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Prolonged survival of baboon renal allografts using idarubicin-conjugated anti-CD4 monoclonal antibodies

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Abstract Tolerance to organ allografts in rodents and pigs can be easily achieved. However, tolerance induction in a large primate model has been more elusive. In this study, we have used an anti-CD4, murine monoclonal antibody as a carrier for the cytotoxic drug idarubicin (IDA) to delete or inactivate alloreactive T-cells responding to a renal allograft in a baboon transplant model. Fourteen Chacma baboons weighing between 15–25 kg received heterotopic renal allografts. Recipient and donor pairs were selected on the basis of ABO compatibility. Seven animals were given no immunosuppression and served as the control group. The remaining 7 animals received anti-CD4 IDA. The first 2 animals in this group received 2 mg IVI intraoperatively and three doses at 48-h intervals thereafter. The last 5 animals received a larger dose of 1 mg/kg, starting 24 h preoperatively and again on postoperative days 2 and 5. The untreated animals promptly rejected their allografts with a mean survival of 10 days. The survival of the 2 animals treated with 2 mg anti-CD4 IDA was 7 days each. However, the animals treated with 1 mg/kg anti-CD4 IDA survived 7, 18, 20, 40 and > 40 days. Peritransplant administration of anti-CD4 IDA prolonged renal allograft survival in a large primate model. This unique immunoconjugate has the potential of tolerance induction.

Key words Idarubicin · Anti-CD4 monoclonal antibody · Baboon renal allograft · Tolerance induction

Introduction

The concept of T-cell deletion or inactivation using monoclonal antibodies in order to induce tolerance to transplanted organs is well established. By attaching a cytotoxic agent to a monoclonal antibody, higher doses of the cytotoxic agent can be delivered to the selected target cells. The anthracyclin drug idarubicin inhibits the enzyme topoisomerase II, leading to apoptosis of actively dividing cells. Idarubicin coupled to an anti-CD3 monoclonal antibody has been shown to induce alloantigen specific tolerance in a vascularised mouse cardiac allograft model [1]. In a series of ongoing experiments we are evaluating the immunosuppressive efficacy of these immunoconjugates in a baboon renal allograft model [2]. This report focuses on the efficacy of the anti-CD4 idarubicin antibody.

Materials and methods

Surgery

Fourteen adult Chacma baboons, weighing between 15–25 kg and of either sex underwent heterotopic renal transplantation. Donor-recipient pairs were selected on the basis of AB blood group compatibility only. Crossover transplants were performed between donor-recipient pairs. The left kidney from each baboon was harvested and transplanted into the right iliac fossa of the recipient. Ne-

phrectomy of the remaining right kidney was performed at the completion of the implantation.

Immunosuppression

The antibody used is a murine anti-CD4 monoclonal antibody developed against human lymphocytes. We have shown that this antibody has been crossreactive with baboon lymphocytes. The antibody is of the IgG1 isotype and was conjugated to idarubicin. Seven baboons received no immunosuppression and formed the control group for this series of experiments. Anti-CD4 idarubicin was administered to two animals at a dose of 2 mg given intravenously and commencing at the time of transplant and again at 48-h intervals for three further doses.

Anti-CD4 idarubicin was administered to the remaining five baboons at a dose of 1 mg/kg. This was commenced 24 h preoperatively as a short intravenous infusion. In addition, methylprednisolone was given simultaneously at a dose of 125 mg. The same dose of anti-CD4 idarubicin was repeated on postoperative days 2 and 5 also under steroid cover. The steroid cover was in order to inhibit the cytokine release syndrome.

Follow up

Graft function was monitored by measuring serum creatinine pretransplant and at weekly intervals. The animals were killed when it was noted that the serum creatinine was elevated or by other criteria as determined by the resident veterinary staff. All tissue was examined grossly and the transplanted kidneys were evaluated histologically. The University of Cape Town ethics committee for animal research approved the protocol. Autopsy was performed within 24 h of death.

Results

The untreated animals promptly rejected the renal allografts, with renal dysfunction evident at the end of the 1st posttransplant week. All these animals were dead by the 14th postoperative day, with a mean survival of 8 days. All seven animals had evidence of severe rejection on histological assessment of the transplanted allograft. The two animals that received the 2 mg of anti-CD4 idarubicin protocol survived for 7 days only, also with severe evidence of rejection on histological evaluation of the allograft.

The five baboons that received the larger dose of anti-CD4 idarubicin starting 24 h preoperatively and with steroid cover survived for 7, 19, 20, 40 and 96 days. The mean survival in this group was 36 days. The longest survivor in this group developed a wasting syndrome characterised by progressive loss of appetite and weight loss necessitating euthanasia.

Discussion

As demonstrated by the control group of animals, allograft rejection occurs predictably just after the 1st posttransplant week in this outbred, non-human primate renal transplant model. The administration of this unique immunoconjugate appears to result in prolonged renal allograft survival. We cautiously conclude that this drug may have a role in future tolerance induction protocols.

References

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