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Cytomegalovirus Disease in Intestinal Transplantation

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OVER THE LAST 4 years, intestinal transplantation has become a feasible therapeutic option for patients with irreversible intestinal failure.[1] However, it has been shown that intestinal transplant recipients have a high incidence of cytomegalovirus (CMV) infection.[2] In this study, we analyzed the incidence of CMV disease and CMV-related mortality after intestinal transplantation.

MATERIALS AND METHODS

From May 1990 to July 1994, 62 patients (22 isolated intestine [I], 29 liver and intestine [I/L], and 11 multivisceral [MV]) received 66 intestinal allografts at our center. There were 28 adults and 34 children, with ages ranging from 6 months to 58 years. Postoperative immunosuppression was with tacrolimus (FK 506), steroids, and in selected cases azathioprine (AZA). Donor and recipient procedures are described elsewhere.[3]

Tissue sampling for CMV was performed when it was clinically indicated. Invasive CMV disease was diagnosed by histopathologic findings and/or by isolation of the virus from tissue specimens. Tissue invasion was determined by detection of typical CMV inclusion bodies along with predominant neutrophilic infiltration and/or unequivocal immunoperoxidase staining of the virus. Isolation of the virus was confirmed by either the shell vial technique or by standard culture.

Forty-three of 62 recipients received gancyclovir prophylaxis (5 mg/kg) twice a day for 2 to 3 weeks in children, and for 3 weeks to 3 months in adults, followed by acyclovir for several months. CMV disease was treated by either gancyclovir (5 mg/kg twice a day), Foscarnet (60 mg/kg three times a day), CMV immunoglobulin (100 mg/kg every 2 weeks), or a combination of these agents.

The effect of CMV disease on patient and graft survival was studied. Chi-square, Kaplan-Meier, and log rank tests were used for statistical analysis. Statistical significance was achieved if the P value was less than .05.

RESULTS

Twenty-one (33%) of 62 recipients developed CMV disease after transplantation during a 2-month to 4-year follow-up period. CMV disease occurred a total of 49 times; 10 patients developed only one episode and 11 patients developed two to eight episodes of CMV disease. The type of CMV diseases seen were graft enteritis (41), native gastroduodenitis (3), hepatitis (2), pneumonitis (2), and retinitis (1). CMV disease occurred more frequently in adults (46%) than in children (20%) ($P < .05$). This trend was more obvious in recurrent CMV disease ($P < .005$). The type of transplant procedure did not affect the frequency of CMV disease (I = 36%, I/L = 24%, MV = 45%).

Table 1 shows the frequency of CMV disease compared to the CMV serology of the donor and recipient. No CMV disease was seen in CMV-seronegative patients receiving CMV-seronegative grafts. A statistical difference was found between this group and the other groups with the frequency of CMV disease ($P < .0005$). Five patients developed persistent CMV disease (>3 episodes in 1 year). Persistent CMV disease was seen only in CMV-seronegative adult isolated intestinal recipients who received CMV-seropositive grafts. The frequencies of CMV disease without (8 of 19, 42%) and with (13 of 43, 30%) gancyclovir prophylaxis were similar. Gancyclovir prophylaxis was not effective in preventing CMV disease.

Table 1. Frequency of CMV Disease and CMV Serology

Donor/Recipient CMV Serology	Follow-up (mo)	Frequency of CMV Disease	Frequency of Recurrent CMV Disease
D−/R−	19	0/26 (0)	0/26 (0)
D−/R+	16	5/12 (41%)	1/12 (8%)
D+/R−	12	10/16 (62%)	7/16 (43%)
D+/R+	9	5/8 (62%)	2/8 (25%)

Overall survival of patients with CMV disease was not significantly worse than patients without CMV disease; however, patients with CMV disease had significantly higher late (>3 months posttransplant) mortality ($P = .0017$) and graft loss ($P = .0008$) than patients without CMV disease. Death after 3 months was defined as late mortality, because the average first onset of CMV infection was 90.7 days.

DISCUSSION

Compared to other types of transplantation, infectious complications occur more frequently after intestinal transplantation, because higher levels of immunosuppression are needed to prevent rejection.[4-6] Our results show that CMV disease occurs frequently after intestinal transplantation and is a major contributing factor in late mortality and graft loss. To prevent CMV disease, CMV-seropositive grafts should be avoided for isolated intestinal transplantation; however, this policy should not be applied to I/L and MV recipients, because they are in dire need of life-saving organ (liver) transplantation. Fortunately, we have not seen persistent CMV disease in I/L or MV transplantation recipients. To reduce the incidence of CMV disease, improvement of prophylactic antiviral therapies and avoidance of

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Supported by research grants from the Veterans Administration and Program project grant DK 29961 from the National Institutes of Health, Bethesda, Maryland.

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0041-1345/95/$3.00/+0

heavy immunosuppression by using new strategies for recipient immunomodulation are required.

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