MODIFICATION OF KIDNEY GRAFT SURVIVAL IN DOG AND MAN BY PRE-OPERATIVE TRANSFUSION TO THE DONOR

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Summary

The present experiments indicate that the transplantation reaction is not solely caused by immunocompetent cells of the recipient, but also by immunocompetent cells in the donor organ. Immunisation of the donor did modify the immune response as demonstrated with kidney grafts in rat, dog and man. In the dog prolonged kidney graft survival by one peroperative blood transfusion was reduced to control level by transfusion of the donor on day -1 with 100ml third party blood. In the rat third party blood transfusion to the donor reduced kidney graft survival significantly, but donor pretreatment with recipient lymphocytes induced significantly prolonged survival. This suggests that the modification of graft survival by donor transfusion is an immunological phenomenon. Immunisation of the donor with recipient cells may induce specific immunoreactive cells in the graft that causes a local graft versus host reaction, which inhibits the rejection reaction. In man 44 recipients were studied who only received blood peroperatively. Significantly impaired graft survival was noted if the donor was not transfused, resulting in 19% 3-month kidney function, versus 61% with transfused donors.

Introduction

The immune reaction has usually been considered to be originated by the response of a cell population to antigenic structures present on stimulator cells.

This concept is probably not valid, for elements other than antigen recognition may be involved in the allogeneic reaction. There is some evidence that stimulation of the immune reaction is an active and not a passive process. Stimulation of responder cells is only observed with metabolically active cells. The present experiments indicate that immunisation of the donor may modify the rejection reaction which suggests that immunologically active cells in the donor organ do actively participate in the immune reaction.
Materials and methods

The studies were performed with kidney grafts in dog, rat and man.

Kidney transplantation in dogs

Adult mongrel dogs were used as donor and recipient. Kidneys were transplanted to the right iliac fossa. Bilateral nephrectomy was performed at the time of transplantation. All recipients were treated with immunosuppressive agents starting the day of transplantation in a dosage of 4mg/kg body weight methylprednisolone and 2mg/kg body weight azathioprine daily during the first 10 days and every other day thereafter. Donor immunisation consisted of transfusion of 100ml whole blood i.v. from a third party donor.

Kidney transplantation in rats

Adult Wag/Rij and BN rats were used. BN kidneys were transplanted into Wag/Rij recipients. Bilateral nephrectomy was performed at the time of transplantation. Donor immunisation consisted of intraperitoneal injection of third party whole blood or recipient lymphocytes.

Kidney transplantation in man

Forty-four patients who had never received blood before transplantation were selected by G Persijn from Eurotransplant. These patients were transfused on the day of transplantation. Eighteen donors received a blood transfusion before transplantation.

F Harder studied the effect of donor transfusion in 69 patients, who were transfused before transplantation. The number of transfusions has not been recorded. All donor nephrectomies were performed by the same team.

Results

Kidney transplantation in the dog

All canine recipients in this experimental model received immunosuppression starting the day of operation, leading to graft survival of 6 to 21 days in 11 controls (Table I). Peroperative treatment of the recipient with 100ml third party blood did induce significantly prolonged graft survival in 12 recipients (group II). Additional treatment of the donor with 100ml third party blood one day before transplantation reduced graft survival to control levels (group III).

Kidney transplantation in the rat

Wag/Rij rats rejected BN kidney grafts in 8–9 days (Table II). Treatment of the donor with 2ml third party blood one day before transplantation reduced renal
TABLE I. Kidney transplantation in dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>Third party cells donor</th>
<th>Number</th>
<th>Survival in days</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>–</td>
<td>11</td>
<td>6-9-10-11-12-13-14-14-15-21</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>day -1 blood</td>
<td>7</td>
<td>6-9-13-14-16-20-21</td>
<td>14</td>
</tr>
</tbody>
</table>

TABLE II. Kidney transplantation in rats (BN → Wag/Rij)

<table>
<thead>
<tr>
<th>Group</th>
<th>Donor Pretreatment</th>
<th>Recipient Pretreatment</th>
<th>Number</th>
<th>Survival in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>–</td>
<td>–</td>
<td>8</td>
<td>8-8-8-8-8-8-8-9</td>
</tr>
<tr>
<td>II</td>
<td>+ 3rd party blood</td>
<td>–</td>
<td>8</td>
<td>5-6-6-6-6-7-7-7</td>
</tr>
<tr>
<td>III</td>
<td>+ recipient lymphocytes (Wag/Rij)</td>
<td>–</td>
<td>10</td>
<td>9-10-10-10-10-11-12-12-13-19</td>
</tr>
<tr>
<td>IV</td>
<td>+ recipient lymphocytes (4 inj.)</td>
<td>–</td>
<td>5</td>
<td>12-12-13-16-17</td>
</tr>
</tbody>
</table>

graft survival in untreated recipients significantly. If on the other hand $1 \times 10^8$ recipient lymphocytes were injected into the donor one day before transplantation, significantly extended graft survival was obtained (group III). Four weekly injections of $1 \times 10^8$ recipient lymphocytes into the donor up until one day before transplantation modified the rejection of subsequently transplanted kidney grafts to a greater extent (group IV). Thus donor immunisation with recipient cells leads to an effect opposite to transfusion of the donor with third party cells.

**Kidney transplantation in man**

A retrospective study has been performed in Leiden and in Basel with peroperatively and preoperatively transfused recipients. The data concerning 44 recipients from Leiden were provided by Eurotransplant. These recipients only were transfused on the day of transplantation. Twenty-six donors had not received blood during the period before transplantation. The 26 recipients of kidney grafts from untreated donors did reject the grafts significantly earlier than the other group of 18 patients with renal grafts from transfused donors, resulting in 3-month kidney graft function of respectively 19% and 61%.

The 69 patients from Basel were transfused before transplantation. All donor nephrectomies were performed by the transplantation team in Basel. Thirty-four donors were not transfused during the period immediately before transplantation. Recipients of kidneys from transfused donors had a 1-year graft survival of 77%.
whereas the recipients of kidneys from non-transfused donors showed 64% 1-year graft survival.

Discussion

The present experiments concern the effect of donor transfusion on graft survival. Passenger leucocytes in the kidney graft are known to play an important role in graft recognition and rejection. We have demonstrated that donor pretreatment with procarbazine and methylprednisolone prolonged canine graft survival significantly, but that a normal rejection reaction can be reconstituted by transfusion of donor cells. The question is whether the passenger leucocytes or stimulator cells in the organ merely present antigenic structures to the recipient or play a more active role in the rejection reaction. The present experiments suggest that kidney transplants may contain stimulator cells which function as immunologically active cells. It appeared that donor transfusion could reduce canine kidney graft survival in transfused recipients. In man donor transfusion appeared to prolong kidney graft survival. In our rat model, donor transfusion with third party cells induced accelerated rejection of BN kidney grafts in Wag/Rij recipients whereas donor immunisation with recipient lymphocytes did induce prolonged graft survival. Recipient cell transfusion of the donor may cause a reactivity of immunocompetent cells in the donor organ, supposedly passenger lymphocytes resulting in a specific activity of these cells (passenger lymphoblasts) towards the responsive cells of the recipient. A local graft versus host reaction may be exerted by these passenger lymphoblasts and in such a way inhibit the rejection process. Transfusion of the donor with third party cells may lead to a non-specific stimulation of passenger lymphocytes which does not result in graft versus host activity. The presence of immunoreactive cells in the target organ that play an active role in the rejection reaction is in accordance with the theories of Lafferty who claims that the stimulator cell must be a metabolically active, immunocompetent cell.

The discrepancy between the experimental data in dogs and rats and those in man may be caused by the difference in experimental designs. The studies in man were performed retrospectively and the transfusion to the donor in man is given for circulation problems in which case not only blood will be infused. The transfused donor in man is therefore a selected patient in contrast to the donor in rat and dog.

In conclusion all experimental data in this study indicate that preoperative transfusion of the donor modifies the rejection reaction. The opposite effects obtained with third party and recipient cell transfusion suggest that immunocompetent cells in the donor organ do actively participate in the rejection reaction.
Open Discussion

KNAPP (Nottingham) I was very interested in your suggestion that we should be concerned about this aspect of the donor’s treatment, and I think it is an important point, but I was also a little concerned about the clinical data presented because the control group studied seemed to have an unusually high failure rate, and I wondered if this represented an atypical group within your experience, or it occurred by chance at the time that you were doing the study, because it does seem to be lower than most of the series that we are seeing these days?

JEEKEL Yes, I don’t think you can talk about a control group, actually, because that has just been a group of 44 patients who received preoperative blood transfusion, and this survival was divided just by looking at the donor transfusion, but I agree that studies in man should be looked upon much more closely as the human donor receives much more than blood when he is in shock. He may receive other treatments as well and that’s maybe the explanation for the difference in results between man and experimental animals.

KNAPP Could I just ask if you compared the two groups for other variables which are known to have an effect upon survival to see that they were similar in every other respect, other than the one you analysed?

JEEKEL You mean clinically?

KNAPP I mean will they match for age, for example, and for duration on dialysis and any other variables? Because that would help convince us that they were similar groups other than the treatment for the donor.

JEEKEL That will be done.

BRYNGER (Gothenburg) I think that this is something that a lot of transplantation surgeons might help with, and go back and work out, and look prospectively for this surprising matter, which we have of course not thought of at all, and which will be very hard to retrieve in retrospect, but if we look at it we might give some addition to your data.