PART XII
TRANSPLANTATION 1
Chairmen: M Leski
           J Traeger

PART XIII
TRANSPLANTATION 2
Chairmen: C Ponticelli
           J M Suc

PART XIV
TRANSPLANTATION 3
Chairmen: C van Ypersele
           J F Bach
PRETRANSPLANT BLOOD TRANSFUSIONS CAN HARM MATCHED KIDNEYS IN DOGS

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Summary

The effect of pretransplant blood transfusion (PBT) and histocompatibility matching on kidney allograft survival was studied in immunosuppressed dogs. PBT was found to be beneficial for related and unrelated mismatched kidney grafts. In contrast, after withdrawal of the immunosuppressants, transfused recipients of related and unrelated matched grafts rejected the kidney significantly more often than non-transfused dogs. Crossimmunisation for minor histocompatibility antigens may be responsible for this adverse effect, but could not be demonstrated in vitro by serology or mixed lymphocyte reactions. The possible deleterious effect of PBT in this model argues against the routine use of pretransplant blood transfusions in man.

Introduction

In man, matching for DR antigens and pretransplant blood transfusions are both individually correlated with prolonged kidney allograft survival [1,2]. Few data, however, are available on the interaction of these two variables. Nevertheless, blood transfusions are given as a matter of routine to prospective recipients no matter whether they receive a DR-matched kidney or not. Blood transfusions carry certain risks such as preimmunisation of the recipient, while DR matching is an expensive affair. It is therefore worthwhile investigating whether or not these two procedures have an additive effect.

Material and methods

Histocompatibility matching was performed using standard tissue typing techniques for the determination of the serologically and lymphocyte defined antigens of the major histocompatibility complex (MHC) of the dog, DLA-A, -B and -D [3–5]. Donor-recipient pairs matched for DLA-D were negative in mixed lympho-
cyte cultures (MLRs) according to previously defined criteria [5]. Transfusions of 100ml of fresh whole blood were given to some of the recipients, four, three and two weeks prior to transplantation. A serological crossmatch test was always performed, but kidneys were transplanted regardless of the outcome. All recipients (see Table I) underwent bilateral nephrectomy at the time of transplantation.

TABLE I. Graft survival times (in days)

<table>
<thead>
<tr>
<th>Donor-recipient pair</th>
<th>Non-transfused</th>
<th>Transfused</th>
<th>Significance Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated mismatched mongrels</td>
<td>9, 10, 11, 12, 12, 12, 21, 26, 49, 51, 63,*</td>
<td>21, 26, 49, 51, 63,*</td>
<td></td>
</tr>
<tr>
<td>mongrels</td>
<td>12, 13, 15, 15, 16, 16, 26, 30,* 35</td>
<td>98, 101, 125, &gt;350, &gt;350</td>
<td></td>
</tr>
<tr>
<td>Related mismatched beagles</td>
<td>9, 12, 12, 13, 16, 17, 50</td>
<td>9, 123,† 168,* &gt;305†, &gt;305†</td>
<td></td>
</tr>
<tr>
<td>matched beagles</td>
<td>&gt;350</td>
<td>&gt;305</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Unrelated matched beagles</td>
<td>212,* 335,* 342, &gt;350, &gt;350, &gt;350, &gt;350</td>
<td>8,* 44, 166, 170,†</td>
<td></td>
</tr>
<tr>
<td>matched beagles</td>
<td>&gt;350, &gt;350, &gt;350</td>
<td>184, 268, 305, &gt;350, &gt;350, p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Related matched beagles</td>
<td>41,* 73,* 171, &gt;350, &gt;350, &gt;350</td>
<td>37, 70, 174, 177, 207, &gt;350, &gt;350, &gt;350, p = 0.16</td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>&gt;350, &gt;350, &gt;350</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = no rejection  
† = positive crossmatch

Standard immunosuppression, viz 1mg/kg body weight prednisolone IV and 2mg/kg azathioprine IV was given for 60 days in the mismatched unrelated group and for 100 days in the other groups. Immunosuppressants were then gradually withdrawn in all surviving dogs. The postoperative day on which the animal died from renal insufficiency or on which the serum creatinine rose above 1000μmol/L was taken as the end-point of graft survival. Autopsy and histological examination were performed in all cases.

Results

Table I presents the graft survival times for the recipients in the different groups. The survival data for some of the mismatched mongrels have already been given in a previous publication [6]. A significant prolongation of graft survival after blood transfusion was observed in the mismatched donor-recipient pairs (unrelated: p < 0.005; related: p < 0.05). In the matched groups, graft survival was so good that blood transfusions could hardly improve it.
In fact we found that after withdrawal of immunosuppressive therapy, transfused recipients rejected the kidney more often than non-transfused dogs. This difference is significant in the unrelated group ($p < 0.01$). The outcome of the crossmatch test was not predictive for the shortened graft survival in the unrelated group. MLRs were performed before transfusion and just before transplantation.

![Graph showing stimulation indices for mixed-lymphocyte cultures (MLRs) before and after blood transfusion in the unrelated matched group.](image)

Figure 1. Stimulation indices determined for mixed-lymphocyte cultures (MLRs) before and after blood transfusion in the unrelated matched group. The numbers in the figure indicate the ranks of the corresponding survival times. A: A culture time of 7 days was chosen for the negative MLRs. Blood transfusion tends to give a rise in stimulation indices in these cases. B: A shorter culture period of 5 days was chosen for the third-party MLRs. Blood transfusion tended to cause a drop in stimulation indices here. Neither in the case of the negative MLRs nor in that of the third-party MLRs could any correlation be found between graft survival and the values of the stimulation indices before or after transfusion, or the rise or fall in stimulation indices.

As may be seen from Figure 1, blood transfusions can cause a rise in the stimulation indices of negative MLRs, but give lower MLRs with third-party controls.

No correlation could be found between graft survival and the outcome of the MLR between recipient and donor, or between the recipient and a third-party control, before or after transfusion. Moreover, the change in MLR is not predictive.
Discussion

The dog seems to provide a suitable model for study of the effect of blood transfusion on the rejection of kidney transplants, since it allows considerable variations of the test parameters [6,7 and present paper]. The adverse effect of blood transfusions in matched donor-recipient pairs after withdrawal of the immunosuppressive drugs, as found in this study, is unexpected but may be explained in terms of crossimmunisation to undefined antigens of the kidney donor caused by the blood transfusions. However, we were not able to demonstrate this crossimmunisation in vitro. Of the two recipients with a positive crossmatch, one rejected the kidney while the other did not. Blood transfusions were found to cause a rise in the stimulation indices of negative MLRs and a drop in the stimulation indices of positive MLRs. However, those changes in MLR activity were not reflected in graft survival times. Other, more sensitive, in vitro tests might permit identification of antigens responsible for late graft loss.

The observed potentially harmful effect of pretransplant blood transfusions may have implications for kidney transplantation in man. Attempts to withdraw immunosuppressants in human recipients whose grafts had been functioning well for long periods often result in acute loss of the graft [8]. The results of our experiments suggest that pretransplant blood transfusions may be responsible for inducing this late graft loss, and hence that recipients of matched grafts may be able to do with lower doses of immunosuppressants (with their potentially harmful side-effects) to maintain graft function if they do not receive blood transfusions before transplantation.

At present, recipients of DR-matched grafts have an excellent one-year graft survival with or without transfusions. In view of the relatively low gene frequencies of DR antigens, a large number of potential recipients will be able to receive a DR-matched graft. Few data are available on the interaction of blood transfusion and DR matching in man; however, the results of the present study in the dog suggest that it may be wise not to give blood transfusions as a matter of routine to all potential recipients, but rather to wait (if possible) until a DR-matched kidney becomes available. Transfusions not required for other medical reasons should thus be reserved for patients who are unlikely to receive a DR-matched kidney, e.g. those with uncommon phenotypes, or for urgent cases where there is no time to wait until a DR-matched kidney turns up.

Acknowledgments

This study was financed by Grant C 80.260 from the Dutch Kidney Foundation. Azathioprine was kindly provided by Wellcome Nederland BV.

References

1 Ting A, Morris PJ. Lancet 1980; ii: 282
3 Vriesendorp HM et al. Transplantation 1971; 11: 440

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Open Discussion

CHATTERJEE (Sacramento, California) A comment first; to draw attention to the fact that with the living related donor transplant, if you have a four antigen match and negative MLR with the recipient, nobody would think of giving a blood transfusion to that particular recipient. It is not beneficial, I do not know whether it is harmful, but nobody is doing that — that is one thing for certain.

From the practical point of view, I do not know about Europe but for the States I can say that it is almost impossible to predict which recipient is going to get which DR type. When you are talking about DR type I take it for granted that you are talking about a 2 DR match, not a 1 DR match. A 1 DR match will not have any beneficial effect at all. If you have a 2 DR match prospective recipient I would like to know how you select your pool, how can you be certain that this patient is going to get a DR match and that patient is not going to get a DR match?

BIJNEN I think that in practice we can put it into the computer programme so that potential recipients that are not transfused are only allotted an identical kidney. If the waiting time becomes too long, then you could discuss whether you should give him a transfusion so that he can receive any kidney.

CHATTERJEE A deliberate blood transfusion policy does not really alter the MLR. Do you actually see a drop in MLR after blood transfusion? That is not my conception. MLC does not alter in spite of better graft survival, that is why the big question is still how blood transfusion works.

BIJNEN It may be that the effect on MLR depends on the time interval between the setting up of the MLR and the last transfusion. In all these experiments we gave transfusions at four, three and two weeks before transplantation, and the last MLR was performed just before transplantation. There was only a time interval of two weeks, and that can, at least in a dog, have an influence on the MLR.

LESKI (Chairman) Well as you know, Broyer this morning and the LA group reported that the results of related transplanted kidneys were better after transfusion, and then Salvatorio reported that donor transfusion to recipients gave excellent results when the cross match was negative before transplantation. Don’t you think there is some discrepancy between your work and these reports?

BIJNEN Well, I think donor transfusions are different from third party transfusions and the mechanism involved for causing prolonged better prognosis might
be different. We transplanted independent of the outcome of the cross match test, because we wanted to avoid possible selection by cross matches which might influence the results. Although in general we see some effect of a positive cross match on graft survival we have very good survivals in spite of positive cross matches.