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Intravenous Hyperimmune Globulin Prophylaxis against Cytomegalovirus Interstitial Pneumonitis after Allogenic Bone Marrow Transplantation

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In an attempt to reduce the incidence of lethal cytomegalovirus (CMV) interstitial pneumonitis after allogenic bone marrow transplantation 49 patients were randomized in a multicenter controlled study to receive either CMV-hyperimmune globulin or a control immune globulin with low anticytomegalovirus titer. Immune globulin was administered intravenously 6 times with 20 days interval, starting on day 7 before transplantation.

Patients receiving CMV hyperimmune globulin or control immune globulin were comparable with regard to age, diagnosis, pretransplant anti-CMV titer, incidence of graft-versus-host disease and transfusions.

In each group, the incidence of histologically proven CMV interstitial pneumonitis during the first 110 days post BMT was recorded. Six of 23 patients in the control group versus 1 of 26 in the CMV hyperimmune globulin group died of CMV interstitial pneumonitis ($p < 0.05$). No significant effect on idiopathic pneumonitis or survival was observed.

INTRODUCTION

Opportunistic cytomegalovirus (CMV) infections occur in more than 50% of patients receiving allogenic bone marrow transplantation (BMT) after conditioning with high-dose chemotherapy and whole-body irradiation. 15-29% of all patients develop lethal CMV interstitial pneumonitis (IP), usually within the first 100 days after transplantation (1). No effective treatment against this condition is available. However, a prophylactic effect of passive immunization with hyperimmune plasma or hyperimmune globulin has been reported (2, 3, 4).

The present report describes the preliminary results of a multicenter controlled study in which patients prior to transplantation were randomized to receive intravenous prophylaxis with either CMV hyperimmune globulin (CMV-HIG) or a control immune globulin (control-IG) with low anti-CMV titer. Prophylaxis was continued until day 93 after BMT and the incidence of lethal CMV-IP before day 110 was recorded.

MATERIALS AND METHODS

Patients admitted to one of the four participating centers for allogenic bone marrow transplantation between October, 1982 and January, 1984 entered the study after informed consent was obtained. Forty-eight patients had acute leukaemia, malignant lymphoma or chronic myelogenous leukaemia, and one patient had severe aplastic anaemia at the time of transplantation (Table 1). All patients were

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conditioned with cyclophosphamide and total body irradiation prior to bone marrow infusion. Methotrexate or cyclosporine A was given as prophylaxis against acute graft-versus-host disease (GvHD).

Patients were included regardless of pretransplant anti-CMV titer.

Granulocyte transfusions were given to only 2 patients. In both cases, the donors were seronegative.

CMV-HIG (Cytotect^R, Biotest, Frankfurt) was obtained from plasma of normal volunteers selected for high anti-CMV titer. Control-IG (Intraglobin^R, Biotest, Frankfurt) was obtained from unselected volunteer donors. IgG molecules were isolated after stabilization with beta-propiolactone.

The IgG antibody titers (ELISA) were 1: 50,000 at a protein concentration of 10 g/100 ml and 1: 2,000 at a protein concentration of 5 g/100 ml, respectively.

CMV-HIG or control-IG were administered intravenously at a dosage corresponding to 0.1 g protein/kg b.w. on days -7, $+13$, $+33$, $+53$, $+79$ and $+93$.

Patients were monitored for serological and virological evidence of CMV-infection. However, results from this part of the study will be reported later.

Diagnosis and classification of IP was based on histological examination of lung tissue obtained by biopsy or at autopsy.

RESULTS

Patients included in the two groups were comparable with regard to age and diagnosis (Table 1). They were similar with respect to remission and relapse state. The single patient with severe aplastic anaemia was randomized to control-IG.

No significant difference in transfusion requirements was observed (Table 2). The pretransplant recipient anti-CMV titer was positive in 60% of the patients, equally distributed between the groups.

Moderate or severe acute GvHD occured in 43% of the patients with approximately the same incidence in CMV-HIG and control-IG treated patients (Table 3).

Table 4 shows the main causes of death before day 110 post BMT. Interstitial pneumonitis was the cause of death in 11 of 49 patients. In 7 cases, histology at biopsy or autopsy was diagnostic of CMV-IP, and this was supported by positive virus cultures. One of 26 CMV-HIG treated patients died from CMV-IP before day 110 in contrast to 6 of 23 in the control group ($p < 0.05$). Four cases of interstitial pneumonitis were classified as idiopathic. One case occurred in the control group, versus 3 cases in the CMV-HIG group (not significant). There was no significant difference between the groups with regard to total survival on day 110.

Two patients in the CMV-HIG group and one patient in the control-IG group died of CMV-IP after day 110, i.e. after cessation of the prophylactic treatment.

DISCUSSION

The present study strongly suggests that the incidence of lethal CMV-IP can be markedly reduced by CMV-HIG prophylaxis. Clearly, there is a need for an extended study in order to determine the optimal duration of prophylaxis after BMT. Several other questions remain to be answered: First: Analysis of serological and virological data may elucidate the question, whether CMV-HIG is capable of reducing the incidence of non-lethal CMV infection in BMT patients. Second: It remains to be determined, whether CMV-HIG is effective in all patients or whether the effect is confined to patients who are seronegative prior to transplantation. Third: CMV infections are known to occur more frequently in patients with GvHD (1). With the design used in the present study it may be possible to analyse the interesting interplay between infection and GvHD seen in patients receiving allogenic BMT.

CONCLUSION

Intravenous prophylaxis with CMV-hyperimmune globulin reduces the incidence of CMV interstitial pneumonitis occurring within 110 days post BMT.

Hôwever, the optimal duration of CMV-hyperimmune globulin prophylaxis remains to be determined.

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Table 1 Patient categories.

	CMV-HIG	Control-IG
Total number:	26	23
Age range, yrs	7-43	11-38
Age median, yrs	22	23
AML	9	12
ALL	6	7
AUL	2	0
CML (chronic phase)	8	3
Malignant lymphoma	1	
Severe aplastic anaemia		1

Table 2 Transfusions, mean number of units per patient.

	CMV-HIG	Control-IG
Whole blood	0.6	1.1
Thrombocytes	23	19
Erythrocytes	3.6	4.6
Granulocytes	0	0.2

Table 3 Incidence of acute graft-versus-host disease.

Grade	CMV-HIG	Control-IG	Total
0-mild	16	12	28
Moderate-severe	10	11	21

Table 4 Main causes of death before day 110.

	N	DEATH BEFORE DAY 110			
		CMV-IP[x]	Idiopathic IP	Other causes	Total
CMV-HIG	26	1	3	3	7 (27%)
Control-IG	23	6	1	2	9 (39%)

[xx]

[x] By histological criteria

[xx] $P < 0.05$ (x^2, two-sided test, Yates correction)