Minor histocompatibility antigen HA-8 mismatch and clinical outcome after hla-identical sibling donor allogeneic stem cell transplantation

We analyzed the clinical outcome of 146 adult patients receiving an HLA-identical sibling donor stem cell transplant depending on HA-8 matching status. The presence of an HA-8 mismatch was associated with an increased risk of severe acute graft-versus-host disease and with a worse overall survival.

The occurrence of graft-versus-host disease (GVHD) is the major complication after an allogeneic hematopoietic stem cell transplant and is the main cause of post-transplant morbidity and mortality despite donor and recipient compatibility for the HLA loci. Among the most widely studied factors contributing to GVHD are the minor histocompatibility antigens (mHAg), particularly HA-1. A new mHAg, HA-8, has been recently described. HA-8 is expressed ubiquitously in tissues and its presentation on the cell surface is restricted by HLA-A*0201. As a consequence of the intracellular processing of the protein in the proteasome, two different HA-8 peptides differing in the first amino acid position are generated: RTLDKVLEV (HA-8) and PTLDKVLEV (HA-8). The affinity of HLA-A*0201 for HA-8' and HA-8' is similar, but only the HA-8' peptide is recognized on the cell surface by the HA-8-specific cytotoxic T lymphocytes. In vitro assays show that the differential recognition is due to the poorly TAP-mediated endoplasmic reticulum transport of HA-8'.

The main objective of this study was to confirm the association of HA-8 mismatch with the clinical outcome after an HLA-identical sibling-donor allogeneic hematopoietic stem cell transplant. We retrospectively studied 146 adult HLA-A*0201 positive patient/donor pairs, transplanted at 13 Spanish transplant centers from 1995 to 2002. All the patients underwent the allogeneic transplant with a myeloablative conditioning regimen, and received non-T-cell depleted grafts. The diagnoses were: acute myelogenous leukemia (n=43), acute lymphoblastic leukemia (n=19), chronic myeloid leukemia (n=46), myelodysplastic syndrome (n=8), Non-Hodgkin’s lymphoma (n=13), Hodgkin’s disease (n=1), severe aplastic anemia (n=8), multiple myeloma (n=3) and other malignancies (n=5). The median age was 34 years (range: 15-59) and the preparative regimen was mainly busulfan-cyclophosphamide (44 cases) or cyclophosphamide-total body irradiation (44 cases). The majority of patients (129) received GVHD prophylaxis based on cyclosporine and short-course methotrexate. The remaining patients received cyclosporine alone (11 cases) or cyclosporine + prednisone (6 cases).

Genotyping of HA-8 was performed by PCR-SSP with allele-specific primers as previously described. Homogeneity between HA-8 antigen mismatched donor-recipient pairs and the non-mismatched pairs was performed using the \( \chi^2 \) test for qualitative variables and Student’s t-test for continuous variables. Statistical incidence estimates were used to determine the cumulative incidence of acute GVHD, relapse and transplant related mortality in the presence or absence of the HA-8 mismatch. Transplant-related mortality was defined as death due to causes other than disease relapse.

The Kaplan Meier method was applied to analyze overall survival and disease-free survival. Curves were compared using the log-rank test. Fisher’s exact test was used to evaluate differences in chronic GVHD. Multivariate analyses were performed with Cox regression models to calculate the probability of relapse, overall survival, transplant-related mortality and GVHD. \( p \) values are two-sided and those lower than 0.05 were considered statistically significant. No adjustments were made for multiple comparisons.

One hundred and forty-six HLA-A*0201 positive donor-recipient pairs were included in the study. Recipient HA-8 disparity was detected in nineteen cases (13%). No statistical differences between the HA-8 mismatched and the non-mismatched groups were detected in the homogeneity study.

No association between HA-8 disparities and grades II-IV GVHD was found (44% in the HA-8 mismatched
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Key words: HA-8, acute GVHD, stem cell transplantation.

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Table 1. Multivariate analysis for GVHD grades III-IV and overall survival (n = 146).

<table>
<thead>
<tr>
<th></th>
<th>GVHD grades III-IV</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>0.265</td>
<td>0.015-1.02 (1.00-1.05)</td>
</tr>
<tr>
<td>Disease status</td>
<td>0.303</td>
<td>&lt;0.001-0.26 (0.15-0.46)</td>
</tr>
<tr>
<td>Donor’s CMV</td>
<td>0.653</td>
<td>0.338-1.334</td>
</tr>
<tr>
<td>Patient’s CMV</td>
<td>0.669</td>
<td>0.183-3.330</td>
</tr>
<tr>
<td>Male recipient-</td>
<td>0.363</td>
<td>0.033-5.330</td>
</tr>
<tr>
<td>Female donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitized donor</td>
<td>0.026</td>
<td>2.55 (0.91-7.12)</td>
</tr>
<tr>
<td>Source of SC</td>
<td>0.072</td>
<td>0.198-3.589</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>0.966</td>
<td>0.358-2.358</td>
</tr>
<tr>
<td>HA-8 mismatch</td>
<td>0.0009</td>
<td>4.07 (1.46-11.36)</td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; SC: stem cells. Sensitized donor is defined as a donor who has had previous pregnancies or transfusions.

The disease status 0.303 and has had previous pregnancies or transfusions.

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