COMORBIDITIES IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Introduction

Allogeneic conventional HCT is considered potentially curative for patients with malignant or non-malignant hematological diseases. Conditioning regimens for conventional HCT have been intensified to the limits of organ tolerance in order to optimize disease eradication. Consequently, serious toxicities to organs, such as gut, lung, kidney, heart, and liver have been observed which, additionally, have limited the ability to deliver adequate doses of postgrafting immunosuppression needed for control of GVHD. Until recently, these regimen-related toxicities associated with myeloablative conditioning have limited allogeneic HCT to patients without significant co-morbidities who were less than 55 to 60 years old. This age restriction has been unfortunate since the median ages of patients with most candidate diseases for HCT, e.g., acute and chronic leukemias, myelodysplasia (MDS), multiple myeloma, and lymphomas, have ranged from 65 to 70 years.

In an effort to expand treatment options for patients with hematological malignancies a number of nonmyeloablative or reduced intensity regimens have been introduced to older and medically infirm patients before allogeneic HCT from related or unrelated donors (1-7). The conditioning regimen’s major role has been host immunosuppression. The approach has relied predominantly on the generation of donor T cell (and/or NK cell)-mediated graft-versus-tumor effects for eradication of cancer. The use of these regimens have expanded the use of HCT to include elderly and medically infirm patients with various hematological disorders (8).

Age has been frequently cited as an important prognostic variable in HCT. Historical age cutoffs have been 55 and 60 years, respectively, largely influenced by the type of HCT donor (related versus unrelated). The reason for the age cutoffs has been prohibitive regimen-related toxicity and mortality in older patients. It has also been suggested that older patients were at higher risk of GVHD resulting in worse survivals. Most reports on age and HCT outcomes, however, have ignored comorbidities, which might have been confounding factors. Several investigators have studied single organ comorbidities in the context of predicting same organ toxicity after HCT. Comprehensive assessment of the interaction between multiple comorbidities and their impacts on HCT outcomes has become increasingly important given both increasing age of the Western population along with increasing prevalence of cancer and comorbidities(9) and the increasing enrollment of patients aged >60 years in HCT clinical trials (10).

Comorbidities using the Charlson Comorbidity Index (CCI)

In the field of cancer, investigators have found variable interactions between a given primary disease and different comorbidities based on type and severity of organ involvements. As a result, several indices have been created to rate the impacts of different comorbidities on the primary disease. The Charlson Comorbidity Index (CCI)(11) included 19 comorbidities which have been selected and weighted based on their strength of associations with mortality. The CCI has been the most widely used comorbidity index to predict mortality risks in various solid malignancies (12-14).

The CCI has been used in a retrospective study to compare pretransplant comorbidity differences among recipients of nonmyeloablative (n=60) and myeloabl-
relative HCT (n=72) from unrelated donors (15). At the time of HCT, nonmyeloablative patients had higher CCI scores compared to myeloablative patients (scores of 1-2 and ≥3, 35% and 18% compared to 12% and 0%, respectively, P<0.0001) at the time of HCT.

After HCT, nonmyeloablative patients experienced less (32% versus 69%, P<0.0001) overall grade IV (life-threatening) toxicities than myeloablative patients. The lessened cumulative incidences of day 100 (12% versus 18%, P=1.4) and 1-year (20% versus 32%, P=1.4) NRM among nonmyeloablative patients did not reach statistical significance. After adjustment for pretransplant differences, including comorbidity scores, statistically suggestive or significant lower hazard ratios (HR) for day 100 (0.2, P=0.07) and 1-year (0.3, P=0.04) NRM were found for nonmyeloablative patients, confirming the importance of a single scoring system for comorbidities. In multivariate analyses of risk factors for outcomes, comorbidities as scored by the CCI, proved to be the only independent factor for predicting overall grade IV toxicity (HR were 2.9 and 5.5 for scores 1-2 and ≥3, respectively, p=0.06) and NRM (HR were 2.4 and 10.5, respectively, p=0.04). Cumulative incidence and Kaplan-Meier curves showed linear increases in overall grade IV toxicities, NRM, and worsening survival with increasing CCI scores.

An HCT-specific comorbidity index (HCT-CI)

The CCI lacked sensitivity in detecting several comorbidities among HCT recipients, given that scores >0 were detected among only 35% of all HCT patients (12% among myeloablative patients) (15). This was thought to be due to not well-defined definitions of some comorbidities, such as hepatic and pulmonary. In addition, relatively frequent comorbidities among HCT patients, such as infections, were not included in the CCI.

In order to improve sensitivity, a study was designed which included 1055 consecutive recipients of allogeneic HCT between 1998 and 2004 who had various hematological diseases, and of whom 249 received nonmyeloablative and 761 myeloablative conditioning. Patients were randomly assigned to training (n=708) and validation (n=347) sets (16). Novel definitions were modeled for hepatic and renal comorbidities by using actual laboratory data and for pulmonary and cardiac comorbidities by using test results of organ function. Also, new integer weights of comorbidities were calculated based on HRs from Cox proportional hazard models of 2-year NRM, which were adjusted for disease risk, age, and conditioning regimen intensity. The new HCT-CI consisted of 17 comorbidities including three comorbidities that were not represented in the CCI, obesity, peritransplant infections, and psychiatric disturbances. HCT-CI scores of 0, 1, 2, 3, and ≥4 predicted 2-year NRM of 9%, 14%, 27%, 41%, and 43%, respectively, among patients of the training set.

When applied to data from the validation set, HCT-CI scores of 1-2 and ≥3 were found in 34% and 28% of patients compared to CCI scores of 1 and ≥2 in only 10% and 3% of patients, respectively. Most importantly, HCT-CI scores of 0, 1-2, and ≥3 showed linear predictions of NRM (14%, 21%, and 41%).

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>Patients</th>
<th>NRM (%)</th>
<th>Relapse (%)</th>
<th>OS (%)</th>
<th>RFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (HCT-CI scores 0-2 and low-risk diseases)</td>
<td>Myeloablative (n=138)</td>
<td>11</td>
<td>14</td>
<td>78</td>
<td>75</td>
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<td></td>
<td>Nonmyeloablative (n=28)</td>
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<td>33</td>
<td>70</td>
<td>63</td>
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<tr>
<td>Group II (HCT-CI scores 0-2 and intermediate and high-risk diseases)</td>
<td>Myeloablative (n=176)</td>
<td>24</td>
<td>34</td>
<td>51</td>
<td>43</td>
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<td></td>
<td>Nonmyeloablative (n=34)</td>
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<td>42</td>
<td>57</td>
<td>56</td>
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<tr>
<td>Group III (HCT-CI scores ≥3 and low-risk diseases)</td>
<td>Myeloablative (n=52)</td>
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<td>27</td>
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<td>41</td>
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<tr>
<td></td>
<td>Nonmyeloablative (n=19)</td>
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<td>37</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Group IV (HCT-CI scores ≥3 and intermediate and high-risk diseases)</td>
<td>Myeloablative (n=86)</td>
<td>46</td>
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<td></td>
<td>Nonmyeloablative (n=44)</td>
<td>29</td>
<td>49</td>
<td>29</td>
<td>23</td>
</tr>
</tbody>
</table>

*Donors were either related (n=103) or unrelated (n=276).2 5
and survival (71%, 60%, and 34%), respectively. In addition, HCT-CI scores had higher discriminative power than CCI scores both for NRM (c statistic of 0.692 versus 0.546, P < 0.001) and survival (c statistic of 0.661 versus 0.561, P < 0.001).

**HCT-CI and outcomes after conditioning regimens of different intensities**

Patients with acute myeloid leukemia (AML) or myelodysplasia (MDS). A recent study compared outcomes among patients with AML (n=391) or MDS (n=186) given either nonmyeloablative (n=125) or myeloablative HCT (n=452) (17). The median age of nonmyeloablative patients was 60 years compared to 46 years among myeloablative patients. In an initial analysis of outcomes among all patients, high HCT-CI scores and high disease risk independently predicted non-relapse mortality (NRM, p<0.0001 and p=0.004), overall survival (OS, p<0.0001 and p<0.0001), and relapse-free survival (RFS, p<0.0001 and p<0.0001), respectively. This allowed dividing patients into four risk groups based both on comorbidities and disease risks (Table 1).

Cumulative incidences of NRM tended to be lower and relapse rates higher among nonmyeloablative compared to myeloablative patients resulting in comparable rates of OS and RFS across all risk groups, even though nonmyeloablative patients were older than those given myeloablative conditioning. Novel anti-tumor agents combined with nonmyeloablative HCT should be explored among patients with high comorbidity scores and advanced disease (17).

**Patients with lymphoma or chronic lymphocytic leukemia (CLL).** Myeloablative allogeneic HCT has been associated with high regimen-related mortality (up to 60%) among patients with lymphoma or CLL (18-21). A recent analysis compared outcomes among 152 older (median age, 60 years) patients given nonmyeloablative conditioning to those among 68 younger (median age, 46 years) patients given myeloablative conditioning, stratifying for the HCT-CI (22).

Patients without comorbidities both in the nonmyeloablative and myeloablative cohorts had comparable NRM, OS, and progression-free survivals (Figure 1). However, nonmyeloablative patients with comorbidities had lower NRM (p = 0.009) and better OS (p = 0.04) than myeloablative patients (Figure 2). These differences became more significant after adjusting for other variables; also adjusted progression-free survival was better (p = 0.01). This suggests that younger patients with comorbidities would benefit from reducing conditioning intensity.
Conclusion

The HCT-CI provided simple and reliable scoring of pre-transplant comorbidities that predicted NRM and survival. The index still needs validation among larger patient samples in multi-center settings. Comorbidity data used in the index will likely become as important as defining cancer diagnosis, disease stage and other, more familiar prognostic variables (23).

References


