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Seronegative blood products prevent primary cytomegalovirus infection after bone marrow transplantation

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SUMMARY Seventy one patients underwent bone marrow transplantation for aplastic anaemia or haematological malignancy, 39 as allografts and 32 as autografts. All patients who were seronegative to cytomegalovirus received blood product support exclusively from seronegative community blood donors; seropositive patients received unscreened products. In no patients was there any attempt to reduce cytomegalovirus (CMV) infection by giving prophylaxis with immunoglobulin, and granulocyte transfusions were not given. The incidence of cytomegalovirus infection in the seronegative recipients (22 allograft, 15 autograft) was 0%; in the seropositive recipients 16 (63%) in allografts and 17 (18%) in autografts. These results suggest that provision of exclusively seronegative blood products is an important contribution for seronegative transplant recipients, but make little impact in autologous transplantation where the incidence of infection is low.

About a quarter of all patients undergoing allogeneic bone marrow transplantation develop pneumonitis. In about half of these cases cytomegalovirus is implicated[1 2] but is so seldom responsive to treatment[3 4] that current hopes of reducing this complication depend on strategies of prevention. Graft versus host disease (GVHD) is an important risk factor[5] and its more effective prevention may also reduce the incidence of cytomegalovirus (CMV) pneumonitis. Infection with CMV in these immunosuppressed patients may be caused by: (i) reactivation of latent virus in the host who can be identified as seropositive on examination before transplantation; (ii) transmission of virus through blood products from community donors; or (iii) in the bone marrow donation itself. It would seem logical for patients who have not previously been exposed to the virus (those who are seronegative) to receive blood products which were least likely to represent a risk of transferring the virus (from seronegative donors). CMV infections acquired by transfusion in newborn infants of seronegative mothers can be prevented by exclusive use of seronegative blood donors.[6]

We report our experience in 71 consecutive adult bone marrow transplant recipients. Those who were seronegative before transplantation received exclusively seronegative blood products, and those who were seropositive received unscreened products.

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Patients and methods

Seventy one consecutive adult patients undergoing bone marrow transplantation were studied. Thirty nine received allogeneic marrow (five with aplastic anaemia and 34 with haematological malignancy), and 32 received autologous marrow transplant for acute leukaemia.

Serological state for CMV was determined by the anti-complement immunofluorescence test (ACIF).[7] Patients whose titre was less than 1·4 were designated CMV seronegative and thereafter received blood products from a pool of community donors who were CMV seronegative. Current CMV state of each donor was rechecked immediately after donation, seropositive patients receiving unscreened products from community donors where the observed incidence of seronegativity was 42%.

Thirty seven patients (22 allograft and 15 autograft) were found to be seronegative and 34 patients (17 allograft and 17 autograft), were seropositive. The distribution of patients by age, diagnosis, conditioning protocol and prophylaxis by GVHD was similar in both groups (table 1). Details of conditioning protocols and management after transplantation have

Table 1 *Characteristics of 71 patients according to treatment group*

	Seronegative recipients		*Seropositive recipients*	
	Allograft	*Autograft*	*Allograft*	*Autograft*
Case No	22	15	17	17
Age				
Mean	21	27	27	38
Range	(13–37)	(18–43)	(15–38)	(19–54)
Diagnosis				
Leukaemia	19	15	15	17
Aplastic anaemia	3	0	2	0
Conditioning				
Cyclophosphamide + TBI	19	4	15	7
Cyclophosphamide alone	3	0	2	0
Melphalan + TBI	0	11	0	10
GVHD prophylaxis				
Cyclosporin A	9		7	
T cell depletion	13		10	
Donor CMV state				
Seronegative	16		7	
Seropositive	6		10	

been reported.[8 9] All of the allograft patients received bone marrow from HLA-fully matched MLC non-reactive sibling donors.

Of the 22 seronegative allograft recipients, six received marrow from a seropositive donor; of the 17 seropositive recipients, 10 received bone marrow from seropositive donors. After transplantation all patients were monitored for evidence of CMV infection, the criteria of which were isolation of virus grown in culture, a four-fold increase in CMV serology, or both. Routine culture of throat and urine and serology was undertaken every one to four weeks after transplantation for 150 days. The minimum follow up in these patients is 150 days.

Interstitial pneumonitis was characterised by tachypnoea, hypoxia, fever, and pulmonary infiltration on chest *x*-ray picture. Definitive diagnosis was attempted by fibre optic bronchoscopy and bronchial lavage, with culture and direct immunofluorescence. All patients received oral Co-trimoxazole to prevent *Pneumocystis carinii* infection.

Results

Of the 71 patients entered into the study, one patient, a seropositive allograft recipient, died within 40 days due to non-engraftment and acute renal failure without evidence of CMV infection. Of the 70 evaluable patients (table 2), no seronegative patients showed evidence of viral infection or pneumonitis, despite the fact that six of 22 seronegative allograft recipients received seropositive donor marrow. Ten of 16 seropositive allograft recipients developed CMV infection which was significantly greater than the seronegative allograft recipients ($p \leqslant 0{\cdot}001$). Four of these patients also developed pneumonitis (three CMV and one idiopathic) which was also significantly greater than the seronegative allograft recipients ($p \leqslant 0{\cdot}02$). The three seropositive patients who developed CMV pneumonitis all received marrow from seronegative donors. Three of 17 (18%) seropositive autograft recipients developed CMV infection. This incidence could not be shown to be significantly different from seronegative recipients of either an allograft or autograft.

The incidence of acute GVHD grades I–II did not differ between the allogeneic groups. Although three seropositive patients developed grade III–IV GVHD compared with one of the seronegative group, this was not significant.

The blood product requirement did not differ between the groups. Of the seronegative patients, the allograft patients received 19 red cell and 134 platelet

Table 2 *Incidence of cytomegalovirus infection, interstitial pneumonitis, and GVHD*

	Seronegative recipients		*Seropositive recipients*	
	Allograft	*Autograft*	*Allograft*	*Autograft*
Case No	22	15	16	17
CMV infection	0	0	10	3
Interstitial pneumonitis				
CMV	0	0	3	0
Idiopathic	0	0	1	0
Acute GVHD				
Grade I–II	4		3	
Grade III–IV	1		3	

Table 3 *Individual red cell and platelet transfusion required during first 90 days after transplantation*

	Seronegative blood products		*Unscreened blood products*	
	Allograft	*Autograft*	*Allograft*	*Autograft*
Red cells	19	19	33	18
Platelets	134	114	133	119

transfusions, and the autograft patients 19 red cell and 114 platelet transfusions. The seropositive allograft patients received 33 red cell and 133 platelet transfusions and the autograft patients 18 red cell and 119 platelet transfusions (table 3).

Discussion

The results of this study show that CMV seronegative bone marrow transplant recipients who receive marrow from seronegative donors do not get CMV infection when given exclusively seronegative blood products. These results are in agreement with the findings of Bowden *et al*[10] whose group of patients were fully protected from CMV infection, which contrasts with the findings of studies in which immunoglobulin providing only partial protection was given as prophylaxis.[11–13] The significantly lower number of CMV infections in the seronegative allograft recipients may not only be due to the provision of seronegative blood products but also to the predisposition of the seropositive allograft recipients to reactivate latent CMV[14] which can lead to clinical infection. Only six seronegative allograft recipients received marrow from seropositive donors, therefore we have insufficient data to exclude donor seropositivity as a risk factor in developing CMV infection. All three seropositive allograft recipients who developed CMV pneumonitis received marrow from seronegative donors, and although we have insufficient data in this study to make any firm conclusions, Grob *et al* have shown that non-immune donors are associated with a significantly higher incidence of severe CMV infections when their marrow is given to seropositive recipients.[15]

Our results also show that the incidence of CMV infection is low in autograft recipients, irrespective of their serological state, and could not be shown to be influenced by the provision of seronegative blood products. Although the incidence of CMV infection was not clearly defined, it was rare in a previous report on a smaller group of patients.[16] Furthermore, on review of a larger number of autograft patients who had similar conditioning protocols, pneumonitis of all aetiologies was unusual.[17]

The incidence of CMV infection in seropositive autograft recipients receiving untested products could not be shown to be different from that in seronegative autograft recipients receiving seronegative products. Our inability to show a difference may be because no difference exists; if so, the provision of CMV seronegative blood products may be unnecessary in seronegative autograft recipients. Alternatively, these findings could represent numbers too small to show such a difference.

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