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Abstract

One-hundred-nine HLA-haploidentical living related renal transplants have been retrospectively analysed to compare the effect of donor-specific blood transfusion (DST) and different immunosuppressive regimens on graft survival and acute rejection. The recipients were divided into four groups according to the immunosuppressive therapy. Group 1 (n = 44): conventional therapy with posttransplant azathioprine (AZP) + methylprednisolone (MP). Group 2 (n = 25): pretransplant DST + posttransplant AZP + MP. Group 3 (n = 12): triple-drug therapy with posttransplant AZP + MP + cyclosporine (CS). Group 4 (n = 25): pretransplant DST + posttransplant AZP + MP + CS. The five-year actuarial survival rates for groups 1, 2, 3 and 4 were 48%, 73%, 79%, and 89%, respectively. The graft survival rate in group 3 was significantly (p less than 0.01) better than that in group 1. The transfusion effect was reduced, and appears as a 10% improvement in the graft survival in the cyclosporin era compared with a 25% improvement at pre-cyclosporin era. Furthermore, the incidence of the first rejection episode was decreased in recipients that received DST. The present study revealed that DST, as pretransplant conditioning has a definite impact on rejection-free long-term graft survival in HLA-haploidentical living-related kidney recipients and the most favorable outcome in such patients could be achieved by DST pretreatment in conjunction with posttransplant triple-drug therapy including cyclosporine.

KEYWORDS: living-related kindney transplantation, donor-specific blood transfusion (DST), cyclosporine

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Renal Transplantation from HLA-Haploidentical Living-Related Donors: The Effects of Donor-Specific Blood Transfusions and Different Immunosuppressive Regimens

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One-hundred-nine HLA-haploidentical living related renal transplants have been retrospectively analysed to compare the effect of donor-specific blood transfusion (DST) and different immunosuppressive regimens on graft survival and acute rejection. The recipients were divided into four groups according to the immunosuppressive therapy. Group 1 (n = 44): conventional therapy with posttransplant azathioprine (AZP) + methylprednisolone (MP). Group 2 (n = 25): pretransplant DST + posttransplant AZP + MP. Group 3 (n = 12): triple-drug therapy with posttransplant AZP + MP + cyclosporine (CS). Group 4 (n = 25): pretransplant DST + posttransplant AZP + MP + CS. The five-year actuarial survival rates for groups 1, 2, 3 and 4 were 48%, 73%, 79%, and 89%, respectively. The graft survival rate in group 3 was significantly ($p < 0.01$) better than that in group 1. The transfusion effect was reduced, and appears as a 10% improvement in the graft survival in the cyclosporin era compared with a 25% improvement at pre-cyclosporin era. Furthermore, the incidence of the first rejection episode was decreased in recipients that received DST. The present study revealed that DST, as pretransplant conditioning has a definite impact on rejection-free long-term graft survival in HLA-haploidentical living-related kidney recipients and the most favorable outcome in such patients could be achieved by DST pretreatment in conjunction with posttransplant triple-drug therapy inculding cyclosporine.

Key words : **living-related kidney transplantation, donor-specific blood transfusion (DST), cyclosporine**

Kidneys from living-related donors (LRD) are widely used to treat end-stage renal disease (ESRD) in Japanese transplantation centers. Starting from 1974, 109 primary living-related kidney transplantations have been performed in our institution. Donor-specific blood transfusions (DST) protocol was pioneered in order to achieve better renal allograft survival through alteration of the immune response of potential recipients. We have previously shown that the induction of immuno-regulatory factors following DST correlated well with the outcome of kidney graft

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survival (2-4). In this study we present the influences of DST and different immunosuppressive regimens on allograft survival in 109 haploidentical LRD kidney transplants.

Materials and Methods

Study population. This study consists of 109 LRD kidney recipients who received transplants between 1974 and 1991. According to pretransplant DST and posttransplant immunosuppressive regimens, recipients were classified into four groups. Conventional therapy group (group 1). From 1974 to 1981, 44 patients received LRD grafts with conventional azathioprine (AZP) and methylprednisolone (MP) immunosuppression. DST + conventionel therapy group (group 2). From 1982 to 1986, 25 patients were pretreated with DST and received conventional immunosuppression. Triple-drug therapy group (group 3). From 1986 to 1991, 12 patients received triple-drug therapy consisting of cyclosporine (CS), MP and AZP. And the DST + triple-drug therapy group (group 4). From 1986 to 1991, 28 patients of this group were pretreated with DST and received triple-drug therapy.

Demographic data of patients is provided in Table 1. There were no significant differences with regard to age,

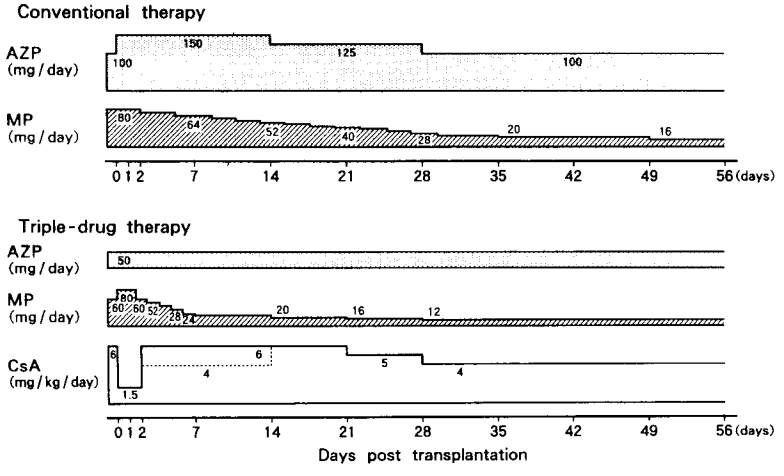

Fig. 1 Posttransplant immunosuppressive regimens. AZP, azathioprine; MP, methylprednisolone; CS, cyclosporine.

Table 1 Patient characteristics[a]

Immunosuppression groups	AZP + MP (Group 1)	DST + (AZP + MP) (Group 2)	CS + AZP + MP (Group 3)	DST + (CS + AZP + MP) (Group 4)
Number of patients	44	25	12	28
Male/female	29/15	19/6	11/1	21/7
Patients age (years)[b]	25.6 ± 5.0	28.9 ± 5.6	29.7 ± 8.3	27.7 ± 7.6
Months on dialysis[b]	21.2 ± 15.9	28.9 ± 22.9	20.7 ± 13.2	31.9 ± 35.0
Number of pretransplant Units of third-party Blood[b]	7.8±8.6	6.9±8.9	4.1+4.7	5.8±4.8
HLA-matching	Haploidentical	Haploidentical	Haploidentical	Haploidentical

a: Mean±SD

b: Significant differences were not found between the groups

months on dialysis, number of pretransplant third-party blood transfusions among the four groups. All patients were HLA-haploidentical parent-to-child donor recipient combinations. The leading cause of ESRD was chronic glomerulonephritis.

DST protocol. Three transfusions, each of approximately 200 ml of fresh whole blood from the potential kidney donor were administered at two-week intervals. Transplantation was carried out only if the final T-cell crossmatch was negative which was performed two to four weeks following the third DST.

Posttransplant immunosuppressive protocols. Our posttransplant immunosuppressive regimens during the early posttranslant period are shown in Fig. 1. From three to six months after transplantation, the dose of CS was reduced to 2-4 mg/kg/day, AZP was given at a dose of 50 mg/day and MP at a dose of 8 mg/day. Rejection episodes were treated by intravenous administration of MP (2-3 g given within 3-5 days) without increasing the daily dose of oral steroid.

Allograft loss for any reason and patient death with a functioning allograft were considered as an allograft failure. Actuarial allograft survival was calculated with the Kaplan-Meier method. Differences between groups were determined using Student's t test with $p < 0.05$ being considered as significant.

Results

Graft survival. Fifty-seven potential recipients entered the DST protocol and 4 (7 %) were sensitized to the donor during the transfusion process. All four patients were placed on the cadaveric waiting list and excluded the study while the others have received LRD renal allografts. Actuarial graft survivals according to immunosuppressive modality are shown in Fig. 2. The graft survival rate in triple-drug therapy (82 % at 3 years and 79 % at 5 years for group 3) was significantly much better ($p < 0.01$) than in conventional therapy (52 % at 3 years and 48 % at 5 years for group 1). The addition of DST, increased the 5 year graft survival rate in both of the aforementioned groups. In the preCS era, the use of DST with the posttransplant conventional therapy resulted in a significantly improved 5 year graft survival rate of 74 %, with compare to 48 % which was observed in conventional therapy only group ($p < 0.01$). In the CS era, the patients who received triple-drug therapy with DST had a better 5 year graft survival (89 %)

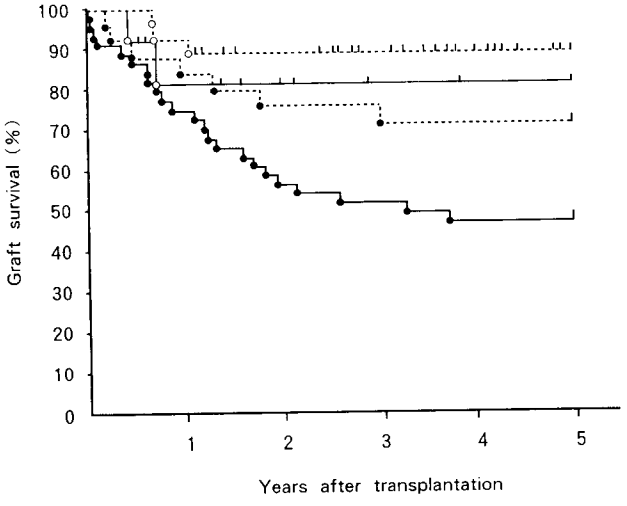

Fig. 2 Acturaial graft survivals according to different immunosuppressive modalities. Group 4: (○---○) pretransplant DST and posttransplant triple-drug therapy (n = 28), Group 3 (○——○) posttranspant triple-drug therapy (n = 12), Group 2 (●---●) pretransplant DST and posttransplant conventional immunosuppression (n = 25), Group 1 (●——●) posttransplant conventional immunosuppression (n = 44).

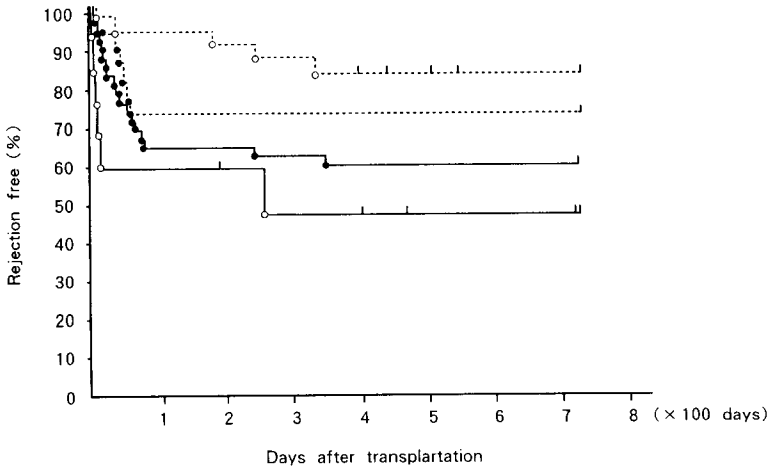

Fig. 3 Percent of living -related donor renal allograft recipients free from a first rejection episode. Group 4: (○---○) pretransplant DST and posttransplant triple-drug therapy (n = 28), Group 3 (○—○) posttransplant triple-drug therapy (n = 12), Group 2 (●---●) pretransplant DST and posttransplant conventional immunosuppression (n = 25), Group 1 (●—●) posttransplant conventional immunosuppression (n = 44).

than patients who received triple-drug therapy without DST (79 %). This difference was not statistically significant. The best 1 and 5 year graft survival rates were observed in DST + triple-drug therapy group, reaching 93 % at 1 year and 89 % thereafter.

Acute rejection episodes. The incidence of first acute rejection episode in DST + triple-drug therapy group was significantly lower than in the other three groups at 100 days after transplantation. Eighty-six percent of the DST + triple-drug treated and 74 % of the DST + conventional therapy received patients remained rejection free at 2 years after transplantation (Fig. 3). The rejection episodes were more frequently encountered in patients who did not receive DST.

Discussion

Four striking findings have emerged from the present study: 1. The best graft survival (89 % at five years) could be achieved by a combination of pretransplant DST and posttransplant immunosuppression with triple-drug therapy including CS; 2. The graft survival in triple-drug therapy group (79 % at five years) was significantly ($p < 0.01$) better than in conventional immunosuppressive therapy group (48 % at five years); 3. the DST program prior to transplantation clearly improved the results of LRD grafts in both the pre-cyclosporine (73 % at five years) and cyclosporin eras (89 % at five years); and 4. The DST significantly decreased the incidence of first rejection episode in both pre and postcyclosporin eras. Thus, the present study showed that DST, as pretransplant conditioning, has a definite impact on rejection-free long-term graft survival in haploidentical living-related donor-recipient pairs.

Similar results have been reported by others (5-7). In a recent study, Sanfilipo *et al.* (6) reported better graft survival in cyclosporine-treated living related donor kidney transplant recipients given DST (82 % at 3 years) compared to cyclosporine-treated recipients (79 % at 3 years). These results are somewhat lower than in our present series. Furthermore, they have claimed that for the first-transplant, one-haplomatchad recipients, the rate of graft loss after six-months remained relatively constant at 9–12 %. In our study there was no graft loss

after 1-year posttransplantation in patients who received triple-drug therapy with DST. This fact, concurring with the low rate of early rejection episodes may be related to improvement of graft survival in DST-treated recipients.

Another point which deserves emphasis is the decremention of the beneficial effect of DST protocol during the CS era. The 25 % improvement of graft survival in the pre-cyclosporin era was reduced to approximately 10 % improvement of graft survival, when DST was used in addition to conventional and triple-drug therapies, respectively. These observations are in agreement with those of Opelz and associates (8), who observed the striking decrease in the beneficial effect of pretransplant blood transfusions in cyclosporin era. The reason for this change in the effect of transfusions remains unknown. The most plausible explanation is that the patient management, including better handling of base line immunosuppression and rejection treatment, has improved so that the higher immunologic reactivity in nontransfused patients is compensated.

The mechanisms involved in the beneficial effect DST remain unclear. We have previously reported that the induction of antiidiotypic antibodies (2, 3) and/or suppressor cells (4) following DST correlated well with the reduction of rejection episodes and with better graft survival. The better understanding of the DST mechanism may point the way to the clinical application of DST-induced immunoregulatory factors. In conclusion, we believe that the best result for a transplant recipient who has an HLA-haploidentical living-related donor, can be achieved by pretransplant DST and immunosuppression with triple-drug therapy including cyclosporine.

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