The feasibility of reduced-intensity allogeneic hematopoietic stem cell transplantation from a related donor with HLA one-antigen with or without one-allele mismatch

It is still unclear whether reduced-intensity stem cell transplantation (RIST) from an HLA-mismatched related donor is feasible for hematologic malignancies. In the current study on the use of antithymocyte globulin (ATG) in 13 patients, we focused on this issue by evaluating regimen-related toxicities, engraftment, graft-versus-host disease (GVHD), infection, and overall survival. Our results suggest that this procedure may be acceptable for patients without a matched related donor.

A total of 13 patients underwent RIST from a serologically HLA one-locus mismatched related donor between March 2000 and September 2002. The characteristics of these patients are shown in Tables 1 and 2. Both HLA antigen and allele matching were generally evaluated, since any disparity in HLA allele typing was considered to be a risk factor in allogeneic hematopoietic stem cell transplantation from an unrelated donor. We defined HLA one-locus mismatch as any mismatch of one HLA -antigen, with or without a one-allele mismatch.

The conditioning regimen consisted of cladribine (0.66 mg/kg) or fludarabine (180 mg/m²), busulfan (8 mg/kg), and rabbit anti-thymocyte globulin (ATG; 5 mg/kg in 2 patients, and 10 mg/kg in 16 patients). Infectious prophylaxis procedures have been described previously. Prophylaxis against GVHD was performed with cyclosporine (CSP) alone in the initial 7 patients. Thereafter, short-term methotrexate (MTX) was added to CSP in the subsequent 6 patients because of the observation of severe acute GVHD in the earlier group. Patients who developed grade II–IV acute GVHD were treated with methylprednisolone at a dose of 1-2 mg/kg/day iv. Infectious disease was defined as an illness associated with symptoms and signs consistent with an infection, with microbiological documentation of a pathogen. Microbiological documentation consisted of the isolation of a pathogen by culture from a sterile or non-sterile site, or by histologic or immunohistochemical evidence. The primary endpoint of this study was the evaluation of engraftment, defined as >0.5 × 10⁹/L absolute neutrophil count (ANC) or >1.0 × 10⁹/L white blood cell count (WBC), and the toxicities associated with the procedure. The secondary end-points included evaluation of the extent of GVHD and infectious episodes. Differences in incidence were evaluated using Fisher’s exact test. Actuarial overall survival was estimated by the Kaplan-Meier method.

We found that all of the patients tolerated our RIST regimen and organ toxicities were limited to less than grade II hepatic and stomatitis/gastrointestinal toxicity, except in one patient (UPN 389) who developed subdural hematoma. The median number of CD34+ cells infused was 3.6 × 10⁶/kg (range, 2.2 to 7.3 × 10⁶/kg, Table 1) and the median duration of neutropenia was 12 days (range, 7-20, Table 1). Chimerism analysis was performed on days 30, 60, 90, 120, 180, 240, 300 and 360, and we confirmed that 11 of the 13 patients achieved engraftment from this HLA-mismatched transplantation. This result further suggests that our regimen, incorporating ATG, enables successful engraftment by overcoming the HLA barrier that is limited to HLA one-antigen with or without one-allele, as recently reported by Gajewski et al. One patient developed primary graft failure and the rapid emergence of recipient-type hematopoiesis on day 17, suggesting that our regimen is not truly myeloablative, and that the RIST procedure, relative to conventional transplantation with a myeloablative regimen, saves patients by retaining the ability of the marrow space to be repopulated by the recipient’s own cells.

Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th>UPN</th>
<th>Sex</th>
<th>Age</th>
<th>Disease</th>
<th>Status at transplant</th>
<th>Regimen</th>
<th>HLA mismatched locus</th>
<th>RRT grade</th>
<th>CD34</th>
<th>Duration of neutrophil</th>
<th>CD18</th>
</tr>
</thead>
<tbody>
<tr>
<td>267</td>
<td>M</td>
<td>29</td>
<td>AML</td>
<td>CR</td>
<td>2CdA/Bu ATG</td>
<td>DRB1 (antigen)</td>
<td>0</td>
<td>2.23</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>295</td>
<td>M</td>
<td>27</td>
<td>RMS</td>
<td>NR</td>
<td>2CdA/Bu ATG</td>
<td>DRB1 (antigen)</td>
<td>0</td>
<td>7.29</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>349</td>
<td>M</td>
<td>34</td>
<td>MDS</td>
<td>NR</td>
<td>Flu/Bu ATG</td>
<td>B (antigen) + A (allele)</td>
<td>1(hematopoietic) / 2 (stomatitis)</td>
<td>2.8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>384</td>
<td>M</td>
<td>53</td>
<td>RMS</td>
<td>Flu/Bu ATG</td>
<td>2CdA/Bu ATG</td>
<td>B (antigen) + A (allele)</td>
<td>2 (stomatitis)</td>
<td>4.38</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>389</td>
<td>M</td>
<td>58</td>
<td>ALL</td>
<td>CR</td>
<td>Flu/Bu ATG</td>
<td>B (antigen) + A (allele)</td>
<td>0</td>
<td>2.39</td>
<td>9</td>
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</tr>
<tr>
<td>426</td>
<td>F</td>
<td>54</td>
<td>MDS</td>
<td>Flu/Bu ATG</td>
<td>2CdA/Bu ATG</td>
<td>B (antigen) + DRB1 (allele)</td>
<td>0</td>
<td>6.98</td>
<td>14</td>
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</tr>
<tr>
<td>434</td>
<td>M</td>
<td>47</td>
<td>MM</td>
<td>Flu/Bu ATG</td>
<td>B (antigen) + A (allele)</td>
<td>1(hematopoietic)</td>
<td>4.03</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>446</td>
<td>F</td>
<td>57</td>
<td>AML</td>
<td>Flu/Bu ATG</td>
<td>2CdA/Bu ATG</td>
<td>B (antigen) + A (allele)</td>
<td>0</td>
<td>4.04</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>496</td>
<td>F</td>
<td>24</td>
<td>ARCC</td>
<td>Flu/Bu ATG</td>
<td>A (antigen)</td>
<td>2 (stomatitis) / 1 (gastrointestinal)</td>
<td>3.57</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UPN: unique patient number; RMS: rhabdomyosarcoma; MDS: myelodysplastic syndrome; ARCC: adrenal cortical carcinoma; CR: complete remission; NR: no remission; CD34: total CD34 cell dose×10⁹/kg; neut: neutropenia.
Another interesting finding of our study was that the incidence of grade II-IV acute GVHD depended on the type of GVHD prophylaxis (CSP alone vs. CSP/MTX; \(p = 0.015\), Table 2), but not on additional HLA allele disparity \(\left(p = 0.99\right)\). Furthermore, grade III-IV acute GVHD developed in 3 patients in the CSP-alone group, and was directly related to their mortality. Currently, most GVHD prophylaxis in RIST procedures involves CSP alone when using ATG or CAMPATH-1H.6,7 However, our observation further supports the recently published notion that GVHD prophylaxis should be intensified in RIST procedures.8 Although the data are still limited due to the small number of patients and short follow-up period, our results suggest that MTX did not suppress engraftment and was essential for preventing GVHD in RIST, at least from a related donor with HLA one-antigen with or without one-allele mismatch.

Profound immune suppression by the conditioning regimen could contribute to the high incidence of infection (10/13, 77%), and particularly CMV antigenemia (Table 2).

However, this could still be managed by response-oriented preemptive therapy guided by the level of CMV antigenemia.4 Four patients developed serious fungal diseases and subsequently died, and in most of these cases death was attributed to the use of steroid therapy for the treatment of acute GVHD.

Four patients, including 3 who were not in remission at transplantation, are currently alive in CR (Table 2). Overall, the early transplant-related mortality (TRM) on days +100 and +200 was 31% (4/13) and 39% (5/13), respectively. The estimated overall survival was 46%, with a median follow-up of 193 days (range: 8-553 days, Figure 1).

In summary, the results of this study suggest that RIST from a related donor with HLA one-antigen with or without one-allele mismatch could achieve allogeneic engraftment and that GVHD could be adequately prevented by using MTX in addition to CSP. The development of severe acute GVHD led to a high mortality rate due to complicated infections which were induced by the intense use of steroids for the treatment of GVHD.

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Chimerism-directed adoptive immunotherapy in the prevention and treatment of post-transplant relapse of leukemia in childhood

We present the role of frequent monitoring of hematopoietic chimerism in the prediction of post-transplant relapse and our initial experience with adoptive immunotherapy in the prevention and treatment of hematologic malignant diseases in the University Hospital Motol, Prague. Between January 1997 and June 2001 we performed a total of 54 unmanipulated allogeneic HSCT from HLA-identical siblings (28) or matched unrelated donors (26) in 50 consecutive children with hematologic malignancies in the University Hospital Motol, Prague. Fifty-two evaluable follow-ups from eighty-four patients at a median age of 10 years (2-18 years) with acute lymphoblastic leukemia (ALL; 18/17), acute myelogenous leukemia (AML; 17/14), chronic myelogenous leukemia (CML; 8), myelodysplastic syndrome (MDS; 6) and juvenile myelomonocytic leukemia (JMML; 3) were included in this prospective chimerism study. Written informed consent was obtained from the parents. We analyzed HC in peripheral blood samples using polymerase chain reaction of variable number of tandem repeats (APoB1, 2, 3).

Figure 1. Kaplan-Meier estimates of relapse-free survival for the CC and the MC groups. Forty-four patients were evaluable for RFS. RFS for the CC group was 20/22, whilst that for the MC group was 11/22. RFS for the MC group was 7/9 as compared to 4/13 for that in the MC group.