Research Letter

Effect on Long-Term Mortality of HLA-DR Matching in Heart Transplantation

Human leukocyte antigen (HLA) matching exerts a protective effect in organ transplantation, ensuring better graft function, fewer episodes of rejection, longer graft survival, and the possibility of lower immunosuppression.[1−3] However, the precise influence of HLA incompatibility in heart transplants remains to be determined, and prospective HLA matching is seldom achieved. We previously demonstrated that the odds of in-hospital mortality after heart transplantation is greater in the case of HLA-DR mismatch.[4] The goal of the present study was to evaluate the effect of DR mismatch on long-term mortality.

Methods

We enrolled 158 consecutive patients who underwent heart transplantation from 2000 to 2008 in a single Italian institution. Mortality data were collected through March 2017. Variables were: recipient and donor age, sex, and weight, acute kidney injury assessed by means of the RIFLE criteria, pulmonary vascular resistance (PVR), ischemia duration, troponin I, reoperation, and recipient and donor HLA-A, -B, and -DR. HLA matches were rated from 0 to 2, where 0 denotes the full match between the HLA loci of donor and recipient, 1 means 1 mismatch and 2 indicates a complete mismatch of the same loci. HLA was determined with the use of serologic and molecular techniques (complement-dependent cytotoxicity and polymerase chain reaction amplification with sequence specific primers); both were used to control data by means of 2 different assays. Induction therapy of antithymocyte globulin or thymoglobulin was administered in all patients. Rejection was defined by biopsy-proven status (grade $\geq$2R/3A) requiring treatment within 1 year after transplantation.[5] The study was approved by the local Ethical Committee and performed in accordance with the Helsinki Declaration.

Statistical Analysis

The analysis was conducted on 140 subjects after the exclusion of 18 patients who died in-hospital. Data are expressed as mean $\pm$ SD for continuous variables, and as percentage for categoric variables. To identify significant factors associated with long-term mortality, we used the chi-square test for categoric variables and the *t* test for continuous variables. Normal distribution of scalar parameters was assessed by means of Kolmogorov-Smirnov analysis. All parameters, with the exception of PVR and troponins, were normally distributed. Log-transformation improved normality of troponins and slightly improved that of PVR. We used Cox regression analysis to evaluate the effect of HLA-A, HLA-B, and HLA-DR mismatch, evaluated as a continuous variable on mortality. The variables included in the Cox model were those with a P value $<.10$ in univariate analysis (donor age and sex, recipient sex, and induction therapy) and those considered to be clinical relevant, such as recipient age, HLA-A, -B, and -DR mismatch, and 1-year rejection. Statistical analyses were performed with the use of SPSS software 13.0. A P value of $<.05$ was considered to be significant.

Results

The mean age of the 158 consecutive patients was 48.9 $\pm$ 13.1 years, and 125 (79.1%) were male. Mean length of follow-up was 107.0 $\pm$ 59.6 months; median follow-up was 123 months (interquartile range [IQR] 52.7−151 months). 18 patients died in the first 30 days, 23 (16.4%) had biopsy-proven rejection, and 60 patients (42.9%) died during follow-up (Supplemental Table 1); female sex, DR mismatch, and induction therapy were statistically different between the deceased and survivors. DR mismatch was significantly higher (1.50 $\pm$ 0.6 vs 1.23 $\pm$ 0.7; $P = .024$), whereas no significant differences were found in the other variables. Cox regression analysis demonstrated a hazard ratio of 1.624 (95% confidence interval 1.036−2.547; $P = .035$) for DR mismatch, independently from the effect of donor and recipient age and sex, HLA mismatch induction therapy, and rejection at 1 year. (Supplemental Table 2 and Fig. 1)

Discussion

This single-center retrospective study shows that HLA-DR is independently associated with long-term heart transplant survival with n hazard ratio of 1.624 for each level of mismatch. A previous study demonstrated a significant association between improved graft survival and DR mismatching over 1, 5, and 10 years after transplantation.[6] Our results and other studies[2,3] show that the effect of DR mismatch on mortality is independent from other clinical and immunologic variables. Therefore, more research is necessary to evaluate if donor selection according to mismatched antigens improves outcomes if ex situ perfusion demonstrates benefit by facilitating long-distance donations. Calcineurin minimization and withdrawal also may be related

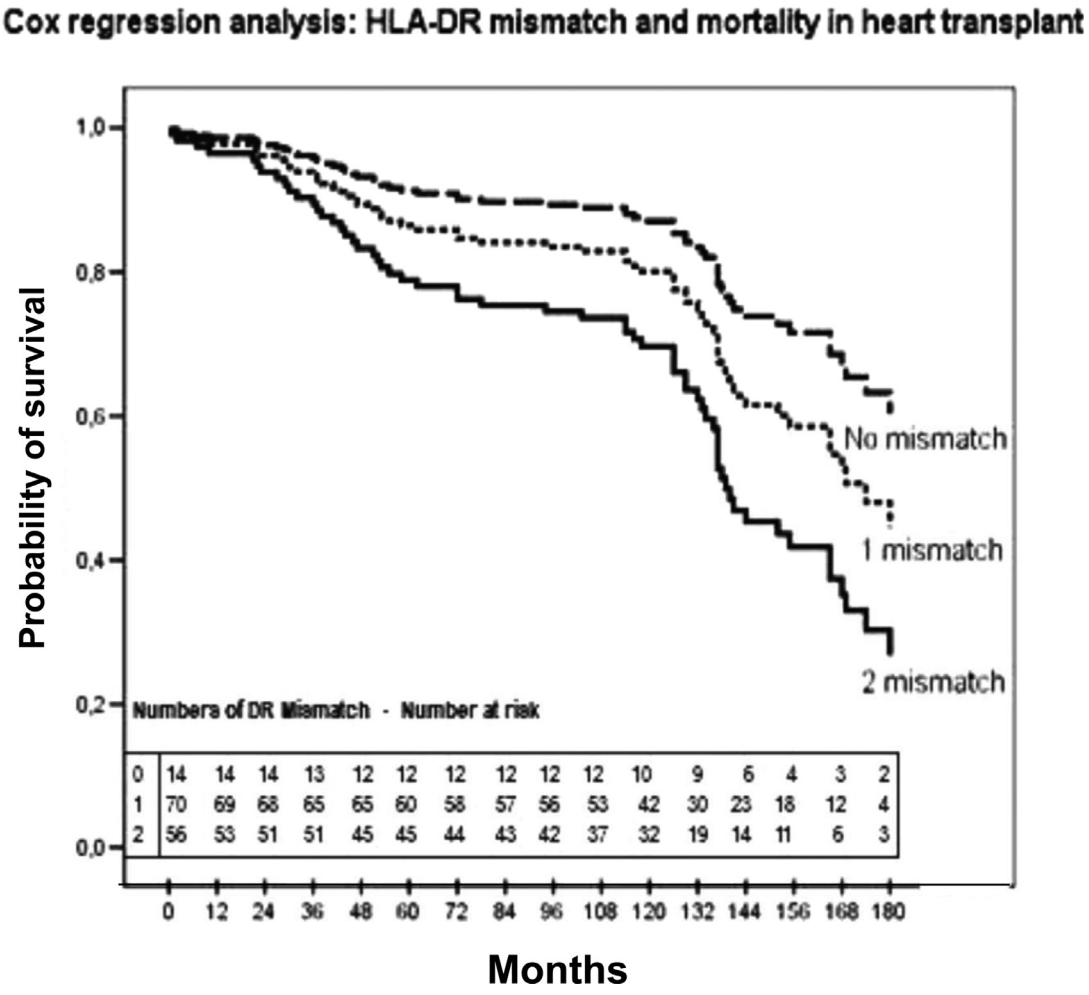

Fig. 1. Cumulative survival and HLA-DR mismatch (MM) in heart transplantation. Cox regression analysis demonstrates an HR of 1.624 (95% CI 1.036−2.547; $P = .035$) for HLA-DR MM, independently from the effect of recipient age, donor age, recipient sex, donor sex, HLA-A MM, HLA-B MM, induction therapy, and rejection at 1 year.

to the immunogenicity of the mismatch and may be appropriate for a selected cohort of matched patients.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2019.01.008.

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