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Age adjusted hematopoietic stem cell transplant comorbidity index predicts survival in a T-cell depleted cohort ☆

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Abstract
Objectives: Allogeneic hematopoietic stem cell transplant (HCT) continues to evolve with the treatment in higher risk patient population. This practice mandates stringent update and validation of risk stratification prior to undergoing such a complex and potentially fatal procedure. We examined the adoption of the new comorbidity index (HCT-CI/Age) proposed by the Seattle group after the addition of age variable and compared it to the pre-transplant assessment of mortality (PAM) that already incorporates age as part of its evaluation criteria.
Methods: A retrospective analysis of adult patients who underwent HCT at our institution from January 2010 through August 2014 was performed. Kaplan-Meier's curve, log-rank tests, Cox model and Pearson correlation was used in the analysis.
Results: Of the 114 patients that underwent allogeneic transplant in our institution, 75.4% were $\geq$40 years old. More than 58% had a DLCO $\leq$80%. Although scores were positively correlated (correlation coefficient 0.43, $p < 0.001$), HCT-CI/Age more accurately predicted 2-year overall survival (OS) and non-relapse mortality (NRM) in patients with lower (0—4) and higher

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(5–7) scores (52% and 36% versus 24% and 76%, $p = 0.004$, 0.003 respectively). PAM score did not reach statistical significance for difference in OS nor NRM between the low (<24) and high-risk (≥24) groups ($p = 0.19$ for both).

Conclusions: Despite our small sample population, HCT-CI/Age was more discriminative to identify patients with poor outcome that might benefit from intensified management strategies or other therapeutic approaches rather than allogeneic HCT.

Introduction

Allogeneic hematopoietic cell transplantation often presents the only curable therapeutic option for patients suffering from hematologic malignancies. While originally available to the young and fit, it is being increasingly utilized for patients of older age and with more comorbidities [1]. An inverse correlation of conditioning related toxicity and a better understanding of the graft versus leukemia effect, have led to allogeneic HCT being available for those patients in their 6th and 7th decade of life [2–4].

However, it is crucial to understand treatment related mortality from HCT in order to better identify those patients who would benefit from an alternative treatment approach or intensified supportive measures to optimize their outcome.

The first attempts to predict outcome were made using the Charlson comorbidity index (CCI) [5] in 2004 when its application in 134 allogeneic HCT recipients allowed to predict non-relapse mortality in myeloablative and non-myeloablative regimens [6]. The same group used a larger cohort to create the Hematopoietic stem cell transplant comorbidity index (HCT-CI), which added variables such as obesity, psychiatric disturbances and infection to the pre-transplant evaluation [7]. Since then, this scoring system has been accepted in multiple institutions as a commonly used tool for evaluating patients undergoing allogeneic HCT including our transplant center.

In an attempt to include more variables such as age, disease status and source of graft as potential factors on transplant outcome, Pariman et al formed a 50 points scoring system, the pre-transplant assessment of mortality (PAM) score. Both scoring systems have been validated in different patient populations [8–11]. Age has been a controversial predictor in transplant outcome; a study from the US showed poor prediction of allogeneic HCT mortality when elderly patients were stratified by age [12]. The European experience reported similar outcome of patients with age above 50 [13]. Sorror et al studied the effect of addition of age to HCT-CI and was able to show that age ≥40 years carried worse prognosis and deserved to be amended to HCT-CI scoring system to facilitate patients' stratification prior to transplant [14].

Since this introduction of age variable to HCT-CI score, to our knowledge, there have been no studies to verify the utility of this new scoring system and how it compares to the PAM score in an independent patient cohort. We aimed to compare the two scores and to verify their applicability in our population.

Methods

This is a retrospective analysis of 114 consecutive patients who underwent allogeneic HCT at the University of Kentucky between January 2010 and August 2014. The study was approved by the institutional review board.

Patients and transplant procedure

All adults, 18 years or older, carrying a diagnosis of malignant or benign conditions warranting an allogeneic HCT were included. Data including pre-transplant organ function, underlying disease, and donor type (matched sibling donor (MR), matched unrelated donor (MUD), and mismatch donor (MMR)) [15]. A match was defined as 10 out of 10 HLA match. Conditioning regimens were categorized according to previously defined criteria [16]: Disease was categorized based on the revised disease risk index [17]. Myeloablative regimen (MA) included total body irradiation (TBI) of ≥5 Gy single dose or ≥8 Gy fractionation, Busulfan (Bu) >8 mg/kg orally or >4000 AUC intravenously. Non myeloablative (NMA) regimens included TBI ≤2 Gy ± a purine analog. All other regimens were considered reduced intensity regimens (RIC) including regimens containing Bu that do not meet MA definition, and Fludarabine (Flu)+Melphalan (Mel). Graft versus host disease (GVHD) prophylaxis was done with tacrolimus ± methotrexate. In vivo T cell depletion was done with alemtuzumab or ATG as part of conditioning regimen based on treating physician discretion.

Patients were kept in the hospital until neutrophil engraftment, defined as an absolute neutrophil count >50 $0 \times 10^3/\mu L$ for three consecutive days. Acute GvHD was evaluated based on predefined criteria [18]. PAM score and HCT-CI/Age were calculated for all patients as described [14,15].

Statistical analysis and end points

Using the Contal and O'Quigley method [19], the ideal cut-off points were determined for both PAM (≥24) and HCT-CI/Age (≥5) that would be able to separate the population into two groups depending on outcome. The cohort was then divided into two groups (low and high risk) using the predefined cutoff points for both comorbidity scores. Overall survival (OS) and non-relapse mortality (NRM) rates at two years were calculated and compared for both groups using Kaplan-Meier curves and log rank tests and competing risk methods respectively. Cox models were utilized to calculate

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