Stem Cell Transplantation

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.

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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.[1] Among the most widely studied factors contributing to GVHD are the minor histocompatibility antigens (mHAg),[2] particularly HA-1.[3,4] A new mHAg, HA-8, has been recently described.[5] 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^R) and PTLDKVLEV (HA-8^P). The affinity of HLA-A*0201 for HA-8^R and HA-8^P is similar, but only the HA-8^R 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^P.

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 (82 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.[5] Homogeneity between HA-8 antigen mismatched donor-patient pairs and the non-mismatched pairs was performed using the χ^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.

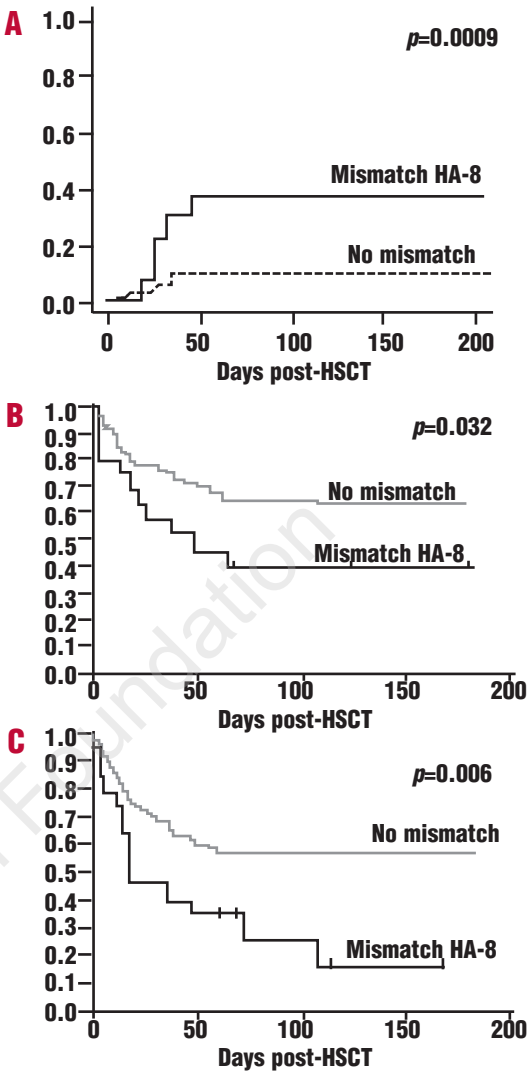

Figure 1. A. Cumulative incidence of grades III-IV GVHD on the basis of the presence or absence of HA-8 mismatch. B. Univariate analysis testing the correlation between overall survival and HA-8 disparity. C. Disease-free survival in the presence or absence of the HA-8 mismatch.

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

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

	GVHD grades III-IV		Overall survival	
	p	OR (95% CI)	p	OR (95% CI)
Age	0.265	–	0.015	1.02 (1.00-1.05)
Disease status	0.303	–	<0.001	0.26 (0.15-0.46)
Donor's CMV	0.653	–	0.338	–
Patient's CMV	0.669	–	0.183	–
Male recipient-Female donor	0.363	–	0.334	–
Sensitized donor	0.026	2.55 (0.91-7.12)	0.065	–
Source of SC	0.072	–	0.198	–
GVHD prophylaxis	0.966	–	0.358	–
HA-8 mismatch	0.0009	4.07 (1.46-11.36)	0.032	1.98 (1.01-3.89)

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

group and 38% in the non-mismatched group; p=0.64) in contrast to results previously reported.[6] However, the presence of an HA-8 mismatch was associated with severe grades (III-IV) of acute GVHD (39% versus 10%; p=0.0009) (Figure 1A). Multivariate analysis confirmed the association (HR, 4.07; 95% CI, 1.46-11.36; p=0.007).

The overall survival rate was also influenced by a donor-recipient disparity in HA-8 (38.8% in the mismatched group vs. 64.7% in the non-mismatched group; p=0.032) (Figure 1B). Multivariate analysis detected the HA-8 mismatch as an independent risk factor for overall survival rate (odds ratio, 1.98; 95% CI, 1.01-3.89; p=0.046). Table 1 shows the results obtained in the multivariate analysis for severe acute GVHD and overall survival.

The disease-free survival rate was also worse for the HA-8 mismatched patients (HA-8 mismatch: 17.2% vs. no HA-8 mismatch: 57%; p: 0.006) (Figure 1C). We did not detect statistically significant differences in transplant-related mortality (32% versus 17%; p=0.16) or chronic extensive GVHD (42.9% vs. 26.8%; p=0.222).

To the best of our knowledge, this is the first study that reports worse overall survival and disease-free survival after an HLA-identical sibling-donor allogeneic hematopoietic stem cell transplant in the presence of an HA-8 mismatch. Overall survival is reduced nearly 2-fold in the presence of the mismatch. This association between HA-8 disparity and worse overall survival is attributable to the higher incidence of severe, acute GVHD.

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