD severity or syndrome classification. Baseline patient and transplantation variables were examined for association with the development of chronic GVHD (restricted to classic and overlap cases). Prior acute GVHD within 100 days post-HCT and having a relation as a donor were significantly associated with the devel-

Table 1. Baseline socio-demographic, disease, and transplantation variables of the 100-day landmark cohort.

Variable	Frequency	%
Median age, years	49 (range 21-69)	
Disease		
Aplastic anemia/paroxysmal nocturnal hemoglobinuria	6	2%
Acute lymphoblastic leukemia	24	10%
Acute myelogenous leukemia	105	43%
Chronic myelogenous leukemia	18	7%
Myelodysplastic syndrome/ myeloproliferative disorder	48	20%
Non-Hodgkin's lymphoma/chronic lymphocytic leukemia/Hodgkin's lymphoma	35	15%
Plasma cell disorder	5	2%
Other leukemia	1	< 1%
Donor relation		
Sibling	116	48%
Unrelated	126	52%
HLA matching		
8/8 match	208	86%
≤ 7/8 match	34	14%
Sex matching		
Male recipient/female donor	57	24%
Others	185	76%
Cytomegalovirus matching (recipient/donor)		
Neg/neg	53	22%
Neg/pos	24	10%
Pos/neg	82	34%
Pos/pos	81	34%
Year HCT performed		
2004	12	5%
2005	65	27%
2006	65	27%
2007	75	31%
2008	25	25%
GVHD prophylaxis		
Tacrolimus/methotrexate	190	79%
Tacrolimus/mycophenolate	50	21%
Tacrolimus/rapamycin	2	< 1%
ATG delivered among mismatched donors	29/34	85% of MMUD
Rituxan delivered among NHL cases	10/33	30% of NHL

NHL: non-Hodgkin's lymphoma; HCT: allogeneic hematopoietic cell transplantation; HCT: allogeneic hematopoietic cell transplantation; ATG: anti-thymocyte globulin.

opment of chronic GVHD. Upon multivariable analysis, only having a relation as a donor was significantly association with the development of chronic GVHD (with reference of unrelated donor, sibling donor OR 0.38, 95% CI 0.16 – 0.88; *P*=0.025). The occurrence of acute GVHD before day 100, donor and recipient age, and male recipient/female donor gender pairing were not found to be significantly associated with the development of chronic GVHD on multivariable analysis.

Overall survival

We first examined overall survival of patients affected by any form of GVHD beyond day 100 (including those with late acute and chronic GVHD) and compared the overall survival of these patients with that of patients without GVHD. Those without any GVHD manifestations had a significantly inferior overall survival (*P*<0.0001). Next, we excluded those patients who never had any GVHD manifestations after day 100, and examined overall survival according to GVHD syndrome (late acute, classic, overlap). Those with late acute and overlap GVHD had significantly inferior overall survival compared to those with classic chronic GVHD (Figure 1A).

Limiting the sample to only those with overlap or classic chronic GVHD, we examined overall survival according to NIH global severity and type of chronic GVHD onset. Greater global severity was associated with significantly worse overall survival (Figure 1B). While patients with *de novo* and quiescent forms of chronic GVHD had similar outcomes, those with progressive onset of chronic GVHD had an inferior overall survival (Figure 1C). Univariable analysis utilizing a time-dependent Cox model demonstrated that moderate to severe global severity was associated with significantly worse overall survival (HR 3.21, 95% CI 2.02–5.08, *P*<0.0001). Among organs affected by chronic GVHD, moderate to severe gastrointestinal (HR 3.83, 95% CI 2.25–6.53, *P*<0.0001), liver (HR 3.26, 95% CI 1.9–5.6, *P*<0.0001), and lung (HR 3.39, 95% CI 1.54–7.4, *P*=0.002) involvement were associated with significantly worse overall survival.

Multivariable analysis was then performed using a time-dependent Cox model. NIH global chronic GVHD severity was significantly associated with overall survival. This effect was adjusted for time from transplantation, age, HCT-CI score, chronic GVHD onset type and onset platelet count (Table 4). These data confirmed an independent association of NIH global chronic GVHD severity with overall survival.

Non-relapse mortality and disease relapse

Non-relapse mortality was significantly associated with NIH chronic GVHD global severity (Figure 2A). Overlap

Table 2. Patients' characteristics at the onset of chronic GVHD.

Onset characteristics (*classic and overlap cases only*)	Frequency (%)	Onset of organ involvement (*classic and overlap cases only*)	Frequency (%)
Classic	62 (34%)	Skin	45 (27%)
Overlap	106 (59%)		
Progressive	12 (7%)	Mouth	49 (29%)
De novo	23 (14%)		
Quiescent	133 (79%)		
Time from HCT to chronic GVHD	Median 165 days (range 100-968)	Eye	28 (17%)
Platelet count ($\times 10^9$/L)	Median 114 (range 8-379)	GI	83 (50%)
Performance status		Liver	58 (35%)
80% or greater	84%		
70% or less	16%		
Bilirubin	Median 0.4 (range 0.3-5.4)	Lung	5 (3%)
Albumin	Median 3.8 (range 1.6-4.7)	Joints	0 (0%)
		Genitourinary	0 (0%)

**onset characteristics for classic chronic and overlap subtype cases only (excluding the 13 cases of late acute GVHD).*

Table 3. Chronic GVHD organ involvement and maximal organ severity for duration of follow up (limited to cases of classic and overlap subtype chronic GVHD).

Skin	
None	69 (41%)
Mild	48 (29%)
Moderate	33 (20%)
Severe	17 (10%)
Mouth	
None	57 (34%)
Mild	94 (56%)
Moderate	13 (8%)
Severe	3 (2%)
Eye	
None	86 (52%)
Mild	58 (35%)
Moderate	18 (11%)
Severe	5 (3%)
Gastrointestinal	
None	44 (26%)
Mild	69 (41%)
Moderate	37 (22%)
Severe	17 (10%)
Liver	58 (35%)
None	52 (31%)
Mild	43 (26%)
Moderate	
Severe	14 (8%)
Lung	
None	144 (86%)
Mild	7 (4%)
Moderate	7 (4%)
Severe	9 (5%)
Joint	
None	140 (84%)
Mild	19 (11%)
Moderate	7 (4%)
Severe	1 (1%)
Genitourinary	
None	159 (95%)
Mild	3 (2%)
Moderate	3 (2%)
Severe	2 (1%)
Global severity score	
Mild	25%
Moderate	46%
Severe	29%

and late acute GVHD were not significantly associated with greater non-relapse mortality compared to classic chronic GVHD (Figure 2B). Progressive onset was associated with significantly greater non-relapse mortality compared to the *de novo* and quiescent presentations (Figure 2C). Among individual affected organs, moderate to severe gastrointestinal ($P<0.0001$), and liver ($P=0.002$) involvement had significantly greater non-relapse mortality compared to mild involvement. No significant associations were detected between chronic GVHD severity and non-relapse mortality among the remaining affected organs.

Multivariable analysis adjusted for time after HCT confirmed the following relationships: (i) with mild global chronic GVHD as the reference, moderate (HR 3.86, 95% CI 1.17–12.73, $P=0.03$) and severe chronic GVHD (HR 10.06, 95% CI 3.07–32.97, $P<0.001$) were significantly associated with non-relapse mortality; (ii) chronic GVHD type (classic *versus* overlap) was not significantly associated with non-relapse mortality; (iii) with progressive onset as the reference, *de novo* (HR 0.29, 95% CI 0.1–0.89, $P=0.03$) and quiescent (HR 0.29, 95% CI 0.12–0.7, $P=0.006$) onset GVHD were associated with significantly lower non-relapse mortality; and (iv) higher platelet count at diagnosis of chronic GVHD (HR 0.91, 95% CI 0.85–0.98, $P=0.012$) was associated with significantly less non-relapse mortality.

Primary disease relapse was strongly associated with both the occurrence and global severity of chronic GVHD. Multivariable analysis adjusted for time after HCT confirmed this effect. With mild chronic GVHD as the reference, moderate (HR 0.25, 95% CI 0.11–0.56, $P=0.001$) and severe (HR 0.13, 95% CI 0.05–0.37, $P<0.001$) chronic GVHD were associated with significantly less relapse.

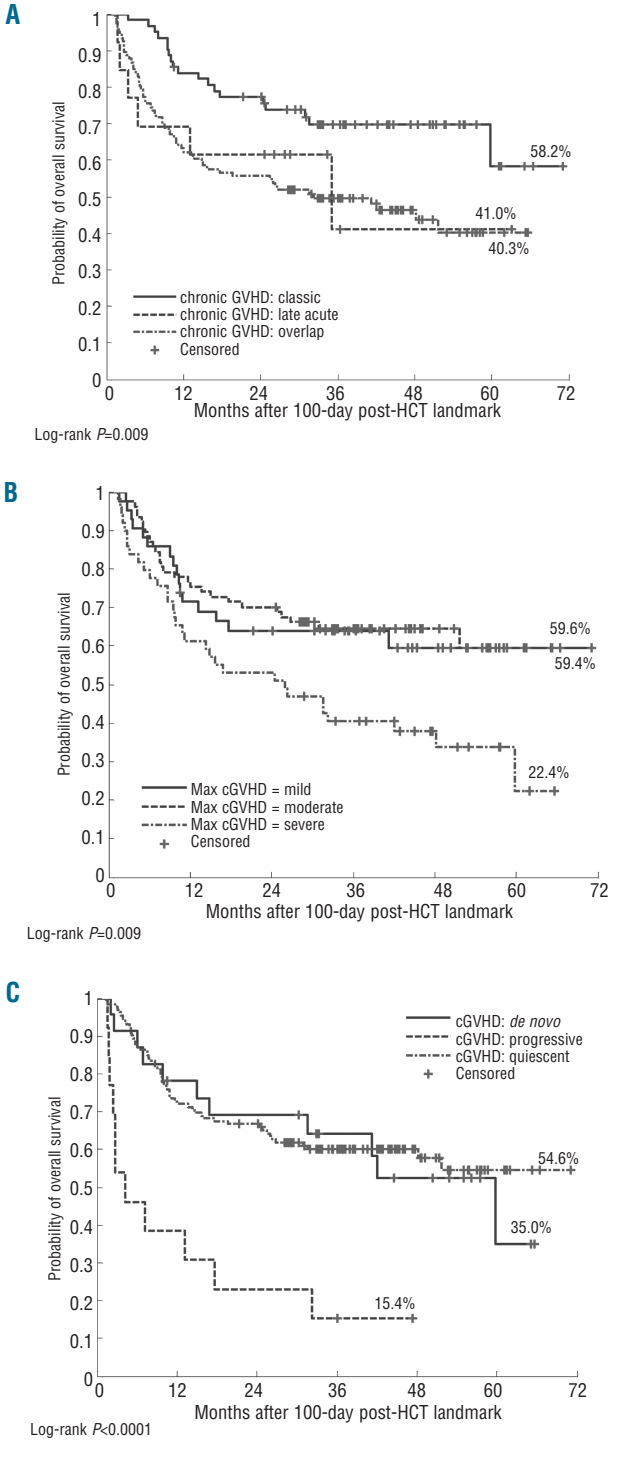

Figure 1. Overall survival from 100-day landmark stratified by (A) GVHD syndrome (classic *versus* overlap *versus* acute), (B) NIH global severity score (mild, moderate, severe), and (C) chronic GVHD onset type (*de novo*, quiescent, progressive).

Discussion

Chronic GVHD is an important source of late transplant-related morbidity, mortality, functional impairment, and

Table 4. Multivariable analysis of overall survival from the 100-day landmark.

Variables	*P* value	Hazard Ratio		
		Point Estimate	95% C.I. Lower	Upper
Chronic GVHD overall score				
None or mild		reference		
Moderate or severe	<.0001	2.92	1.802	4.73
Chronic GVHD type				
Progressive		reference		
De novo	0.003	0.244	0.095	0.624
Quiescent	<.0001	0.24	0.119	0.484
Chronic GVHD				
Classic	0.432			
Overlap				
Platelet (per 10×10^9/L increase)	0.007	0.936	0.892	0.982
Bilirubin (per 1 mg/dL increase)	0.897			
HCT CI total (per 1 increase)	0.033	1.145	1.011	1.298
Time from HCT to chronic GVHD onset (per 10 days increase)	0.001	0.928	0.887	0.97
Acute GVHD				
None	0.176			
Grade 1				
Grade 2				
Grade 3 or 4				
Age (per 10-year increase)	0.009	1.36	1.08	1.72

impaired patient-reported quality of life. Thus, efforts to improve its assessment, risk prediction, and clinical care are of utmost importance. Following the 2005 NIH Consensus Conference, there have been major proposed changes in the diagnosis, classification, and grading of severity of the syndrome. The association of these proposed changes with meaningful transplantation outcomes requires validation. Several retrospective studies have studied the impact of the proposed chronic GVHD classification and severity grading on important transplantation outcomes including survival, non-relapse mortality, and discontinuation of immune suppression. Given the potential impact of heterogeneity in transplantation conditions on the resultant outcomes in these analyses, we aimed to investigate these issues in a large consecutive series of HCT recipients conditioned with pharmacokinetically targeted doses of IV busulfan and fludarabine who received peripheral blood stem cell transplantation at a single center, focusing on the association of the proposed chronic GVHD syndrome classification and global severity of GVHD determined according to NIH criteria with transplantation outcome.

The primary conclusion of this analysis is the marked association between the chronic GVHD global severity and both overall survival and non-relapse mortality among this transplantation cohort. These data support the prognostic importance of the proposed NIH severity grading criteria, and indicate the need for further clinical and research effort to improve outcomes for such patients. These conclusions are in keeping with those previously reported on the use of the NIH severity grading: Cho *et al.* demonstrated that the global severity of GVHD was significantly associated with outcome.[10] and Perez-Simon *et al.* reported significant associations of global GVHD severity with GVHD-related mortality and 5-year overall survival.[11] Our analyses further demonstrate the increased risk for mortality in patients with moderate to severe gastrointestinal, hepatic, and pulmonary chronic GVHD manifestations.

In addition to global severity of chronic GVHD, multivariable analysis also demonstrated significant associations between progressive onset of chronic GVHD and platelet count and both overall survival and non-relapse mortality. These findings are in keeping with published data. However, our analysis did not support previously reported risk factors for mortality in chronic GVHD, such as bilirubin levels,[12-14] Karnofsky performance status,[2,15-17] female donor/male recipient pairing,[12,13] HLA mismatch,[13,16] older donor age,[13] and prior acute GVHD.[12,13,16] Additionally, insufficient data did not permit analysis of previously reported risk factors including response of chronic GVHD to therapy,[18,19] and steroid dose.[13]

While overlap and late acute GVHD were associated with inferior outcome in univariable analysis, multivariable analysis did not support an independent association of chronic GVHD classification with overall survival or non-relapse mortality. These data do not bring further clarity to the mixed conclusions reached in previous retrospective analyses: Jagasia *et al.* reported significant differences in overall survival according to the classification of classic *versus* overlap *versus* late acute GVHD, with the major finding that overall survival was significantly worse in those with any manifestation of acute GVHD.[20] Arora *et al.* reached similar conclusions, with significantly greater transplant-related mortality and worse overall survival for those patients with late acute GVHD.[21] Conversely, in a retrospective analysis of 740 patients re-classified according to the NIH criteria, Vigorito *et al.* found no significant difference in major outcomes (overall survival, non-relapse mortality, relapse, or discontinuation of immune suppression) between those with late acute GVHD and those with chronic GVHD.[13] Future studies, in particular prospective

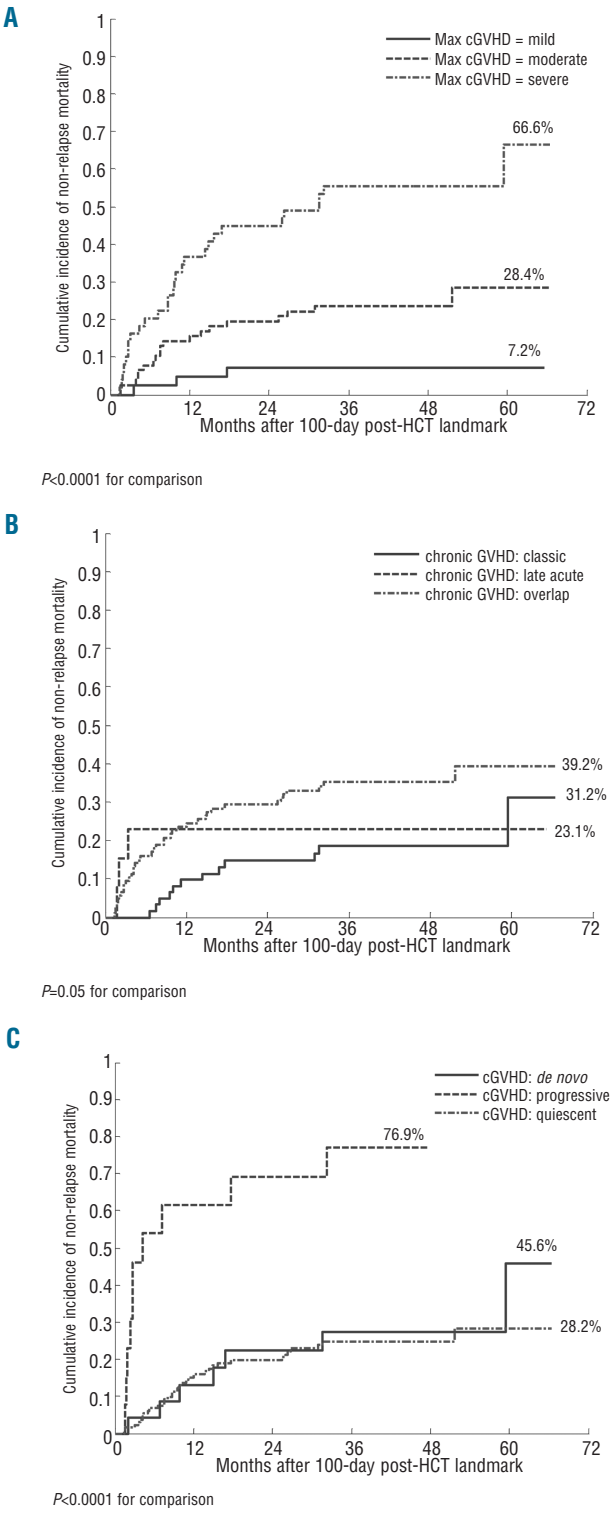

Figure 2. Cumulative incidence of non-relapse mortality according to (A) GVHD global severity, (B) chronic GVHD syndrome (classic, overlap, late acute), and (C) onset type (*de novo*, quiescent, progressive).

studies with standardized data collection, are needed to shed further light onto the relationship between GVHD classification (late acute, classic and overlap chronic GVHD) and transplant outcome.

While this analysis benefits from the overall sample size and greater uniformity in transplantation conditions, we do acknowledge several limitations to the work. First, the retrospective nature of this analysis has inherent limitations. Inadequacy of patients' medical records may lead to missing data and misclassification. In addition, not all manifestations scored as chronic GVHD were confirmed by biopsy, and it is possible that certain manifestations could have resulted from unrelated causes such as infections or adverse drug effects. While this concern is relevant in usual clinical practice, misclassification could have been further compounded in the process of medical record abstraction. These shortcomings highlight the need for prospective standardized collection of data on chronic GVHD classification and severity for validation of the proposed NIH Consensus Criteria. Furthermore, while the studied outcomes of overall survival, non-relapse mortality, and primary disease relapse are clearly vital transplantation outcomes, our data do not capture other meaningful patient-reported measures relevant to chronic GVHD outcomes. In particular, as chronic GVHD has an important impact on patients' symptom burden,[22] functional impairment,[23] and quality of life,[4,24,25] we cannot report here a comprehensive assessment of the impact of chronic GVHD severity on patients' overall experience.

In summary, our data demonstrate the significant association of chronic GVHD global severity, evaluated using the NIH Consensus Conference criteria, with mortality in a modern cohort of patients who received pharmacokinetically targeted IV busulfan and fludarabine conditioning and transplantation of peripheral blood stem cells. These data argue for further advances in clinical care and research to improve outcomes in such patients. Further progress will be made through the analysis of prospectively acquired data that adequately capture the far-reaching impact of chronic GVHD on transplantation outcome.

Authorship and Disclosures

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References

1. Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program. 2008:134-41.
2. 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(2):406-14.
3. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9(4):215-33.
4. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. Blood. 2009;114(1):7-19.
5. 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. Biol Blood Marrow Transplant. 2005;11(12): 945-56.
6. 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(8):2912-9.
7. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15 (6):825-8.
8. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals Of Statistics 1988;16: 1141-54.
9. Fine J. A proportional hazards model for the subdistribution of a competing risk. JASA. 1999;94:496-509.
10. Cho BS, Min CK, Eom KS, Kim YJ, Kim HJ, Lee S, et al. Feasibility of NIH consensus criteria for chronic graft-versus-host disease. Leukemia. 2009;23(1):78-84.
11. Perez-Simon JA, Encinas C, Silva F, Arcos MJ, Diez-Campelo M, Sanchez-Guijo FM, et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the National Institutes Health scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. Biol Blood Marrow Transplant. 2008;14(10):1163-71.
12. Stewart BL, Storer B, Storek J, Deeg HJ, Storb R, Hansen JA, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. Blood. 2004;104 (12):3501-6.
13. Vigorito AC, Campregher PV, Storer BE, Carpenter PA, Moravec CK, Kiem HP, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood. 2009;114(3):702-8.
14. Wingard JR, Piantadosi S, Vogelsang GB, Farmer ER, Jabs DA, Levin LS, et al. Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. Blood. 1989;74(4):1428-35.
15. Akpek G, Lee SJ, Flowers ME, Pavletic SZ, Arora M, Lee S, et al. Performance of a new clinical grading system for chronic graft-versus-host disease: a multicenter study. Blood. 2003;102(3):802-9.
16. Pavletic SZ, Smith LM, Bishop MR, Lynch JC, Tarantolo SR, Vose JM, et al. Prognostic factors of chronic graft-versus-host disease after allogeneic blood stem-cell transplantation. Am J Hematol. 2005;78(4):265-74.
17. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980; 69(2):204-17.
18. Arora M, Burns LJ, Davies SM, Macmillan ML, Defor TE, Miller WJ, et al. Chronic graft-versus-host disease: a prospective cohort study. Biol Blood Marrow Transplant. 2003;9(1):38-45.
19. Arora M, Nagaraj S, Wagner JE, Barker JN, Brunstein CG, Burns LJ, et al. Chronic graft-versus-host disease (cGVHD) following unrelated donor hematopoietic stem cell transplantation (HSCT): higher response rate in recipients of unrelated donor (URD) umbilical cord blood (UCB). Biol Blood Marrow Transplant. 2007;13(10):1145-52.
20. Jagasia M, Giglia J, Chinratanalab W, Dixon S, Chen H, Frangoul H, et al. Incidence and outcome of chronic graft-versus-host disease using National Institutes of Health consensus criteria. Biol Blood Marrow Transplant. 2007;13(10):1207-15.
21. Arora M, Nagaraj S, Witte J, DeFor TE, MacMillan M, Burns LJ, et al. New classification of chronic GVHD: added clarity from the consensus diagnoses. Bone Marrow Transplant. 2009;43(2):149-53.
22. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2002;8(8):444-52.
23. Herzberg PY, Heussner P, Mumm FH, Horak M, Hilgendorf I, von Harsdorf S, et al. Validation of the human activity profile questionnaire in patients after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2010;16(12): 1707-17.
24. Fraser CJ, Bhatia S, Ness K, Carter A, Francisco L, Arora M, 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 (8):2867-73.
25. 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;117(17):4651-7.