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Long-term related kidney graft survival in high-risk patients after monitored donor-specific transfusion protocol

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Abstract Altogether 57 patients were included in the related kidney transplantation program. Forty-four recipients were mixed lymphocyte culture (MLC) negative or slightly positive (SI < 7) against their mother/father donor, and most of them showed Fcγ RII [erythrocyte antibody inhibition (EAI)] blocking antibody in their sera as the consequence of previous random transfusion. Thirteen patients showed significantly high MLC reactivity against their prospective parent donor (SI > 7) and had no EAI blocking antibody in their sera. The latter group was immunized either by buffy coat or purified platelets obtained from their donor in general two or three times at biweekly intervals. The indication for transplantation of donor-specific transfusion (DST)-treated patients was based on the appearance of EAI antibody and a significant reduction in the MLC reactivity (9 patients). DST patients had 100% kidney graft survival for 5 years and the DST untreated ones 75%. Suggested responsible factors for this observation are the haploidentity in HLA and the induction of suppressive immune regulation by DST.

Key words Transfusion effect · Suppressive regulation · Related transplantation · Blocking antibody

Introduction

Following the first observation of Opelz et al., the beneficial effect of a certain number of pretransplant transfusions for kidney graft survival was proved by experimental and clinical studies and utilized in both cadaver and live related donor transplantation practice [9, 23]. At a later stage with the appearance of the new and more effective suppressive regimens (cyclosporin, rapamin, ALG, OKT3, etc.) the significance of the transfusion effect was questioned. It was claimed that better graft survival rate had been achieved as a result of the introduction of more specific drugs and better immunosuppressive products, which may surpass the beneficial effects of transfusion [8, 21, 25]. Recently, however, in spite of these debates more experimental and clinical data were published which supported without doubt the suppressive immunomodulating and/or tolerance-inducing effect of transfusion [1, 3, 11, 19, 22]. These findings, for example, revealed that the transfusion donor and the recipient have to have a certain degree of histocompatibility barrier in order to have this beneficial effect. Haploidentity or mismatching in only one class II MHC antigen or differences in the minor histocompatibility antigens are, in general, representatives of these conditions [4–6]. Furthermore, it was clarified that these beneficial effects depend on the qualitative and quantitative characteristics of blood products and the time interval between transfusion and transplantation [26]. Better graft survival can be observed if cells expressing class I histocompatibility antigens alone are transfused into the recipient and transfusion is carried out on not more than one for three occasions [2, 7, 14, 17, 18].

Our own previous studies have confirmed that if the above-described blood products are applied, cell-medi-

ated immunosuppressive regulation can be detected in vitro in parallel with the appearance of "blocking" IgG antibodies [11]. On the other hand, sensitization against HLA antigens, as is well known, significantly shortens the survival of kidney grafts and increases the seriousness of rejection [9]. Therefore, the use of the above-mentioned immunological monitoring methods in a related kidney transplantation program with donor-specific transfusion (DST) is recommended for judging whether sensitization or suppressive regulation were induced. Based on published data as well as on our own observations, we launched a program in related donor kidney transplantation where DST was employed only in targeted cases where, besides the haploidentity, strong in vitro immunoreaction against the related donor was present.

Materials and methods

Fifty-seven young hemodialyzed patients have been selected to take part in the related kidney donor transplantation program. In all cases, one of the parents offered their kidney for transplantation. General data on the patients and donors have been summarized in Table 1. More detailed clinical data about the patients involved in the study can be found elsewhere [12]. The immunogenetic HLA genotype was determined by a conventional serological typing method [20, 24] and the mixed lymphocyte culture (MLC) test was done by a previously published method and evaluated by relative response (SI) calculation [2]. Blocking antibody testing was carried out by the erythrocyte antibody inhibition (EAI) method and also in MLC test, where the culture medium was supplemented with the patient's serum [10].

DST was carried out within the 3 months prior to transplantation. In general, 200 ml unseparated fresh blood was infused into the patients. In four patients purified platelets were transfused where leukocyte contamination was less than 1×10^5. DST pretreatment was carried out on a minimum of two occasions while the maximum number of treatments was four, depending on the appearance and required titer value of the blocking antibody in the patient's serum. If anti-HLA cytotoxic antibody was found in the serum, immunization was stopped at once. Following transplantation, patients received conventional immunosuppressive therapy with the application of azathioprine, cyclosporine, and steroids. In certain cases OKT3 was administered during rejection crises [12]. Statistical analysis was carried out as described elsewhere [13].

Results

Immunogenetic data of the 57 patients selected for the program are summarized in Table 1. MLC tests carried out with the cells of the patient and the selected haploidentical parent donor were negative or slightly positive in 44 cases between recipient and donor, which means a value of less than 7 according to the SI index. These patients during their hemodialysis treatment also received random transfusion therapy. In 13 cases the recipients showed a strong positive MLC reaction against the donor cells representing an SI value higher than 7. In these cases blocking antibody could not be detected in the sera either with repeated MLC or EAI blocking tests. As a result of DST carried out in 13 cases, blocking antibody induction failed and the MLC reaction value increased in four patients. These patients were put back onto the cadaver donor waiting list. In 8 cases, as a result of DST, EAI blocking antibodies appeared in the patients' sera with increasing titer values, and MLC reaction values decreased spontaneously and became negative in the presence of the patient's own serum. Immunological data of two representative patients of these 8 cases are summarized in Fig. 1.

Table 1 Basic data of patients involved in the related kidney transplantation program with donor-specific transfusion *(DST)* *(MLC* Mixed lymphocyte culture)

	With DST	Without DST
Number of patients	13	48
Age (mean, years)	21	22
Gender (male/female)	8/5	31/26
MLC (SI mean)	21.2	< 7.0
Sex ratio (%) donor/recipient		
Male-female	0	10
Male-male	33	21
Female-male	45	31
Female-female	22	38

Graft survival in cases of DST patients compared to related donor transplanted ones without DST treatment is presented in Fig. 2. Kidney graft survival rates of patients who received DST and performed blocking antibody were 100% for 6 years and 67% for 9 years. In comparison, kidney graft survival rates of patients not receiving DST were 58% for 6 years and 48% for 9 years. If we include the ninth patient where DST failed to induce blocking antibody production into the calculation, the 100% kidney survival time is less, as is shown in Fig. 3. In spite of the very low number of cases presented in the study, the difference between the values is significant. It is more remarkable and in accordance with our previous studies that, in cases of DST-treated patients, in the first period after transplantation (0–9 months) rejection reaction, if it appeared, was mild.

Discussion

The beneficial effect of DST seems to be transitional for the first posttransplant period. As is shown, the survival of kidney grafts under normal conditions decreases at the same rate each year after transplantation; that is, immunological rejection can destroy the graft in the first year as well as 5–10 years after transplantation [9]. In

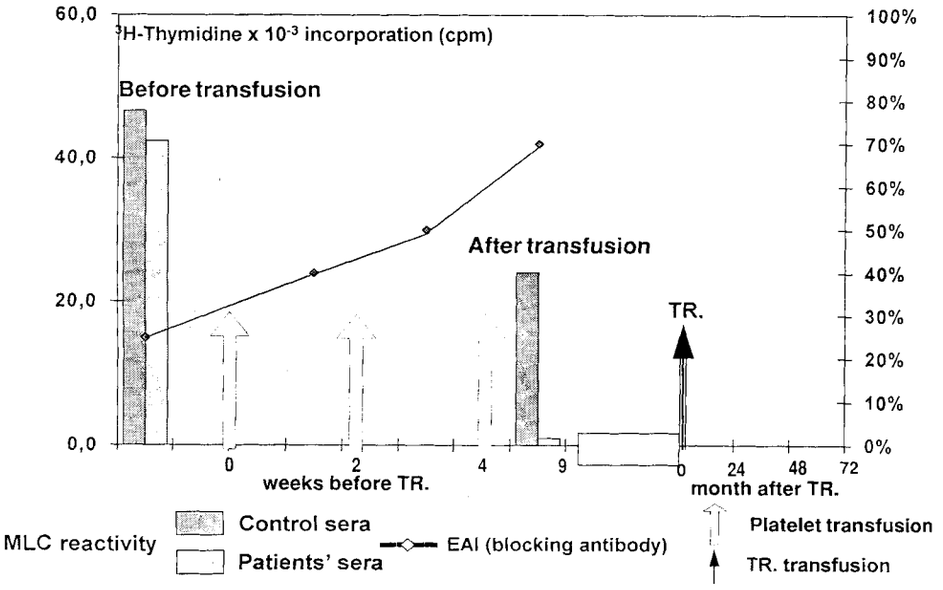

Fig. 1 The efficacy of donor-specific transfusion *(DST)* on the induction of suppressive immune regulation (*EAI* Erythrocyte antibody inhibition, *MLC* mixed lymphocyte culture, *TR.* transplant)

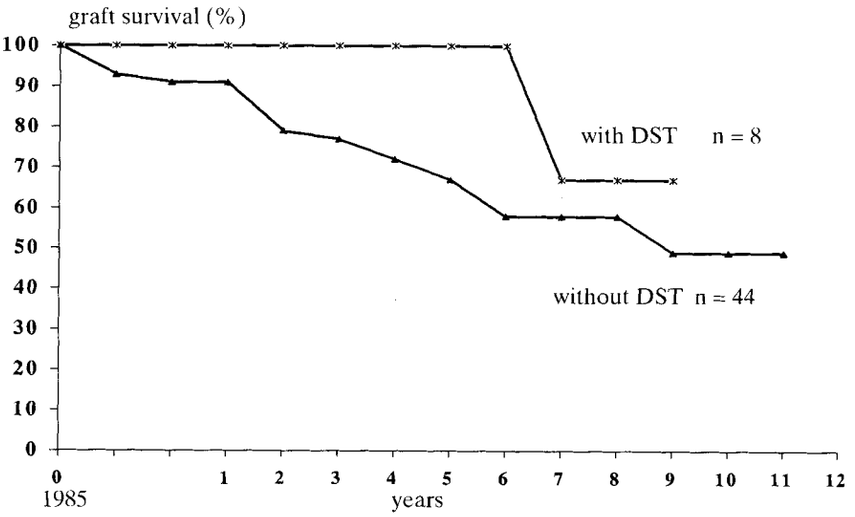

Fig. 2 Living related kidney graft survival (1985)

DST cases, loosing a graft in the late posttransplant period was mostly due to rejection accompanied by serious virus infection (CMV).

The above-described better graft survival and immunoregulatory effect of DST is in agreement with our data published recently [16]. In our study it was found that in cases of cadaver kidney transplantations the graft survival is significantly better in patients who had a high titer of EAI blocking antibodies produced by random transfusion. According to our assumption, in cases of suitable major histocompatibility antigen matching condition (haploidentity), a secondary, polymorphic system (TLX/CD46/MCP) expressed on peripheral blood lymphocytes may be responsible for the appearance of blocking antibody and/or the development of a suppressive mechanism. Thus, in successfully immunized DST patients between the transfusion donor-recipient pairs incompatibility is present in this antigen system, while in the other, unsuccessful cases, this condition does not occur. Our assumptions are supported by the immunotherapy of targeted transfusion applied in recurrent habitual abortion cases, where, with the selection of incompatible donors in this polymorphic antigen system, the induction of blocking antibodies and/or a cell-mediated suppressive mechanism was successful [15].

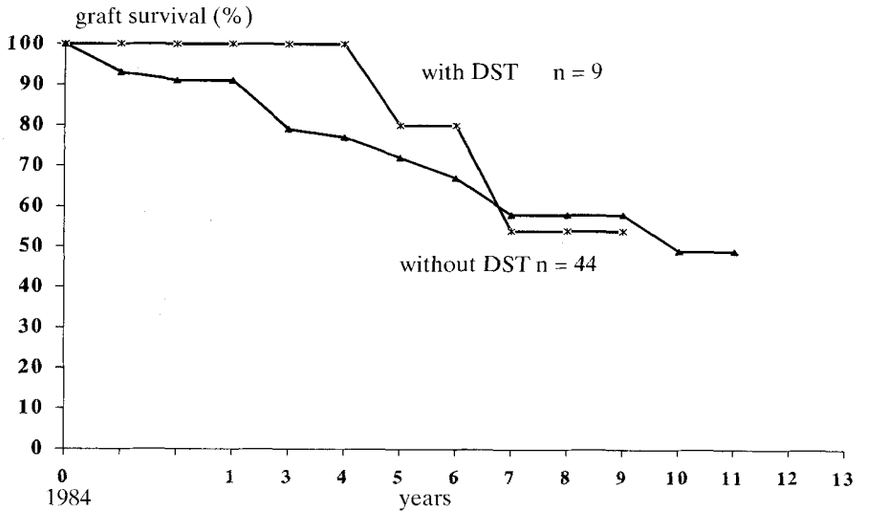

Fig.3 Living related kidney graft survival (1985)

Summarizing our results, it can be concluded that targeted DST therapy in related donor kidney transplantation cases within certain immunogenetic conditions can induce a suppressive immune regulatory mechanism – even if recipients show a strong immune reaction against the prospective donor – resulting in significantly prolonged kidney graft survival. In the background of the immunosuppressive mechanism, humoral and cell-mediated factors play an equal role.

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