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No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients

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Summary:

A randomized multicentre study was conducted to evaluate the effect of anti-CMV hyperimmune globulin in the prophylaxis of CMV infections in CMV seronegative allogeneic BMT patients who received a transplant from a seropositive donor or who had received blood products unscreened for CMV during the treatment before BMT. Twenty-eight patients were included in the study. Thirteen were randomized to receive and 15 not to receive intravenous CMV hyperimmune globulin. A dose of 0.4 g/kg of immunoglobulin was given on day −8 and 0.2 g/kg on days −1, +7, +14, +21, +28, +35, +42, +56 and +70 in relation to the day of transplantation. Among the 15 patients not given immunoglobulin CMV was isolated in three, and two of them developed clinical CMV disease. In addition, one more patient developed CMV antibodies without virus isolation. In five of the 13 patients given immunoglobulin the virus could be isolated, and four of them developed CMV disease. One additional patient showed seroconversion but no other findings of CMV infection. The incidence of acute and chronic GVHD was similar in the two arms. There was no significant difference in survival. In conclusion, the present results do not indicate a beneficial effect of CMV hyperimmune globulin infusions in the prophylaxis of CMV infection or disease in seronegative allogeneic bone marrow transplant recipients from a seropositive donor.

Keywords: cytomegalovirus hyperimmune globulin; cytomegalovirus infection; allogeneic bone marrow transplantation

Cytomegalovirus (CMV) infection is very common after allogeneic bone marrow transplantation (BMT)[1,2] and may cause serious, even fatal disease. Specific prophylaxis of CMV infection is possible with antiviral drugs and CMV hyperimmune globulin or plasma.[3–5] The prophylaxis may be particularly important for CMV seronegative patients who become exposed to the virus by a marrow graft from a CMV positive donor or by blood products. Several randomized trials of the effectiveness of CMV hyperimmune globulin or plasma in the prevention of CMV infection and disease in BMT patients have given conflicting results.[4,6] We have carried out a randomized multicentre trial to study the effectiveness of intravenous CMV hyperimmune globulin in the prevention of CMV infection and disease in seronegative bone marrow transplant recipients who received a transplant from a seropositive donor or had been given blood products unscreened for CMV before BMT.

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Patients and methods

Patients

Twenty-eight CMV seronegative patients treated with allogeneic BMT were included in the study. All the patients were CMV seronegative as determined by ELISA-based techniques at each centre 3–4 weeks prior to the transplantation. They either received a transplant from a CMV seropositive donor (25 patients), or the transplant was from a seronegative donor but blood transfusions unscreened for CMV had been given during the treatment before the transplantation (three patients). The patients were randomized to receive ($n = 13$) or not to receive ($n = 15$) CMV hyperimmune globulin. Patient characteristics are shown in Table 1. The pretransplant conditioning and GVHD prophylaxis were given according to routine practice at each centre. More than half of the patients received low-dose acyclovir for herpes simplex virus prophylaxis, but no other prophylactic antiviral agent was permitted. The immunoglobulin treated and control groups were similar, no significant differences were observed.

Immunoglobulin

The CMV hyperimmune globulin was produced by the Finnish Red Cross Blood Transfusion Service (Helsinki, Finland). Plasma was collected from selected plasmapheresis donors with high antibody titre against CMV. EIA (Cytomegalovirus IgG EIA kit; Labsystems, Helsinki, Finland) was used for screening, and the cut-off limit was set to a level adopted by the Massachusetts Public Health

Table 1 Patient characteristics, conditioning, and GVHD prophylaxis

	CMV-Ig+ n = 13	*Controls n = 15*
Age, median (range)	26 (9–55)	33 (2–51)
Sex, male:female	8:5	11:4
Diagnosis		
Acute myeloid leukaemia	3	2
Acute lymphatic leukaemia	4	3
Acute undifferentiated leukaemia		1
Chronic myeloid leukaemia	5	4
Myelodysplastic syndrome		1
Myeloma		3
Lymphoma		1
Fanconi's anaemia	1	
Acute leukaemia or chronic myeloid leukaemia		
1st remission or chronic phase	6	8
>1st remission or chronic phase	6	2
Donor		
HLA-identical sibling	11	14
Unrelated donor	2	1
CMV positive donor	12	13
Unscreened blood products	1	2
Conditioning		
Bu + CY	8	6
TBI + CY	4	9
Procarbazine + CY + TAI + ATG	1	
GVHD prophylaxis		
CsA + short MTX	7	7
CsA + short MTX + MP	1	4
MTX	3	2
MTX + short CsA	1	1
MTX + MP	1	1
Acyclovir prophylaxis		
Yes	5	11
No	8	4

CMV-Ig + = CMV hyperimmune globulin-treated patients; TAI = total abdominal irradiation; ATG = antithymocyte globulin; MP = methylprednisolone.

Biologic Laboratories (Boston, MA, USA), where Dr Jeanne Leszczynski kindly performed the comparative testing of the plasma. Of the Finnish blood donor population, 7% have a titre which is equal to or higher than the cut-off limit. The plasma was fractionated in the Central Laboratory of the Swiss Red Cross Blood Transfusion Service (Basel, Switzerland) using the same method as for the fractionation of Sandoglobulin (Swiss Red Cross Blood Transfusion Service). In this method the Fc-portion of the immunoglobulin is not affected. The final product was tested for the presence of neutralizing anti-CMV antibodies in the Statens Bakteriologiska Laboratorium (Stockholm, Sweden) and in the Bernard Nocht-Institute (Hamburg, Germany). The batch of anti-CMV intravenous immunoglobulin used in this study contained 80 Paul Ehrlich units (PEU)/mg.

A 6% solution of the hyperimmune globulin was administered in the dose of 0.4 g/kg on day −8, and in the dose of 0.2 g/kg on days −1, +7, +14, +21, +28, +35, +42, +56, and +70 in relation to the day of transplantation.

CMV serology and isolation

CMV IgG antibody concentrations were determined with ELISA methods in routine use at each centre 3–4 weeks before the transplantation to confirm the seronegativity of the patient, on the days of immunoglobulin administration before the infusion (or on the corresponding days in the control group), and on days +90, +120, +150 and +180. CMV antibody concentrations were also determined on the day after the immunoglobulin infusion.

Conventional CMV culture, shell vial rapid culture, or direct demonstration of early antigen (collectively called CMV isolation hereafter), as in routine use at each centre, was carried out on blood, urine, and pharyngeal swab samples on the same days as the antibody determinations. CMV isolation was also done from bone marrow aspirates, lung or liver biopsies, and bronchoalveolar lavage fluid whenever performed because of a clinical problem during the study period.

CMV infection and CMV disease

A patient was regarded as having a CMV infection when the virus was demonstrated with any of the above mentioned techniques or when there was a seroconversion. A patient with positive CMV isolation who had symptoms or signs typically caused by this virus (cytopenia, fever, interstitial pneumonia, gastroenteritis, hepatitis, retinitis) with no obvious other cause was regarded as having CMV disease.

Blood transfusions

The red cell and platelet transfusions given to the patients during and after the transplantation were from CMV negative donors and/or filtered.

Statistics

The characteristics of the study groups were compared using Fisher's exact test. Kaplan–Meier survival curves were analysed with the log-rank test.

Results

Thirteen patients were randomized to receive immunoglobulin. The average increase of serum anti-CMV IgG level was 143 Abbott units (AU) (4.8 PEU)/ml after a 0.4 g/kg dose and 108 AU (3.6 PEU)/ml after a 0.2 g/kg dose.

Ten out of the total 28 patients developed CMV infection and six had CMV disease. Four patients had CMV isolated from blood, four from urine, three from the throat, one from a liver biopsy, and one from broncho-alveolar lavage fluid. The median time from the transplantation to the first isolation was 49 days.

Among the 13 patients who received immunoglobulin, the virus could be isolated in five (Table 2). Four of them developed CMV disease. One had cytopenia and fever, one interstitial pneumonia, one pneumonia, hepatitis and cytopenia, and one hepatitis. In two of the four patients with CMV disease, seroconversion could not be evaluated because of immunoglobulin infusions and early death. Two of the three remaining patients with positive CMV isolation seroconverted. One additional patient had a seroconversion,

Table 2 CMV infection, CMV disease and GVHD

	CMV-Ig+[a] *(n = 13)*	*Controls (n = 15)*
CMV isolation	5	3
CMV seroconversion	3/7 (6 NE)[b]	2
CMV disease	4	2
Acute GVHD	7	6
Grades II–IV	4	2
Chronic GVHD[c]	3/10	6/15

[a]CMV hyperimmune globulin treated patients.
[b]CMV antibody status not evaluable because of immunoglobulin treatment and early death.
[c]Evaluable patients.

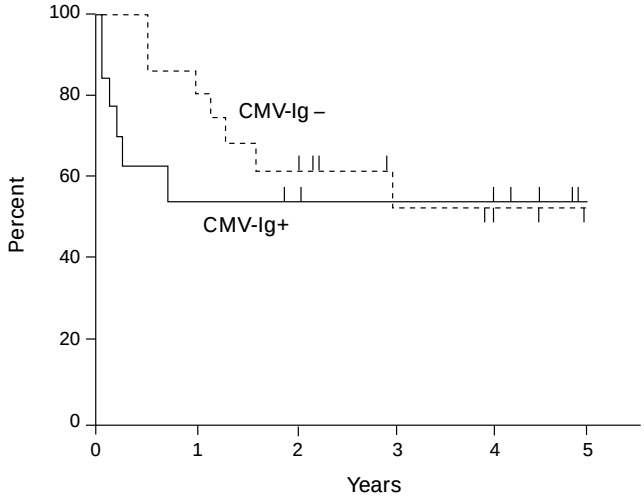

Figure 1 Survival in the immunoglobulin-treated patient group and the control group.

but CMV could not be isolated and there were no clinical signs of CMV disease.

Among the 15 patients not given immunoglobulin CMV could be isolated in three patients. Two of them developed CMV disease, hepatitis in one and pneumonia and cytopenia in the other. One of the patients with CMV disease showed seroconversion, the other patients with positive CMV isolation did not seroconvert. Furthermore, one additional patient developed CMV antibodies, but attempts to isolate the virus were negative, and the patient had no clinical symptoms.

Of the four patients given immunoglobulin prophylaxis who developed CMV disease, two had received low-dose acyclovir prophylaxis against herpes simplex virus. Both patients in the control arm who had CMV disease had been given prophylaxis with low-dose acyclovir. Two of the four patients with CMV infection but no CMV disease had received acyclovir.

One of the three patients who had a seronegative donor but had received unscreened blood products developed CMV infection but no CMV disease.

There was no difference between the study groups in the incidence or severity of GVHD (Table 2). There was no clear association between the presence of GVHD and CMV disease. Of the six patients with CMV disease, two had no GVHD, two had acute GVHD grade I and two grade II.

Figure 1 shows the Kaplan–Meier survival curves of the patients given immunoglobulin and the controls. The survivals did not differ significantly.

Discussion

In this study CMV seronegative allogeneic BMT patients who received a transplant from a CMV seropositive donor or who had received blood transfusions unscreened for CMV had no apparent benefit from treatment with CMV hyperimmune globulin. There was no reduction in CMV infection, disease or seroconversion as compared with patients not given immunoglobulin.

The effects of CMV hyperimmune globulin infusions in the prevention of CMV infection and disease in CMV seronegative BMT recipients have been studied in several trials. Meyers *et al*[7] and Winston *et al*[8] observed a reduction in either CMV infection or CMV disease as a result of CMV hyperimmune globulin administration. No effect was seen in the study of Bowden *et al*.[9] Among seronegative recipients of marrow from a seropositive donor, Bowden *et al*[10] found a reduction of CMV infections in patients given CMV hyperimmune globulin prophylaxis, but there was no difference in the incidence of CMV disease. In other studies no positive effect was found in this subgroup of patients.[7,9] With the exception of the study by Bowden *et al*,[10] the numbers of seronegative recipients of a graft from a seropositive donor, when specified, have been small, and the present patient material is one of the largest published.

More than half of the patients had received low-dose acyclovir prophylaxis against herpes simplex virus infections. Whether this drug was given or not was, however, probably not an essential factor in the development of CMV infection and disease, since four of the six patients with CMV disease had received acyclovir prophylaxis.

The results of the present study have to be interpreted with caution. The number of patients is relatively small, and there is heterogeneity in the study population in regard to the diagnosis of the underlying disease as well as the management at different centres. However, CMV infection and disease was seen in about 30% of patients given CMV hyperimmune globulin prophylaxis, and it is unlikely that a significant prophylactic effect would have been seen even if the patient groups had been considerably larger, which was the major reason for stopping this trial.

In conclusion, the present results do not indicate a beneficial effect of CMV hyperimmune globulin infusions in the prophylaxis of CMV infection and disease in seronegative allogeneic bone marrow transplant recipients from a seropositive donor.

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