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Clinical factors which influence the long-term survival of kidney allografts donated from haploidentical donors

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All patients with renal transplants are very much concerned about their chance of long-term graft function. Chronic rejection is the most common cause of decline in function and graft failure, and after the first post-transplant year, 3–4 % of recipients lose their graft every year [4]. However, the cause, time of onset and mechanism of decline in graft function are not clear. Also unclear is whether clinical and laboratory parameters may predict patients who are at risk of developing chronic rejection. The aim of this study was to find the marker which may determine long-term graft survival in the azathioprine era and in the cyclosporine era.

Key words: Kidney transplantation – Living donors – Long-term survival

Materials and methods

Between April 1990 and March 1982 155 patients were transplanted with one haploidentical renal allograft. Azathioprine (Aza) and prednisolone (PSL) were used for immunosuppressive therapy. Of 155 cases, 133 had been followed up for over 10 years. After excluding 15 cases with grafts rejected within 1 year and 17 cases of death with a functioning graft, the remaining 101 of the 133 cases were subjected to analysis.

Cyclosporine (CsA) was introduced in our institution in April 1982 [2]. The initial immunosuppressive regimen shown in Fig. 1 was applied to 82 cases with a haploidentical renal allograft. At 1 year after transplantation, CsA had been replaced by Aza in 23 cases, and changed to combination therapy with CsA, Aza and PSL in nine cases, mainly due to nephrotoxicity. From January 1987 a new regimen (regimen 2, Fig. 1), in which the dose of CsA was greatly reduced and supplemented with Aza in order to minimize the nephrotoxicity of CsA, was applied in 33 cases. Of a total 115 cases, eight suffered rejection of their graft and six died with a functioning graft within 1 year. No further deaths occurred after the first year. Of the remaining 101 cases, 61, who were followed for over 5 years, were subjected to the analysis. Clinical and laboratory data at 1 year after transplantation and the clinical records of every case were reviewed and subjected to multivariate analysis using quantification theory II [3]. Clinical and laboratory factors included in the analysis were episodes of acute rejection and liver dysfunction within 1 year and serum creatine (SCr) level, proteinuria, hypertension and immunosuppressive therapy at 1 year after transplantation.

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Results

Marker for predicting 10-year graft function in the Aza era

A variety of factors (Fig. 2) were categorized into groups. These categories were scored by the method of quantification theory II. Each factor score was summed for each case. The distribution of total scores was biphasic and the average total score for the group with 10-year graft function was 0.528 ± 513 (mean ± SD) and the score for the group with rejected grafts was 0.780 ± 1.023. The discriminating point was located at 0.069 and 85 % of cases with a total score higher than this point had 10-year functioning grafts. SCr level at 1 year after transplantation showed the highest correlation coefficient, followed by hypertension, proteinuria etc.

Curves of actual graft failure rates in four groups categorized according to SCr level are shown in Fig. 3. The two groups with SCr level of less than 1.4 mg/dl had significantly lower failure rates than the other two groups.

Table 1. Correlation coefficients for various factors

Factor	Correlation coefficient
SCr level	0.3547
Immunosuppressive regimen (Aza, CsA, Aza + CsA)	0.3389
Proteinuria	0.1571
Hypertension	0.1517
Liver dysfunction	0.1273
Episodes of acute rejection	0.0999

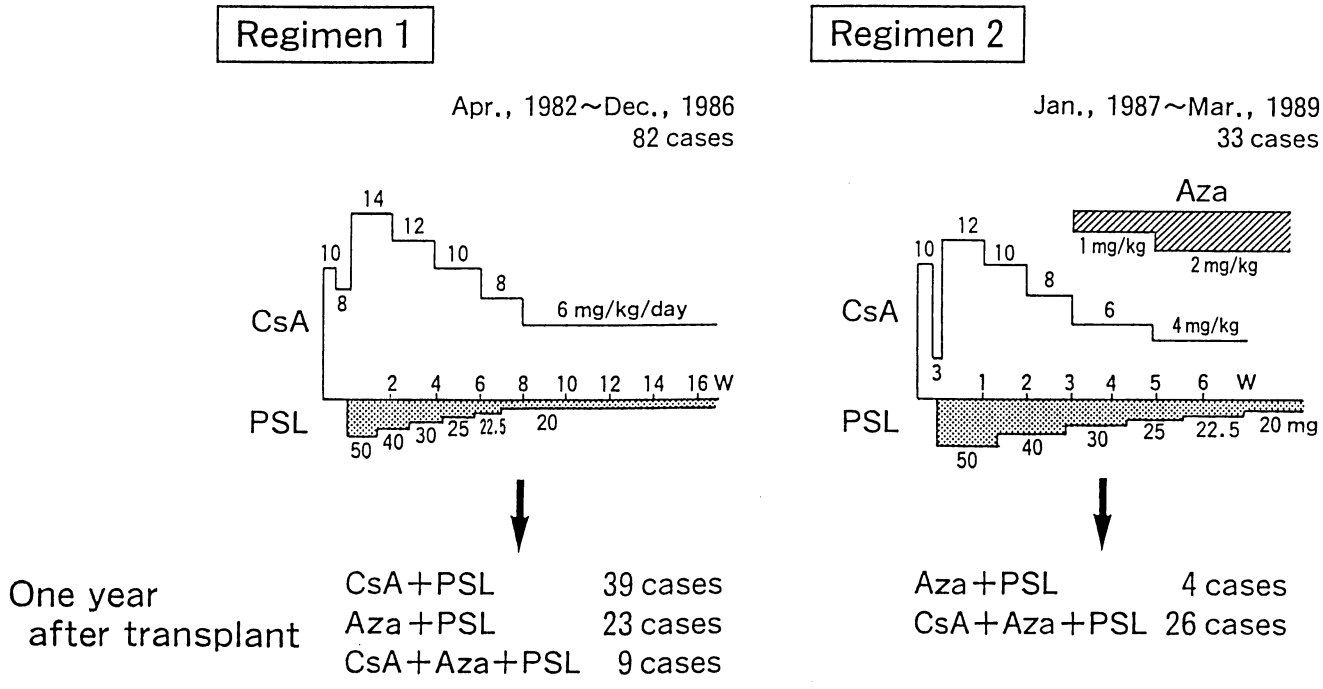
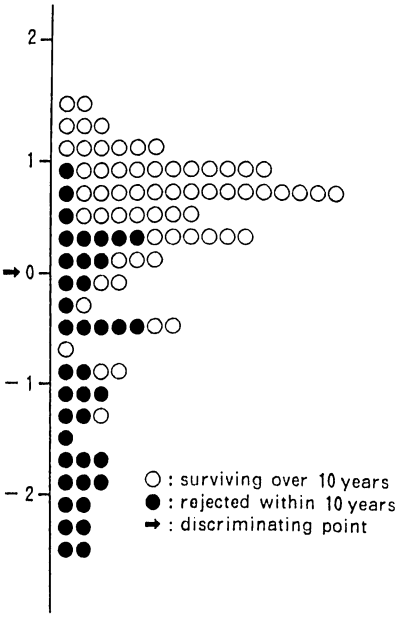


Fig. 1. Initial immunosuppressive regimens and changes of therapy at 1 year after transplantation

Factor	Category	Score
Episode of acute rejection	0 times	0.0938
	1–2 times	0.0775
	3~times	−0.0684
SCr level	~1.0 mg/dl	0.2273
	1.1~1.4 mg/dl	0.3203
	1.5~2.0 mg/dl	−0.3703
	2.1 mg/dl~	−1.1802
Proteinuria	negative	0.1510
	positive	−0.2613
Hypertension	negative	0.3235
	positive	−0.4545
Liver dysfunction	negative	0.1152
	positive	−0.3323
Dose of Aza	≦2.0 mg/kg/day	0.2295
	>2.0 mg/kg/day	−0.1164
Dose of PSL	≦0.2 mg/kg/day	0.1909
	>0.2 mg/kg/day	−0.0628



Factor	Correlation coefficients
SCr level	0.2
Hypertension	0.2
Proteinuria	0.16
Liver dysfunction	0.19
Dose of Aza	0.11
Dose of PSL	0.09
Episode of acute rejection	0.06

Fig. 2. Retrospective analysis for factors which may predict 10-year graft function

Correlation between immunosuppressive regimen and long-term graft survival in the CsA era

A variety of clinical and laboratory factors were analysed in 61 cases followed for over 5 years. Calculated correlation coefficients are listed in Table 1. Of six factors, SCr level and immunosuppressive regimen showed significantly higher values. Cumulative graft failure rates were compared between three groups categorized according to immunosuppressive regimen (Fig. 4). The group receiving combination therapy with CsA, Aza and PSL had a significantly lower graft failure rate than the other two groups.

Discussion

In renal transplantation, the most significant factor determining long-term graft function may be HLA matching [1]. Therefore the subjects analysed in this study were restricted to one haploidentical transplant. From the results of this study, it can be concluded that 1-year graft function

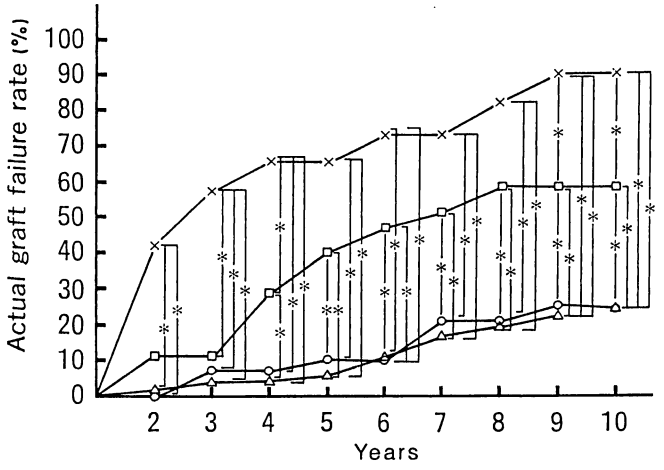


Fig. 3. Curves of actual graft failure rates in four groups categorized by serum creatinine levels at 1 year after transplantation. ○, < 1.0 mg/dl ($n = 28$); △, 1.1–1.4 mg/dl ($n = 44$); □, 1.5–2.0 mg/dl ($n = 17$); X, > 2.1 mg/dl ($n = 12$). * $P < 0.05$

is a reasonable parameter for determining long-term graft function in either the Aza or the CsA era, and combination immunosuppressive therapy with CsA, Aza and PSL may be suitable for achieving long-term graft function. However, in this study, three of 133 cases who died with functioning grafts after the first year were excluded. Although exact analysis may not be possible because of these cases, the influence of this exclusion is too small to invalidate the conclusion.

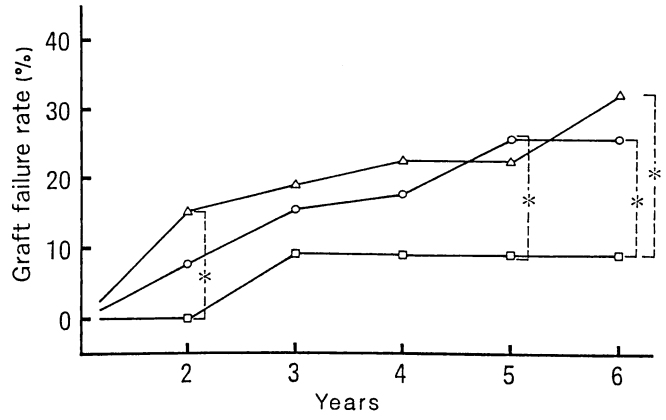


Fig. 4. Curves of cumulative graft failure rates in three groups of recipients treated with CsA + Aza + PSL ($n = 35$), Aza + PSL ($n = 27$) and CsA + PSL ($n = 39$). * $P < 0.05$

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