PRETRANSPLANT CYTOTOXIC ANTIBODIES DO NOT SEGREGATE KIDNEY TRANSPLANT RECIPIENTS INTO RESPONDER AND NON-RESPONDER GROUPS

F Vincenti, W Amend, N Feduska, R Duca, O Salvatierra

University of California, San Francisco, California, USA

Summary

In a study of 687 primary cadaver transplants, we found no correlation between the degree of presensitisation and graft survival. Graft survival was adversely affected in non-transfused recipients and was significantly improved in transfused recipients, independent of the level of presensitisation (63%, 61%, 67% at one year for patients with 0–10%, 11–50%, and 51–100% preformed cytotoxic antibodies, respectively). Humoral presensitisation to HLA antigens does not reflect the immunoresponsiveness of the host to the renal allograft, but it may prolong the wait for a compatible donor kidney.

Introduction

The effect of preformed lymphocytotoxic antibodies on the fate of the kidney allograft remains a controversial subject [1–4]. Opelz et al [5] in 1972 proposed that the pretransplant humoral response to HLA antigens reflected the responsiveness of the host to foreign alloantigens and could be used as a predictor of the outcome of transplantation. Patients were categorised as responders or nonresponders on the basis of their pretransplant cytotoxic antibody levels. Concerns about presensitisation in potential transplant recipients resulted in a more conservative use of transfusions for dialysis patients, which may have contributed to the decline in graft survival in the past several years [6,7]. Review of our experience at the University of California reconfirms our previous findings [2] that humoral presensitisation to panel donor cells is not associated with poor graft survival and does not reflect the subsequent immune responsiveness of the host to allograft alloantigens.

Materials and Methods

Six hundred and eighty-seven primary cadaver kidney transplants were performed at the University of California, San Francisco, between January 1970 and Dec-
ember 1978. No patients were excluded from the survival analysis. Tissue typing was performed by a single laboratory using previously described techniques [8]. Serum from all potential cadaver transplant recipients was screened at monthly intervals by the same laboratory using the fluorochromasia-complement-dependent cytotoxicity test against a panel of cells from 8–12 donors selected to contain all the recognised HLA antigens at the time of testing, as well as blanks at both the A and B loci. Patients were categorised according to the highest level of preformed cytotoxic antibodies before transplantation: 0–10%, 11–50%, and 51–100% of the panel cells reactivity. The last groups reacted against more than 50% of the panel cells on at least two separate screenings. Before transplantation, both the most recent serum sample of each recipient and the most reactive past sample (when a patient demonstrated complement-dependent cytotoxic activity) were used in the cross match with lymphocytes harvested from donor mesenteric lymph nodes. Transfusion data for the majority of patients were collected prospectively from the start of dialysis. For the few patients not entered in the prospective study, transfusion history was obtained from the patient and the records of the blood bank and the dialysis unit. Graft loss was dated from the time of loss of renal function requiring return to dialysis or death from any cause. The statistical methodology used for this study has been described previously [8].

Results

Six hundred and eighty-seven recipients of cadaver kidney transplants were followed for one to eight years. The clinical data of patients with different levels of preformed cytotoxic antibodies are detailed in Table I. The distribution of patients on the basis of pre-transplant blood transfusions within each category of preformed cytotoxic antibodies is shown in Figure 1. There were no significant differences in patient survival among the three groups by levels of preformed cytotoxic antibodies. Graft survival by levels of preformed cytotoxic antibodies is shown in Figure 2. No statistically significant differences in graft survival among the three groups were found. Graft survival in patients within the three categories of preformed cytotoxic antibodies on the basis of pretrans-

<table>
<thead>
<tr>
<th>Cytotoxic Antibody Level (%)</th>
<th>No. of Patients</th>
<th>Transfusions (No. of Units)</th>
<th>Time on Dialysis (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>294</td>
<td>5.9 ± 0.6</td>
<td>11.0 ± 0.5</td>
</tr>
<tr>
<td>11–50</td>
<td>293</td>
<td>7.0 ± 0.7</td>
<td>17.4 ± 0.8</td>
</tr>
<tr>
<td>51–100</td>
<td>100</td>
<td>9.9 ± 1.4</td>
<td>25.7 ± 1.8</td>
</tr>
</tbody>
</table>

TABLE I. Clinical Data on 687 Recipients of Primary Cadaver Transplants According to the Highest Cytotoxic Antibody Level before Transplantation
Figure 1. Distribution of Patients on the Basis of Pretransplant Blood Transfusions Within Each Category of Preformed Cytotoxic Antibodies. Figures in parentheses indicate number of patients.

Figure 2. Actuarial Graft-Survival Curves for 687 Primary Cadaver Transplants According to the Highest Cytotoxic Antibody Level.

plant blood transfusions is shown in Figure 3. In all three groups, nontransfused recipients had a statistically significant poorer graft survival than transfused recipients. In the latter group, those who had developed cytotoxic antibodies prior to transplantation did not have a significantly different graft survival than transfused patients who had not developed cytotoxic antibodies.
Discussion

These results demonstrate no adverse effects of preformed cytotoxic antibodies on graft survival in recipients of primary cadaver kidney transplants. Earlier as well as more recent findings by Opelz et al [5,9] continue to show poorer graft survival in patients whose cytotoxic antibodies react with greater than 50% of the panel donor cells. The recently reported experience from the University of Minnesota [2] parallels our own in showing no relationship between the level of cytotoxic antibody reactivity and graft survival. We believe that the improved graft survival at our institution in patients with preformed cytotoxic antibodies is probably dependent on two factors. The first is the routine use of two sera to perform the donor-specific cross-match: the most recent serum prior to transplantation and the serum that previously had demonstrated the broadest lymphocytotoxic activity. We proceed with transplantation only if both cross-matches are negative. The second factor is the number of monthly screens performed on patients preoperatively. Although detectable levels of cytotoxic antibodies fluctuate with time, the patient remains sensitised. Increasing the number of monthly sera submitted for screening enhances the likelihood of detecting most if not all the preformed cytotoxic antibodies that the patient may have formed. This finding is supported by our previous report that recipients with more than five monthly screens for cytotoxic antibodies had a significantly improved graft survival when compared with those having fewer screens [8]. Our current policy is to have patients on the waiting list for 5–6 months before relying on a negative cross match and then proceeding with transplantation.

Another controversial subject has been the relationship between blood transfusions and preformed cytotoxic antibodies on graft survival. The overall bene-
ficial effect of blood transfusions on graft survival in cadaver transplant recipients is well established [8,9]. Opelz et al [9] have reported that graft survival in transfused patients with no cytotoxic antibodies is greater than transfused patients who had formed cytotoxic antibodies reactive against more than 50% of the panel. Their findings suggest that blood transfusions do not produce a fully salutary effect on allograft survival if they elicit a large number of antibodies. In contrast, our data show no decline in graft survival if blood transfusions are associated with cytotoxic antibodies. Without blood transfusions, patients within all three groups of preformed cytotoxic antibodies have significantly poorer graft survival rates. Transfusions are clearly associated with increased lymphocytotoxic antibodies, but these antibodies do not occur in direct relationship to the number of blood transfusions. Only 40% of the patients in the highest cytotoxic antibody category (51–100%) had more than 5 blood transfusions. Ninety-three patients with preformed cytotoxic antibodies (11–100%) were never transfused. Sensitisation may be unavoidable in some patients even if blood transfusions have not been administered to them. In some patients sensitisation may occur from exposure to non-HLA antigens, possibly from bacterial or viral infections.

Although presensitisation does not affect the outcome of transplantation, it delays finding compatible kidneys because of more frequent donor-specific positive cross-matches, which seems to be the major detrimental effect of preformed cytotoxic antibodies. Avoiding transfusions, however, to prevent presensitisation is not justified in view of the poorer results obtained in nontransfused transplant recipients. Frozen red blood cell preparations induce fewer cytotoxic antibodies [10], but do not appear to have a beneficial effect on graft survival [9]. Means of obtaining the benefits of blood transfusions without their potential for sensitisation are not yet available and deserve further investigation.

Acknowledgment

The authors gratefully acknowledge the editorial assistance of Beverly Hill.

References

2 Ferguson, RM, Noreen, H, Yunis, EJ, Simmons, RL and Najarian, JS (1977) Transplantation Proc., 9, 69
5 Opelz, G and Terasaki, PI (1972) Transplantation Proc., 4, 433
6 Terasaki, PI, Opelz, G and Mickey, MT (1976) Transplantation Proc., 8, 139
10 Fuller, TC, Delmonico, FL, Cosimi, AB et al (1977) Transplantation Proc., 9, 117
Open Discussion

LEGRAIN (Paris) How do you explain your rather low graft survival rate at one year in all groups. What is your patient survival rate at one year?

VINCENTI Our overall graft survival at one year is about 50% in the combined transfused and non transfused patients. In the USA this is an acceptable graft survival. If we just take the patients that have been transfused then the graft survival goes up to 63—65%. Our patients' survival in cadaver transplant in one year is about 90% and at 5 years it is 80%.

MICHIESEN (Belgium) Was your cross match performed only with the last serum available with highest possible titre of antibodies, or what do you do exactly?

VINCENTI We used two serum samples. The last sample prior to transplantation and the one that had previously been shown to have the greatest reactivity. The reason it is important to do multiple screenings in patients that have cytotoxic antibodies is that you can then obtain a serum sample that may have the greatest number or the broadest level of cytotoxic antibodies.

FOTINO (New York) What is the temperature at which you did your cytotoxic antibody screening?

VINCENTI 23°C.

FOTINO Thank you. Because you have quite a high number of patients that seem to have cytotoxic antibodies and they have not received any blood transfusions, I am wondering what your results would be at 37°C.

VINCENTI This is a very good question. I think there may be a proportion of the patients that have auto-antibodies or cold B antibodies that may not appear at 37°C.

DIAMANDOPOULOS (Greece) Were your patients who were given transfusions more anaemic than the ones who were not?

VINCENTI Probably, however the patients' survival between the two groups was the same.

DIAMANDOPOULOS We had found that the more anaemic a patient, the lower his cell mediated immunity. Hence when you correlate blood transfusion and graft survival you really correlate cell mediated immunity and graft survival.

VRIESMAN (Maastricht) I was also surprised that you found a lot of cytotoxic antibodies in your non-sensitised recipients. Since you use rabbit serum as source of complement in your cytotoxic antibody assay, maybe the natural antibody within the rabbit serum may have contributed to the high number of cytotoxic antibodies in patients that were not sensitised by blood transfusions?

VINCENTI I am not sure that I have the answer to your question. I know other
groups have patients that have a lot of cytotoxic antibodies, who have not had blood transfusions. I think maybe viral bacterial infections or some other non HLA antigens may result in cytotoxic antibodies.