Allogeneic hematopoietic cell transplantation outcomes in patients with Richter’s transformation

Approximately 2-10% of chronic lymphocytic leukemia (CLL) cases develop into Richter’s transformation (RT), a more aggressive disease typically manifesting as diffuse large B-cell lymphoma. Targeted therapies such as ibrutinib are now commonly used to treat CLL but the transformation rate remains comparable to the chemoimmunotherapy era. Moreover, these targeted therapies are often used to treat RT despite limited efficacy, and prognosis for these patients is poor. The treatment of RT therefore remains challenging in the current era of targeted therapy.

Table 1. Kaplan-Meier estimates for overall and progression-free survival and estimates of cumulative incidences of non-relapse mortality, relapse, acute graft-versus-host disease and chronic graft-versus-host disease in the competing risks framework.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=28) (95% CI)</th>
<th>High Risk (N=9) (95% CI)</th>
<th>Standard Risk (N=19) (95% CI)</th>
<th>P</th>
<th>Age ≥65 (N=10) (95% CI)</th>
<th>Age &lt;65 (N=18) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-yr OS</td>
<td>53% (33-70)</td>
<td>11%* (0-63-39)</td>
<td>74% (48-88)</td>
<td>&lt;0.0001</td>
<td>40% (12-67)</td>
<td>61% (35-79)</td>
<td>0.16</td>
</tr>
<tr>
<td>4-yr PFS</td>
<td>39% (21-56)</td>
<td>0%</td>
<td>58% (33-76)</td>
<td>&lt;0.0001</td>
<td>10% (6-36)</td>
<td>55% (30-74)</td>
<td>0.006</td>
</tr>
<tr>
<td>4-yr NRM</td>
<td>29% (13-47)</td>
<td>33%* (5-67)</td>
<td>21% (6-42)</td>
<td>0.21</td>
<td>20% (5-29)</td>
<td>34% (13-56)</td>
<td>0.58</td>
</tr>
<tr>
<td>4-yr Relapse</td>
<td>32% (16-50)</td>
<td>56% (16-83)</td>
<td>21% (6-42)</td>
<td>0.054</td>
<td>70% (25-91)</td>
<td>11% (2-30)</td>
<td>0.007</td>
</tr>
<tr>
<td>6 mo. Grade 2-4 aGvHD</td>
<td>30% (19-54)</td>
<td>56% (17-82)</td>
<td>21% (6-42)</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo. Grade 2-4 aGvHD</td>
<td>18% (6-34)</td>
<td>37% (6-71)</td>
<td>11% (1-7-29)</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 yr cGvHD</td>
<td>52% (30-70)</td>
<td>25% (2-5-60)</td>
<td>61% (33-80)</td>
<td>0.43</td>
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</tbody>
</table>

Table 2. Kaplan-Meier estimates for overall survival (OS) and progression-free survival (PFS) by age and disease status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS PFS (95% CI)</th>
<th>sHR (95% CI)</th>
<th>shR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II-IV aGvHD</td>
<td>3.94 (1.36-12.4)</td>
<td>2.05 (0.8-5.09)</td>
<td>7.36 (1.59-34)</td>
<td>0.53 (0.1-2.81)</td>
</tr>
</tbody>
</table>

Logrank was used for comparisons of overall survival (OS) and progression-free survival (PFS). Gray test was used for comparisons of nonrelapse mortality (NRM), relapse and graft-versus-host disease (GvHD). The table presents results of univariable analysis for the effect of grade 2-4 acute GvHD (aGvHD) on outcomes Cox model was used for OS and PFS and cause-specific Cox model was used for NRM and relapse. Occurrence of grade 2-4 aGvHD was treated as a time dependent variable HR: hazard ratio; CI: confidence interval; mo: months; yr: years; cGvHD: chronic GvHD. *3-year estimate as the last patient in this cohort was censored at 36.3 months.
Survivors was 54 months (range: 16-92 month); median OS was not reached and median PFS was 11.2 months. Four-year OS, progression-free survival (PFS), cumulative incidence of non-relapse mortality (NRM) and relapse were 53%, 39%, 29% and 32%, respectively. (Figure 2A and B). The cumulative incidence of grade 2-4 and grade 3-4 acute GvHD at 6 months were 36% and 18%, respectively (Table 1).

As for risk factors, all four patients with low platelet counts (subjects 1, 2, 4 and 5) and six of seven patients with high LDH died within 17 months of alloHCT (subjects 3, 4, 5, 7, 9 and 14) (Figure 1). Due to the small number of patients with high LDH and low platelet counts, these two factors were combined and considered ‘high risk’. Four-year OS was 11% in this high risk group and 74% in the standard risk group (P<0.0001) (Table 1; Figure 2C). In addition, patients who developed grade 2-4 acute GvHD did poorly, with nine of 11 dying within 18 months (hazard ratio [HR] for OS: 3.94, P=0.016) (Figure 1; Table 1). High risk was also associated with poor PFS (4-year PFS 0% vs. 58%, P<0.0001) (Table 1; Figure 2D). Age was not a significant risk factor for OS but was significant for PFS (4-year PFS 10% for age ≥65 vs. 55% for age <65 years, P=0.006) (Table 1; Online Supplementary Figure S1A). Risk factors for NRM included the occurrence of grade 2-4 acute GvHD (HR: 7.08, P=0.017) (Table 1). Risk factors for relapse included age ≥65 years (4-year cumulative incidence 70% vs. 11%, P=0.007) and high risk (4-year cumulative incidence 56% vs. 21%, P=0.05). (Table 1; Online Supplementary Figure S1B and D). Other factors did not affect outcomes. In particular, remission status (CR vs. PR), Eastern Cooperative Oncology Group performance status, HCT comorbidity index, use of targeted therapy prior to alloHCT, number of prior therapies, year of HCT, PET positivity, bulky disease, fluorescence in situ hybridization (FISH) abnormalities and complex karyotype did not affect outcomes.

To our knowledge, this is the largest study reporting outcomes of patients with RT who underwent alloHCT in recent years. We report favorable outcomes for these previously treated patients. Importantly, half of these patients have extended OS, reaching a plateau after 1.5 years post transplant. This suggests that some RT patients could be cured with alloHCT.

For factors that are associated with poor outcome, high risk disease (i.e., low platelet counts and/or high LDH) was significantly associated with shorter OS and PFS. Outcome for patients with standard risk at transplant was excellent (4-year OS and PFS: 74% and 58%, respectively) despite the fact that these patients had failed multiple therapies. In contrast, few patients with high risk showed benefit from alloHCT suggesting that LDH and platelet counts together could be a sensitive marker of residual disease, since radiologic remission status based on PET/CT imaging at transplant was not predictive of outcome. In addition to these factors, advanced age was associated with poor outcome. Interestingly, use of prior targeted therapy was not associated with improved outcome. Similarly, year of transplant and number of prior therapies for CLL or for RT did not affect clinical outcome. These findings are very different from CLL patients who undergo alloHCT in the modern era but resemble observations made in alloHCT of de novo DLBCL, suggesting that disease control and sensitivity to alloHCT may be most critical for an aggressive disease like RT.

The survival outcome reported in the current study compares favorably to previously published alloHCT series in RT. The European Society for Blood and Marrow Transplantation (n=25, 72% RIC) reported 3-year OS.
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41% among 16 patients who received alloHCT in CR/PR, and 17% for nine patients with progressive disease. In a series of single-center studies, Kharfan-Dabaja et al.11 (n=10, all patients were in CR/PR) reported 4-year OS and PFS 50%; Tsimeridou et al.12 (n=17) reported 3-year OS 75% for seven patients who received alloHCT as postremission therapy and 21% for 13 patients who received allo- or autoHCT as salvage therapy. For patients with RT who do not achieve remission, CAR-T cell therapy is a newer option, with recently reported results in a small series (n=9) with limited follow-up by Kitta et al.13 Further and larger studies with longer follow-up are warranted to evaluate the efficacy of this therapy on its own or as a bridge to alloHCT.

This study has some limitations owing to its single-center retrospective design with a small sample size of 28 patients, which nonetheless is the largest study to date. Another limitation is the absence of data on clonal relationship between RT and CLL. Published literature,16 however, shows that the majority (~80%) of RT is clonally related to the preceding CLL, particularly in heavily pretreated patients like these, suggesting that most RT patients in this study were clonally related.

With availability of less toxic/reduced induced intensity conditioning regimens, improved human leukocyte antigen typing, and better GvHD prophylaxis strategies, alloHCT has become a viable and safe treatment option for patients with high risk hematologic cancers, even with advanced age. Our study results show that a sizeable proportion of patients with RT in remission can achieve durable remissions, and that alloHCT should be considered as a treatment option for patients with RT who are fit and have controlled disease.

Haesook T. Kim,1 Peter O. Baker,2 Erin Parry,2 Matthew Davids,2 Edwin P. Alyea,3 Vincent T. Ho,2 Corey Cutler,2 John Koreth,3 Mahasweta Gooyen,2 Rizwan Romee,2 Sarah Nikeforow,2 Joseph H. Antin,2 Jerome Ritz,2 Robert J. Soiffer,3 Catherine J. Wu2 and Jennifer R. Brown2

1Department of Data Science, Dana Farber Cancer Institute, Harvard School of Public Health, Boston, MA; 2Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA and 3Duke Cancer Institute, Duke Medical School, Durham, NC, USA

#CJW and JRB contributed equally as co-senior authors.

Correspondence:
JENNIFER R. BROWN - jennifer_brown@dfci.harvard.edu
HAESOOK T. KIM - htkimc@jimmy.harvard.edu

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Figure 2. Clinical outcomes. (A) Overall survival (OS) and progression-free survival (PFS) and (B) cumulative incidence of non-relapse mortality (NRM) and relapse for the entire cohort. (C) OS and (D) PFS according to the risk group.
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Contributions: HTK conceived and designed the study, performed statistical analysis, interpreted the data and wrote the manuscript; JRB, CJW and MD conceived the study; POB and JRB compiled the outcome data, provided FISH data and annotated the cytogenetic data; JRB and JR edited the manuscript. All authors contributed to the manuscript review and approved the final version for submission.

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References