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Utility of Comorbidity Assessment in Predicting Transplantation-Related Toxicity Following Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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ABSTRACT

Patients with coexisting medical problems may suffer increased toxicity and reduced quality of life after autologous hematopoietic stem cell transplantation (HSCT). The benefit of high-dose therapy for some patients with multiple myeloma (MM) is debatable. Decision tools that aid in identifying those patients with MM most suited for autologous HSCT may avoid the risk of excess toxicity. An objective assessment of comorbidities was performed in 126 patients with MM undergoing autologous HSCT using the Charlson comorbidity index (CCI), the hematopoietic cell transplantation comorbidity index (HCT-CI), and a modified pretransplantation assessment of mortality (mPAM) to determine the strength of association with increased transplantation-related toxicity and increased length of hospital stay (LOS). Any comorbidity scored using the CCI or HCT-CI (score > 0) was associated with an increased number of organ systems with serious toxicity (at least grade 2 toxicity using the Seattle criteria), an increased total sum of toxicity grades for all organs, and prolonged LOS. An mPAM score ≥ 24 was associated with increased LOS. When considering autologous HSCT for a patient with MM, assessment of comorbidities using the CCI or HCT-CI may assist in predicting the risk of transplantation-related toxicity as an adjunct to physician judgment and patient preference.

KEY WORDS

Comorbidity • Multiple myeloma • Autologous hematopoietic stem cell transplantation • Transplantation-related toxicity

INTRODUCTION

Pretransplantation assessment of comorbidities is an important aspect of determining a patient's "fitness" for blood and marrow transplantation. Objective scoring using comorbidity scales and formal pretransplantation assessments have been reported only recently for patients undergoing hematopoietic stem cell transplantation (HSCT). Formal scoring systems for measuring comorbidity have proven useful in predicting increased mortality after allogeneic HSCT [1,2]. Although not clearly demonstrated in previous reports, comorbidities also may increase the risk of nonfatal regimen-related toxicity that can compromise performance status after the transplantation. Balancing regimen-induced toxicity with the benefits of autologous HSCT is particularly important for older patients with hematologic malignancies, such as multiple myeloma (MM).

Several studies have demonstrated improved survival in younger patients with MM undergoing autologous HSCT [3,4]; however, patients of advanced age or with significant comorbidities often are excluded because of the perceived risk of excessive toxicity. Studies of older patients have been less clear regarding a survival advantage with transplantation [5],

and no general consensus has emerged regarding clear exclusion criteria. Decision tools that aid in the selection of patients with MM most suited for autologous HSCT are needed to provide a better rationale for evaluating the risk of transplantation-related morbidity in older patients with coexisting medical problems and to better define those patients most likely to benefit.

In the present study, we addressed the association of pretransplantation comorbidity scores and transplantation-related toxicity in patients with MM. Three different scoring systems were compared: the Charlson comorbidity index (CCI) [6], the hematopoietic cell transplantation comorbidity index (HCT-CI) [1], and a modified pretransplantation assessment of mortality (mPAM) [2]. Herein we report the association of medical comorbidity as measured by the CCI and HCT-CI scoring systems with increased toxicity after autologous HSCT in patients with MM.

PATIENTS AND METHODS

Patients

All patients undergoing autologous HSCT at The Ottawa Hospital between January 2000 and December 2005 for MM and who provided informed consent for the use of medical information for research purposes were included in the analysis. Toxicity data related to a second or subsequent transplantation in any patient were excluded. Patient data and clinical information related to either comorbidity assessment or transplantation-related toxicity outcomes were retrieved from The Ottawa Hospital's blood and marrow transplant registry. In addition, hospital medical records were reviewed for all patients. All patients except 1 patient with concomitant low-grade lymphoma received melphalan 200 mg/m^2 as a conditioning therapy before reinfusion of peripheral blood stem cells. The peripheral blood stem cells were collected in a mean of 1.3 $\pm$ 0.5 apheresis collections (median, 1.0; range, 1-3), and the patients were reinfused with 7.3 $\pm$ 4.7 $\times$ 10^6 CD34$^+$ cells per kg. Five patients underwent a second autologous HSCT. Toxicity data and comorbidity assessments were performed with regard to the first transplantation in all cases.

Pretransplantation Comorbidity Assessment

Table 1 compares the scoring systems for the 3 comorbidity assessment scales used in this study. The CCI and HCT-CI scoring systems are similar, but the HCT-CI incorporates a greater number of comorbidities and assigns more points for certain medical problems. The mPAM incorporates fewer comorbidities, includes age and disease status as important factors, and assigns points for donor type and conditioning regimen. Details of these scoring systems have been published previously [1,2,6]. Clinical data gathered at the time of consultation by the transplantation team or from testing performed before transplantation were used to generate scores for each patient according to the criteria of the CCI, HCT-CI, and mPAM systems. Body mass index could not be calculated for all patients, because data were not available in some cases. It was therefore excluded from the analysis for all patients, affecting scores for the HCT-CI only. In all instances, if data concerning a particular medical comorbidity were not available for an individual, then it was assumed that no abnormality was present, and the scores were applied accordingly.

Table 1. *Pretransplantation Assessment Scoring Systems*

Comorbidity	Scoring System		
	CCI	HCT-CI	mPAM
Arrythmia	-	1	-
Cardiac disease	1	1	-
Inflammatory bowel disease	-	1	-
Diabetes	1	1	-
Cerebrovascular disease	1	1	-
Psychiatric disease	-	1	-
Hepatic disease, mild	1	1	2
Obesity	-	1	-
Infection	-	1	-
Rheumatologic disease	1	2	-
Peptic ulcer disease	1	2	-
Renal disease, moderate/severe	2	2	8
Previous solid tumor	2	3	-
Valvular heart disease	-	3	-
Pulmonary disease, disease	1	3	3-6
Hepatic disease, moderate/severe	3	3	2
Age	-	-	1-5
Donor type	-	-	1-4
Disease risk	-	-	1-12
Conditioning regimen	-	-	1-9

Toxicity Endpoints

The primary endpoint was the number of organs with serious toxicity (organ toxicity grade $\geq$ 2) according to the Seattle criteria (grades 0-4). Details of this toxicity scoring system have been published previously [7]. In addition, secondary measures of toxicity analyzed in the present study were the total sum of toxicity grades for all 8 organ systems captured by the Seattle criteria, stratified into high toxicity ($\geq$ 2 total toxicity grades) and low toxicity ($<$ 2 total toxicity grades), and the length of hospital stay (LOS) after reinfusion of the stem cell graft, stratified according to the median LOS into short ($<$18 days) and long ($\geq$ 18 days). Nonrelapse mortality before day 100 and admission to an intensive care unit (ICU) occurred in only a small number of patients and were not used as toxicity endpoints in this study.

Statistical Methods

Our null hypothesis was that none of the scoring systems for pretransplantation comorbidity assessment would be associated with increased toxicity after

Table 2. *Seattle Criteria for Organ Toxicity after Bone Marrow Transplantation*

Organ	Grade 1	Grade 2	Grade 3
Bladder	Asymptomatic macroscopic hematuria after 2 days from chemotherapy	Macroscopic hematuria after 7 days from chemotherapy or symptomatic	Hemorrhagic cystitis requiring intervention
Renal	Increased creatinine $< 2\times$ baseline	Increased creatinine $> 2\times$ baseline	Requires dialysis
Gastrointestinal	Noninfectious watery diarrhea 500-2000 mL/day	Noninfectious watery diarrhea >2000 mL/day or hemorrhagic stools or subileus	Ileus requiring nasogastric suction and/or surgery or hemorrhagic stools requiring transfusion
Hepatic	Bilirubin >34 and < 102 g/L or weight gain 2.5%-5.0% or AST $>2\times$ and $<5\times$ baseline	Bilirubin >102 and < 340 g/L or weight gain > 5.0% or ascites or AST $> 5\times$ baseline	Bilirubin > 340 g/L or encephalopathy or ascites causing respiratory compromise
Oral Mucositis	Pain and/or ulceration not requiring continuous systemic narcotic	Pain and/or ulceration requiring continuous systemic narcotic	Pain and/or ulceration requiring preventive intubation or aspiration pneumonia
Cardiovascular	Asymptomatic heart enlargement of chest x-ray or asymptomatic ECG changes	Heart failure responsive to diuretics or ECG changes requiring medical intervention	Heart failure unresponsive to medical intervention or severe ECG changes unresponsive to medical intervention
Nervous System	Somnolence but easily rousable	Somnolence with confusion, or other new central nervous system symptoms	Seizures or coma not otherwise explained
Pulmonary	Dypnea without chest x-ray changes or isolated infiltrate or mild interstitial changes	Moderate infiltrates or interstitial changes or 10% decrease in partial pressure of oxygen	Requires >50% O_2 or mechanical intubation

AST, aspartate aminotransferase; ECG, electrocardiogram.

autologous HSCT for MM. All analyses were performed using SPSS for Windows, version 15.0. Scores for the CCI, HCT-CI, and mPAM were used as predictors for logistic regression using increased number of organ systems with ≥ grade 2 toxicity, LOS > 18 days, and increased total sum of toxicity grades for all organs as outcome variables. The continuous variables were mPAM score and LOS. The mean, median, and range were considered before categorization into dichotomous variables was done. The CCI score, HCT-CI score, increased number of organ systems with ≥ grade 2 toxicity, and increased total sum of toxicity grades for all organs were considered ordinal categorical variables, and all possible combinations of the variables were developed and applied to logistic regression before the dichotomous categories with the best fit in terms of odds ratio (OR), 95% confidence interval (CI), and *P* value were selected. Binary logistic regression was performed for the analysis of all events (with 216 events analyzed using 3 independent variables, or 72:1), in accordance with standard methods [8,9]. Univariate logistic regression was performed on the predictor and outcome variables. All values are reported as mean ± 1 standard deviation (SD).

RESULTS

The entire cohort of 126 patients underwent autologous HSCT to treat MM. Patient characteristics are presented in Table 3. Disease stage was assigned using the Salmon-Durie classification system [10] (see Table 2). Insufficient data were available to allow us to assign the International Working Group staging classification [11] for all patients. Historical information regarding preexisting known medical problems was available for all patients. Pulmonary function tests were performed in 51% of the patients, and objective cardiac function

Table 3. *Patient Characteristics*

Patient Characteristic	n = 126
Age, years, mean (range)	56 (33-69)
Male/female, n	72/54
Stage at diagnosis (Salmon-Durie classification), n (%)	
Stage 1	9 (7)
Stage 2	37 (29)
Stage 3	75 (60)
Not available	5 (4)
Days from diagnosis to first transplantation, mean (SD)	409 (650)
Graft $CD34^+$ cells $\times 10^6$/kg, n, mean ± SD	7.3 ± 4.7
Days to neutrophil engraftment, mean ± SD	12.5 ± 3.9
Days to platelet engraftment, mean ± SD	13.8 ± 6.4
Number of organs with toxicity grade ≥ 1, mean ± SD	1.4 ± 1.2
Number of organs with toxicity grade ≥ 2, mean ± SD	0.4 ± 0.8
Total LOS, days, mean (range)	18 (10-80)
Patients requiring ICU admission, n (%)	3 (2.4)
Nonrelapse mortality at day +100, n (%)	1 (0.8)
Pretransplantation CCI score, mean ± SD	0.6 ± 0.8
Pretransplantation HCT-CI score, mean ± SD	1.0 ± 1.3
Pretransplantation mPAM score, mean ± SD	23 ± 3.5

testing was performed in 80% of the patients before transplantation. Alanine aminotransferase (ALT) measurements were not available before transplantation in 10 patients, and pretransplantation serum creatinine values could not be obtained in 3 patients.

Within the total cohort, the mean number of organs with at least grade 1 toxicity was 1.4 ± 1.2. A total of 27 patients (21%) had no toxicity in any organ system, 49 (39%) had toxicity in a single organ system, 31 (25%) had involvement of 2 organ systems, 8 (6.3%) had involvement of 3 organ systems, and 10 (7.9%) had involvement of 4 or more organ systems. Oral mucositis, was the most common toxicity and occurred in 88 patients (70%), whereas gastrointestinal toxicity, the second most common organ system toxicity, occurred in 34 patients (27%). Pulmonary, renal, and cardiac toxicity occurred in 14 (11%), 14 (11%), and 13 patients (10%), respectively. Central nervous system, hepatic, and bladder toxicity were less common, occurring in only 9 (7%), 5 (4%), and 2 patients (1.6%), respectively.

Thirty-one patients (25%) had toxicity of at least grade 2 in 1 or more organ systems, including 22 (17%) with 1 organ system, 5 (4%) with 2 organ systems, 2 (1.6%) with 3 organ systems, and 2 (1.6%) with 4 or more organ systems severely affected. Severe mucositis (16 patients; 13%), cardiac toxicity (8 patients; 6%), gastrointestinal toxicity (6 patients; 5%), and renal impairment (6 patients; 5%) were the most frequent toxicities with toxicity scores ≥ 2 (see Figure 1).

The mean LOS after reinfusion of hematopoietic stem cells was 18 days (range, 10-80 days). Nonrelapse mortality occurred in only 2 patients before day 100 after transplantation; thus, this could not be used as a measure of toxicity in our cohort. Furthermore, admission to the ICU occurred in only 3 cases, and all 3 of those patients were alive at last follow-up. Given the low incidence of ICU admission, this also could not be used as a means of discerning differences in overall toxicity in our cohort.

Charlson Comorbidity Index

Of the total cohort of 126 patients, 68 (54%) scored no points on the CCI scale, 47 (37%) scored 1 point, 5 (4%) scored 2 points, 3 (2.3%) scored 3 points, and 7 (5.6%) scored ≥ 4 points. The most common comorbidities were lung disease, liver abnormalities, and diabetes, with 36 patients (29%), 21 patients (17%), and 8 patients (6.3%) scoring at least 1 point on the CCI for these, respectively (see Figure 2). Only 2 patients (1.6%) scored points in the categories of cardiovascular and renal comorbidities.

Our cohort was divided into low CCI score (0; n = 68) and high CCI score (≥ 1; n = 58). Logistic regression revealed an important trend toward an increased number of organs with serious toxicity in the group with a high CCI comorbidity score (OR = 2.27; 95% CI = 0.99-5.22; P = .053). Comorbidity as measured by the CCI scale was significantly correlated with a high overall sum of toxicity grades (n = 55 with a sum ≥ 2) (OR = 2.19; 95% CI = 1.06-4.49; P = .033) and with prolonged LOS beyond 18 days (OR 4.05; 95% CI = 1.76-9.28; P = .001). Results of logistic regression analysis are summarized in Table 4. Furthermore, dividing the cohort into 2 groups, a low CCI group with 0 or 1 point (n = 115) and a high CCI group with ≥ 2 points (n = 11), led to a significant correlation between high CCI score and the primary endpoint of increased number of organ systems with severe toxicity (OR = 4.32; 95% CI = 1.12-15.3; P = .024) and a significant trend toward increased total sum of organ toxicity grades (OR = 0.96-15.1; P = .058) and increased total LOS (OR = 0.96-11.8; P = .059).

Hematopoietic Cell Transplantation Comorbidity Index

Using the HCT-CI assessment of comorbidity led to a similar association between comorbidity and toxicity in our patients. A total of 66 patients (52%) had a comorbidity score of 0 according to the HCT-CI, 21 (17%) had a score of 1, 17 (13%) had a score of 2, 15 (12%) had a score of 3, and 7 (5.5%) had a score of ≥ 4. The distribution of patients with lung disease, hepatic abnormalities, diabetes, cardiac disease, and renal impairment was identical to that for the CCI (see Figure 2). In addition, 4 patients had comorbidity scores assigned for other diseases not captured by the CCI (3 patients with psychiatric illness and 1 patient with malaria).

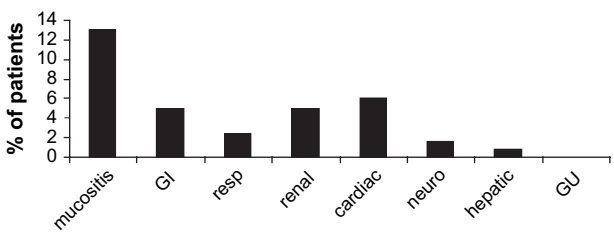

Figure 1. Percentage of patients with serious organ toxicity (at least grade 2) in each of 8 organ systems according to the Seattle criteria.

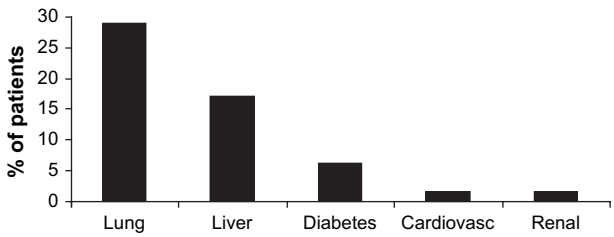

Figure 2. Percentage of patients with points for specific comorbidities using either the CCI or HCT-CI.

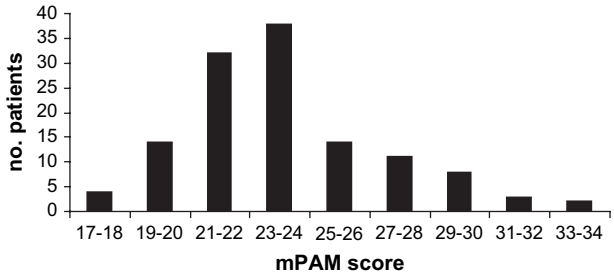

Figure 3. Distribution of patients with specific mPAM scores.

Our cohort was divided into low HCT-CI score (score of 0; n = 66) and high HCT-CI score (score of ≥ 1; n = 60). Logistic regression revealed a significant correlation between high HCT-CI score and an increased number of organs with severe toxicity (OR = 2.50; 95% CI = 1.08-5.80; P = .033). High HCT-CI score also was correlated significantly with our secondary toxicity outcomes of increased sum total of toxicity grades for all organ systems (n = 55 with a sum ≥ 2) (OR = 2.22; 95% CI = 1.08-4.55; P = .03) and prolonged LOS beyond 18 days (OR 5.34; 95% CI = 2.24-12.75; P < .001) (Table 4).

Modified Pretransplantation Assessment of Mortality

None of the patients in the present study scored any points according to the mPAM scoring system with regard to donor type, because all of the patients underwent autologous HSCT. Furthermore, all of the patients had a similar score for disease risk. All but 1 patient also received the identical conditioning regimen of high-dose (200 mg/m^2) melphalan and had the same score; however, 1 patient was treated with melphalan, etoposide, and total body irradiation (500 cGy in a single fraction) for concomitant low-grade lymphoproliferative disease and scored 8 points instead of 4 for the conditioning regimen due to the inclusion of total body irradiation. Many of the patients (103; 82%) scored additional points for increased age (62 patients with a score of 3 for age 50-60 years and 41 patients with a score of 5 for age > 60 years). Thirty-five patients scored additional points for pulmonary function abnormalities (17 with abnormal forced expiratory volume in 1 minute and 18 with a decreased lung CO_2 diffusion capacity), 11 patients scored additional points for elevated serum creatinine level, and 6 patients scored additional points for abnormal ALT values. Figure 3 shows the distribution of mPAM scores in our patients.

Logistic regression revealed no significant correlation between increased mPAM score and the number of organs with severe toxicity. Analysis of the data failed to identify any specific cutoff value for mPAM scores that stratified the cohort into 2 groups that differed in terms of our primary toxicity endpoint; however, when the cohort was divided into low mPAM score (score ≤ 23; n = 83) and high mPAM score (score ≥ 24; n = 43), higher mPAM scores were associated with prolonged LOS beyond 18 days (OR = 3.03; 95% CI = 1.35-12.75; P < .001). Using the same cutoff for low and high mPAM scores revealed a possible trend toward an increased number of organs with severe toxicity (OR = 1.87; 95% CI = 0.82-4.30; P = .14) and a trend toward an increased sum of toxicity grades (OR = 1.93; 95% CI = 0.91-4.09; P = .087). Results of logistic regression analysis are summarized in Table 4.

DISCUSSION

The present study has demonstrated the utility of the CCI and HCT-CI comorbidity scales in identifying patients at risk for increased toxicity after autologous HSCT for MM. Any comorbidity captured by the HCT-CI scoring system was associated with increased serious organ toxicity in our cohort. Further, any comorbidity associated with points on the CCI was associated with a trend toward increased serious toxicity. Comorbidity captured by either the CCI or HCT-CI was associated with prolonged LOS and total sum of organ toxicity scores. The mPAM score was not able to identify patients who experienced serious toxicity, possibly due to the homogeneity of the cohort and the weighting of the transplantation variables in the mPAM scoring system.

Although comorbidity is known to be a critical determinant of mortality after autologous HSCT [1,2], increased comorbidity scores in patients undergoing autologous HSCT for MM was not associated with increased mortality in the present study. But increased toxicity was observed, which may compromise performance status in this patient population. Using the HCT-CI and CCI comorbidity assessment systems to predict nonfatal toxicity after autologous HSCT is a novel use of these systems.

Table 4. *Summary of ORs and 95% CIs after Logistic Regression Analysis*

	CCI Score 0 versus ≥1	HCT-CI Score 0 versus ≥1	mPAM Score ≤ 23 versus ≥ 24
Toxicity grade ≥ 2 in 0 versus ≥ 1 organ	2.27 (0.99-5.22)	2.50 (1.08-5.80)	1.87 (0.82-4.30)
LOS (<18 days vs ≥ 19 days)	4.05 (1.76-9.29)	5.34 (2.24-12.75)	3.03 (1.35-6.77)
Total sum of toxicity grades (<2 vs ≥ 2 total grades)	2.19 (1.06-4.49)	2.22 (1.08-4.55)	1.93 (0.91-4.09)

To date, all of the comorbidity scoring systems assessed in our study have been validated exclusively in patients undergoing allogeneic HSCT, and, to the best of our knowledge, there are no published reports on the role of the HCT-CI in autologous HSCT populations. Overall, the risk of nonrelapse mortality is greater in allogeneic HSCT recipients. Despite the differences between autologous and allogeneic transplantation, our results demonstrate that the CCI and HCT-CI indices are useful predictors of toxicity after autologous HSCT.

One limitation of the present study is the presence of comorbid conditions in < 50% of patients. The most common pretransplantation comorbidity in the MM patients undergoing autologous HSCT was pulmonary disease; cardiovascular conditions were less common. Another limitation of this retrospective analysis is that patients with advanced cardiovascular disease and other serious comorbidities were excluded from transplantation by the treating physicians. Fitness for transplantation has been incompletely defined but frequently involves pretransplantation evaluation with supplementary tests, such as evaluation of left ventricular ejection fraction, chest x-ray, pulmonary function studies, and blood work to assess renal and hepatic dysfunction. Significant abnormalities in any of these tests may be sufficient grounds for exclusion from transplantation in some centers.

We recognize that measuring toxicity after HSCT has limitations. Although the Seattle criteria [7] have been validated for capturing peak toxicity in both allogeneic and autologous HSCT, they do not necessarily reflect global toxicity. Further, toxicity in some organ systems may be more permanent and critical compared with toxicity in other systems. Measures of global toxicity, including LOS, can be affected by many issues and are not specific. Mortality rate typically is < 5% after autologous HSCT in well-selected patients and is less useful as a measure of toxicity. Likewise, transfer to an ICU typically occurs in < 10% of patients but may serve as a useful indicator of toxicity. The development of better-refined toxicity criteria that allow more detailed assessment of organ toxicity is needed.

The present study was limited to examining the impact of comorbidities on acute regimen-related toxicity. But a major concern regarding regimen-related toxicity and acute complications of transplantation is the risk of residual organ impairment that could adversely affect quality of life in the longer term. Many patients are concerned about the impact of aggressive treatment on their overall functional and performance status. Although our study provides insight into the role of comorbid conditions and the risk of toxicity, we cannot comment on the degree of recovery from transplantation-related toxicity or details of their performance status at posttransplantation day 100.

In conclusion, our observations suggest that formal assessment of comorbidities using the HCT-CI or CCI scoring systems in patients undergoing autologous HSCT for MM may serve as a useful adjunct to both clinical judgment and patient preference when balancing the risk of toxicity and the benefits of transplantation.

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