Haematology and Blood Transfusion Vol. 28
Modern Trends in Human Leukemia V
Edited by Neth, Gallo, Greaves, Moore, Winkler

Cyclosporin A Following Matched and Mismatched Family Allogeneic Bone Marrow Transplants

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A. Introduction

Following the use of Cyclosporin A (CSA) in patients with established acute graft versus host disease (GVHD) [1] we initiated a study of CSA to prevent GVHD, because it seemed probable that it would be more effective in this role than for reversing the established process. We initially reported the results of 20 patients who had received matched allogeneic sibling bone marrow transplants and prophylactic CSA for longer than 3 months, only one of whom died of GVHD [2].

B. Present Study

Eighty-four patients with acute leukaemia in remission or early relapse or chronic granulocytic leukaemia in the chronic phase have been included in this study, 60 of whom have had follow-up for at least 1 year. All received a matched transplant from an HLA/MLC compatible sibling after conditioning with cyclophosphamide (1.8 g/m^2 intravenously on two consecutive days) (68 patients) or melphalan (85–100mg/mg^2 i.v. as a single dose) (nine patients) followed 36 h later by total body irradiation (TBI) of 10 Gy from a single cobalt^{60} source at approximately 0.03 Gy/min. Seven patients were conditioned with melphalan alone (180–250 mg/m^2 i.v. as a single dose). Marrow was infused from the sibling donor 24 h after the irradiation or 2–4 days after melphalan alone. The patients were nursed in protective isolation (for approximately 4 weeks until reconstitution) and given therapeutic antibiotics, platelets and granulocyte transfusions as required. The CSA was given intramuscularly 25 mg/kg per day (in two 12 hourly doses) starting 24 h before the infusion of the marrow and continuing for 5 days. From the 6th day, i.e. 4 days after bone marrow transplantation, the drug was administered orally and continued for 6 months at a dose of 12.5 mg/kg per day in two divided doses. This dose was reduced by 50% if the blood urea rose above 20 mmol/litre or there was other unacceptable toxicity and was further reduced if the urea continued to rise. Part way through the study the protocol was changed and patients received oral CSA at a dose of 12.5 or 37.5 mg/kg per day for the first 5 days instead of the intramuscular preparation. The intramuscular route was reinstarted after 23 patients.

C. Results

A retrospective analysis of 26 patients receiving methotrexate as prophylaxis against GVHD showed that 46% of the patients developed acute GVHD and 27% of the patients died of the problem. Of the 84 patients receiving CSA, only three (4%) have died of acute GVHD. However, there was a significant incidence (37%) of biopsy proven acute skin GVHD occurring at the time after grafting when we previously saw fatal GVHD. However, all but three of these patients had resolution of their skin disorder, some of whom received treatment with high-dose methylprednisolone. We do not now feel justified in conducting a controlled trial of CSA versus no treatment to

establish the exact role of this drug in preventing GVHD because the incidence of fatal acute GVHD in our series is so low. However, the Seattle Transplant Group has at present a study comparing CSA with methotrexate following bone marrow transplantation. Although such studies are critical for deciding the best treatment for these patients they alone cannot define the exact role of CSA in preventing GVHD in man, because there has not been a study of methotrexate versus no treatment in man.

That there is an effect of CSA on acute GVHD can be established indirectly from our four patients who, after bone marrow transplants and subsequent relapses, were given high-dose melphalan (180–200 mg/m^2 as a single infusion) followed by a marrow transplant from the same donor as the original transplant. None of these patients had developed acute GVHD when given CSA during the initial period after their first transplant. They were not given the drug after the second transplant and two developed acute GVHD (days 20, 44), one of whom died.

The effect of stopping CSA after 6 months also indicates the influence of the drug on preventing acute GVHD. In our previous methotrexate study, where the drug was given for 102 days after transplant, we did not see the development of acute GVHD longer than 52 days after transplantation. Thirty-eight of the 60 patients in the present study have had their CSA stopped approximately 6 months after transplant and these patients have been followed-up for at least a year from transplantation. Twenty-one of these patients subsequently developed acute GVHD, chronic GVHD or a rash that mimicked the syndrome but was not proven histiologically. The timing of these problems occurs as if the patients had received a bone marrow transplant at the time of stopping CSA. Thirteen of these patients were restarted on CSA and seven received azathioprine and prednisolone (some received both treatment regimens). At present 26 of the 38 patients are alive (16 on no treatment) and 12 have died: nine of relapsed leukaemia and three of infection. It is clear that, unlike patients who have received methotrexate after bone marrow transplantation and then developed acute GVHD where we see little clinical benefit from CSA, patients who have previously received prolonged CSA respond well to re-introduction of the CSA.

D. Mismatched Bone Marrow Transplantation

Following the encouraging results of CSA in matched transplants we embarked upon a study using family member donors who had a varying degree of MHC antigenic mismatch.

Thirty-five patients aged 4–45 years with acute leukaemia have been given allogeneic mismatched bone marrow transplants over a period of 3 years. One donor was a two haplotype mismatch; one differed from the recipient at the D locus only because of BD recombination and the remaining 33 were genotypically one haplotype matches, although more than half of these shared some or all antigens on the mismatched haplotype. In all but one instance there was a positive mixed lymphocyte reaction between donor and recipient. Thirty-one patients were conditioned with cyclophosphamide and TBI as for matched transplants, and four were conditioned with high-dose melphalan (240 mg/m^2) only. Patients received intramuscular or oral CSA for the first 5 days from the day before transplantation followed by oral CSA for 6 months as above. Seven of the first eight patients developed a leaky vascular syndrome (see below) and so a new protocol with the addition of methotrexate during the first 6 days after transplant was devised. The rationale for this has been discussed elsewhere [3]. Fifteen patients received this new protocol – no advantage was seen to accrue from it and five patients had failure of graft take and required regrafting. Thereafter patients reverted to the original protocol and received CSA alone (four of whom were conditioned with melphalan without TBI). Preliminary results are that of the 16 patients conditioned with TBI followed by CSA alone, six remain alive, two have died of leukaemia and two of infections and the remaining six have died of the syndrome involving leaky vascular endothelium, usually resulting in fatal pulmonary oedema with or without a concurrent viral infection. Of the 15 patients

conditioned with TBI followed by CSA plus methotrexate, five are alive, one of whom has relapsed. Ten have died, one of leukaemia, one of acute GVHD, one of a failure of graft take followed by infection and the remaining seven with the leaky vascular endothelial problem with or without a concurrent viral infection.

Engraftment using mismatched marrow has been established in three of four patients receiving conditioning, with melphalan alone. The fourth has required regrafting and is too early to assess. GVHD has not been a major problem and this study will continue.

Pulmonary oedema secondary to leaky vascular endothelium has complicated our mismatched bone marrow transplant programme. Approximately 40% of the patients have died of this syndrome and there have been severe fluid balance problems in many of the remaining patients, particularly during the first 30 days after transplant. A similar syndrome occurred in an occasional patient following a matched transplant (less than 10%) and its possible aetiology has been discussed elsewhere [3]. There is an increased incidence of viral infections in our mismatched bone marrow transplant patients, but it is difficult to assess the significance of these and their possible role in the leaky vascular problem. Many more patients will be required in this study to determine the nature of these problems, but we may be able to improve results by empirical methods. The major prognostic factor for success in mismatched bone marrow transplants appears to be age. Of the 20 patients over the age of 20 who were transplanted, only five remain alive; one of these has relapsed and two are within 30 days of transplant and too early to assess. Fifteen patients under the age of 20 have received mismatched transplantations and eight are alive and in remission (40% actuarial plateau), the longest at 2½ years after transplantation.

E. Summary

One hundred and nineteen patients with leukaemia have received CSA as prophylaxis against acute GVHD following sibling MHC matched (84) or family member mismatched bone marrow transplants (35). Four recipients of matched transplants (3%) died of acute GVHD, a marked improvement on our previous results using methotrexate (26 patients; 27% died of GVHD). Thirty-five patients received mismatched transplants, 15 were under the age of 20 years and eight are alive and in remission, the longest survivor being one at 2½ years after transplant.

References

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