MISMATCHED BONE MARROW TRANSPLANTATION

R. POWLES, G. GOSS, A. PEDRAZZINI, M. CROFTS, H. CLINK, J. MILLAR, B. KHAN AND D. PEREZ

In the United Kingdom, based on family size, the probability of a patient having a histocompatible sibling as a donor is only about 0.3 (1). Moreover, matched transplants are rarely successful for recipients over the age of 45 years. Thus for bone marrow transplantation to make any impact on the management of bone marrow disorders, particularly acute leukaemia, the availability of donors must be extended outside of those with complete identical inheritance of chromosome no. 6. HLA matched unrelated donors are being used to a limited extent to determine the feasibility of their use, but even with very large panels of normal donors the number of such transplants that have been undertaken is so small that no statement can be made on the efficacy of such a treatment. Seattle have previously reported a study in which donors were matched for one haplotype of chromosome no. 6, the other haplotype having antigenic similarities (2). These patients were given methotrexate as prophylaxis to prevent graft versus host disease (GvHD); many of them had active disease at the time of transplantation and in consequence there were many failures, but there were also some long term survivors. However, selecting patients whose donors are more than half identical at the MHC can only slightly extend the proportion of patients eligible for grafting.

Following encouraging results using Cyclosporin A (CyA) in matched grafts (3) we embarked upon a study of unselected patients who did not have MHC matched donors, choosing the most suitable non-matched member of the family as the donor. This study was therefore a report on a procedure that could be applicable to most young patients with acute leukaemia who were in remission and probably could be applied to other diseases also. In the original series (June 1979 to July 1982) 35 patients between the ages of 3 and 45 years were studied (4). There is now a minimum follow-up of 18 months of all patients. Thirty three patients had AML, 2 had ALL, and all received allogeneic mismatched transplants from family members. At the time of grafting 14 patients were in first remission, 15 were in later remission and 6 were in relapse. In 16 cases the donor was a sibling, in 16 a parent and in 4 a
child. This included one patient who received marrow first from her father and then from her child. All patients except one shared one HLA haplotype with the donor, and of the 34 one haplotype mismatched patients, 19 shared one or more antigens of the non-identical haplotype with the donor. All the MLC tests that could be evaluated were at least weakly positive in one direction in the one way test. Of this original series of 35 patients, 31 were conditioned with cyclophosphamide and total body irradiation as for matched transplants (4) and in 4 a single dose of melphalan 240mg/m² (5) was given 7 days after a priming dose of cyclophosphamide (300mg/m²). Patients were given intramuscular or oral Cyclosporin A (CyA) at 12.5 - 37.5mg/kg per day (in two 12 hourly doses) starting 24 hours before the infusion of marrow and continuing for 5 days. From the sixth day the drug was administered orally at a dose of 12.5mg/kg per day (in two 12 hourly doses) for six months. The dose of Cyclosporin A was reduced as renal function deteriorated. The first 8 patients received this protocol and 3 of them died of a previously unseen problem of massive pulmonary oedema of which the immediate cause of death appeared to be occurring 12-48 days after transplant. The essential lesion appeared to be increased permeability of blood vessels and the syndrome was characterised by a fever with fluid retention, a low central venous pressure and low serum albumin usually leading to dyspnoea, cyanosis, massive pulmonary oedema and death despite assisted ventilation. Associated features were convulsions, probably due to foci of localised cerebral oedema. In addition there was also seen a renal lesion characterised by intravascular haemolysis and oliguric renal failure although this latter complication resolved if patients were dialysed. Some features, particularly fluid retention, low serum albumin and renal impairment occurred in most of these first 8 patients. Because pulmonary oedema with leaky vascular problems had not been seen in the original series of 50 patients given mismatched transplants and methotrexate in Seattle (2) we explored the possibility that methotrexate may have been inhibiting a cellular immune reaction occurring immediately after transplant (an in vivo MLR). Laboratory data showed that cyclosporin levels in our patients were not sufficient high during the first two weeks after transplant to inhibit an MLR in vitro. In an attempt to prevent this syndrome the next 15 patients treated in the original series of 35 patients were given methotrexate in addition to Cyclosporin A during the first two weeks after transplant. Nevertheless, 5 of these patients died of this complication, and 6 of the 15 patients required re-grafting because of graft failure presumably