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Five-year results of renal transplantation in highly sensitized recipients

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Abstract A special program for the priority allocation of cadaver donor kidneys to highly sensitized patients was initiated 10 years ago. During the period from 1985 to 1994, 329 transplants were performed at 35 transplant centers. Five-year graft survival rates were: 59 ± 4 % for 156 first grafts, 52 ± 5 % for 133 second grafts, and 18 ± 7 % for 40 third or fourth grafts. The success rates of first and second grafts were comparable with the corresponding success rates of first and second cadaver transplants in non-sensitized recipients reported to the Collaborative Transplant Study. There was a highly significant impact of HLA matching on graft survival. Among first and second grafts, 35 transplants with no mismatches for HLA-B+DR had a 76 ± 8 % success rate at 5 years, compared with a 55 ± 4 % rate for 208 grafts with one or two mismatches and a 37 ± 8 % rate for 46 grafts with three or four mismatches (weighted regression $P < 0.001$).

Key words Presensitization · Highly immunized patients · HLA matching

Introduction

Patients with highly reactive preformed lymphocytotoxic antibodies have an impaired graft success rate and experience prolonged waiting times for transplantation. A special program (called HIT for „Highly Immunized Tray") was initiated in 1985 as a substudy of the Collaborative Transplant Study (CTS) to provide these patients with cross-match-negative kidneys. Patient sera were exchanged every 2 months among 35 transplant centers and cross-match-negative kidneys were allocated with priority to patients participating in the HIT program. Preliminary short-term success rates of these transplants were reported in two previous publications [1, 2]. We now report on a 5-year analysis of 329 transplants performed from 1985 to 1994.

Patients and methods

A description of the technical procedures followed in this program was provided previously [1]. Briefly, patient sera were sent every 2 months to the study center in Heidelberg, Germany, and distributed onto tissue-typing trays. The trays were sent to the tissue-typing laboratories of the participating transplant centers and cross-matches were performed with lymphocytes of local cadaver donors. A second cross-match was performed prior to transplantation in the laboratory of the recipient center. Only patients with a serum reactivity of > 80 % in at least two consecutive screenings 2–3 months apart were accepted for the program. The patients had to have a negative autologous cross-match. During the first 3 years of operation, the HLA match was disregarded. In 1988, a recommendation was made to transplant kidneys with no more than one mismatch on each of the HLA loci HLA-A, HLA-B, and HLA-DR. In 1993, the recommendation was changed to a request for no more than one mismatch on the HLA-B locus and no more than one mismatch on the HLA-DR locus.

The transplants were performed at the following centers: Aachen, Barcelona, Basel, Bern, Berlin, Brussels, Cologne, Düsseldorf, Essen, Frankfurt, Freiburg, Geneva, Gent, Gothenburg, Hannover, Heidelberg, Helsinki, Innsbruck, Kaiserslautern, Lausanne, Leuven, Lübeck, Lund-Malmö, Madrid, Marburg, Milan,

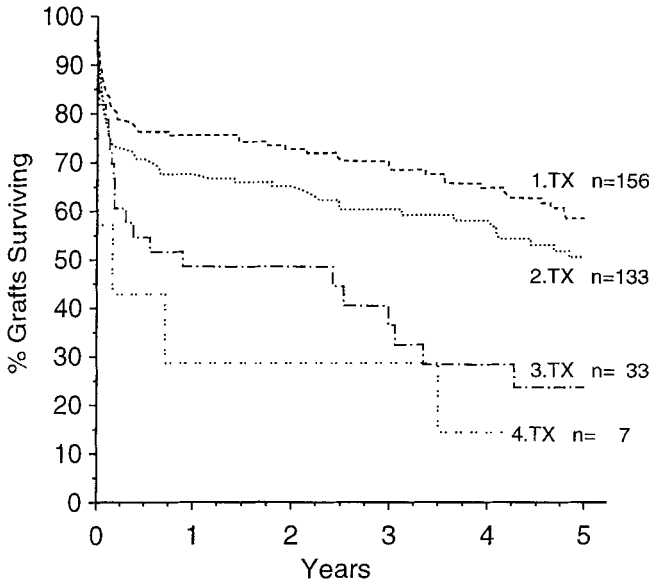

Fig. 1 Graft survival rates in highly immunized cadaver kidney recipients (*1. TX* first transplants, *2. TX* second transplants, *3. TX* third transplants, *4. TX* fourth transplants). The number of patients studied is indicated for each curve

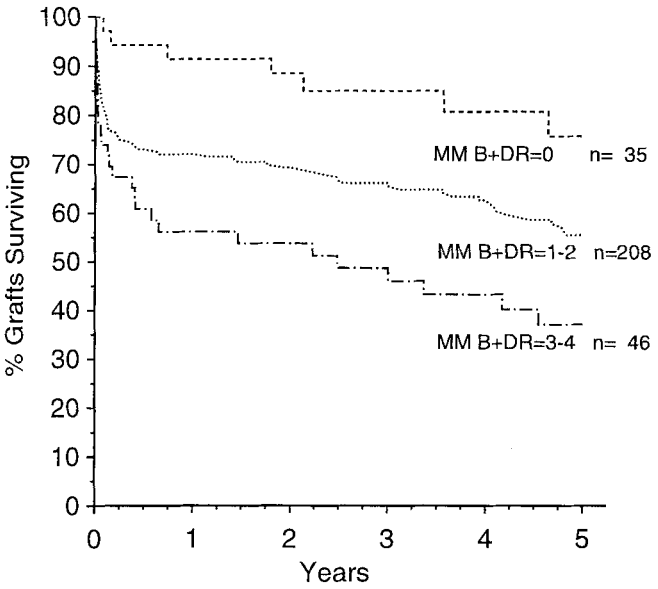

Fig. 2 Influence of matching for the HLA-B and HLA-DR antigens on graft outcome in highly immunized recipients of first or second cadaver transplants. The combined number of mismatched HLA-B and HLA-DR antigens was analyzed (*MM* mismatches). The influence of matching was statistically significant (P regression < 0.001)

Munich, Münster, Prague, Rostock, Tübingen, Vienna, Warsaw, and Zürich.

Graft survival rates were computed by the Kaplan-Meier method. One transplant was excluded because the repeat cross-match was positive but the transplant operation had been carried out without awaiting the cross-match result. No other exclusions were made. Patients who died with functioning grafts were counted as graft failures.

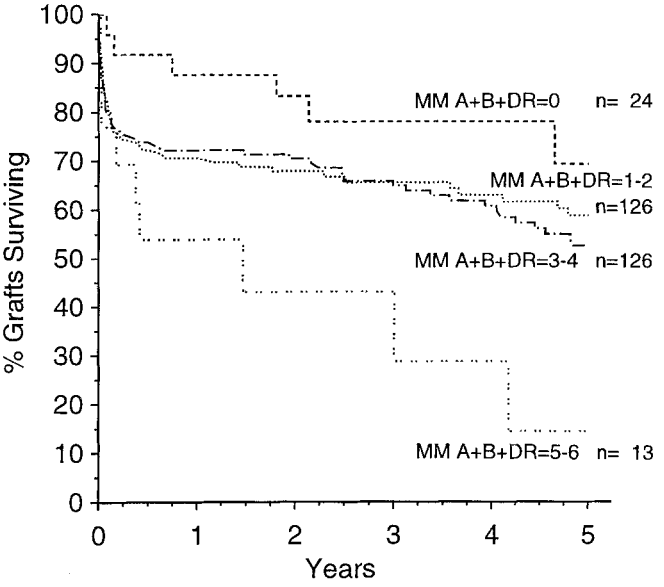

Fig. 3 Influence of HLA-A, HLA-B, and HLA-DR mismatches on graft outcome in highly sensitized patients. Number of mismatched antigens and number of patients studied are indicated (P regression < 0.01)

Results

The 5-year graft survival rates of first, second, third, and fourth cadaver transplants in highly immunized recipients are illustrated in Fig. 1. Remarkably, the $59 \pm 4\%$ 5-year success rate of first grafts is only 1% lower than the success rate of cadaver transplants in all non-sensitized recipients reported to the CTS (P = ns), and it was more than 10% higher than the 5-year success rate in all 1085 CTS-registered recipients with a preformed antibody reactivity of > 80% ($47 \pm 2\%$). The $52 \pm 5\%$ 5-year success rate of second grafts was similar to that of all 821 CTS-registered second transplants into patients with > 80% antibody reactivity ($47 \pm 2\%$). The results of third and fourth transplants, although not significantly different from other third and fourth transplants in highly sensitized recipients reported to the CTS, must be considered unsatisfactory.

The effect of HLA matching on graft survival was analyzed in first and second transplants. Mismatches at the HLA-A and HLA-B loci tended to decrease graft survival, although this did not reach statistical significance. At 5 years, 45 grafts with no mismatches survived at a rate of $66 \pm 8\%$, 196 grafts with one or two mismatches at a rate of $54 \pm 4\%$, and 48 grafts with three or four mismatches at a $47 \pm 8\%$ rate (P = ns). When the HLA-DR locus was analyzed, 92 transplants with no

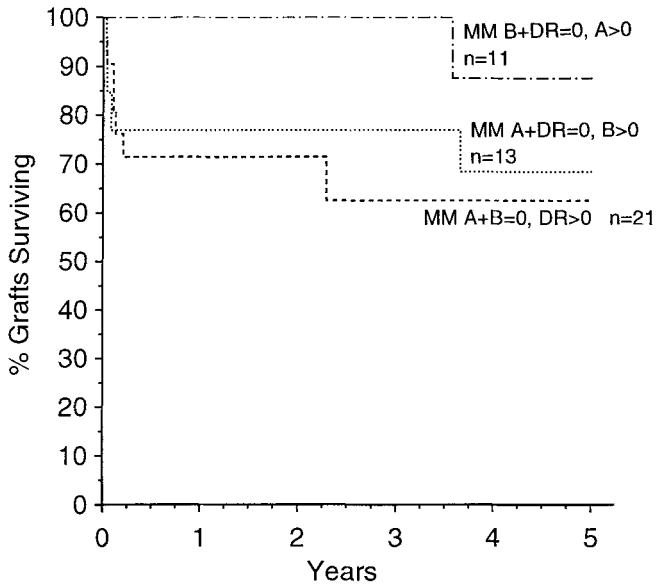

Fig. 4 Survival rates of transplants that were matched at two of the three HLA loci and mismatched at the third locus. Mismatches at the HLA-A locus appeared to be the least harmful

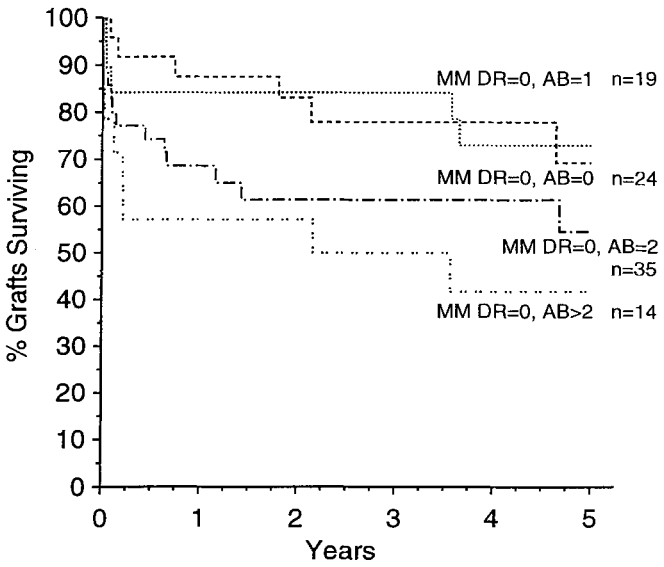

Fig. 5 Analysis of HLA-A+B mismatches in transplants with no HLA-DR mismatches (P regression = 0.06)

mismatches and 167 with one mismatch had similar 5-year survival rates of 60 ± 6 % and 58 ± 4 %, respectively. Thirty grafts with two HLA-DR mismatches survived at a poor 19 ± 8 % rate, significantly lower than the none or one mismatch groups (log-rank $P < 0.001$).

A highly significant impact of HLA matching was found when the combination of HLA-B+DR mismatches was analyzed. Five-year graft survival rates were 77 ± 8 % for grafts with no mismatches, 55 ± 4 % for grafts with one or two mismatches, and 37 ± 8 % for grafts with three or four mismatches (weighted regression $P < 0.001$) (Fig. 2). As shown in Fig. 3, the effect of matching was similar when mismatches at the HLA-A locus were included in the analysis (weighted regression $P < 0.01$). Grafts with five or six mismatches did extremely poorly, but there were only 13 transplants in this group. Further evidence that HLA-A locus mismatches had only a weak influence is shown in Fig. 4. Grafts which were matched at two HLA loci and had mismatches only at the third locus did exceedingly well if the mismatch was at the HLA-A locus. Because of the small numbers of transplants available for analysis, this result must be treated with caution.

An important result is shown in Fig. 5. When grafts with no mismatch at the HLA-DR locus were further separated according to mismatches for HLA-A+B, a deleterious effect of A+B mismatches was apparent (weighted regression $P = 0.06$). Thus, even in the absence of HLA-DR mismatches, mismatches at the HLA-A and HLA-B loci cannot be ignored.

Because there were only 40 third and fourth transplants in the analysis, it was unlikely that a significant effect of HLA matching would be obtained. However, it was disappointing that not even a trend for improved graft outcome was found when mismatches for HLA-DR, B+DR, or A+B were analyzed (data not shown).

Discussion

It is gratifying to see that the encouraging preliminary short-term results of the HIT program which were reported earlier [1, 2] have been sustained in this analysis of a larger patient series with a longer follow-up. Several lessons have been learned:

1. Excellent results can be obtained in highly immunized patients receiving first or second transplants. The outcome of third and fourth transplants, however, has been consistently poor.
2. A negative cross-match alone is an insufficient indicator of a patient's chance of success.
3. HLA matching has a significant influence on graft outcome in highly sensitized recipients of first or second transplants. Since it is not realistic to wait for perfectly HLA-compatible kidneys for all patients, our current policy of accepting donor kidneys with no more than one HLA-DR mismatch and one HLA-B mismatch seems a reasonable compromise.
4. Third and fourth transplants into highly sensitized patients do poorly and there is no evidence so far that better HLA matching improves the results in this group of patients.
5. The efforts involved in the bimonthly serum exchange, tray preparation, and performance of cross-

matches appears amply justified in the light of the very good transplant results obtained. The efficiency of the program would benefit from an increase in the number of potential donors whose lymphocytes are tested on the special cross-match trays. This could be accomplished best by increasing the number of centers participating in the program.

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