1703

Factors Associated With Recurrent Cytomegalovirus Disease After Small Bowel Transplantation

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CYTOMEGALOVIRUS (CMV) disease results from a complex interplay among a variety of factors, the consequences of which are differences in the incidence and severity of CMV disease across different transplant populations.[1-3] In May 1990, the small bowel transplantation (SBx) program was initiated at our institution. In this study we analyze the incidence and timing of CMV disease after SBx and we assess risk factors for CMV disease in this new transplant population.

MATERIALS AND METHODS

Patient Population

From May 1990 to March 1993, 40 patients underwent SBx at the University of Pittsburgh Medical Center. Four patients died during the first month after transplantation and were excluded from the study. The study population included 36 patients who received 38 grafts. There were 20 adults and 16 children with an age range between 6 months and 50 years. Thirteen patients (36%) received an isolated SBx, 18 (50%) received SBx and liver and 5 (14%) received multivisceral grafts.

Immunosuppression and CMV Prophylaxis

Immunosuppression included FK 506 and steroids as previously described.[4] Twenty-five patients (69%) were treated also with azathioprine. Twenty-two patients received ganciclovir prophylaxis between 21 and 90 days after SBx. Sixteen children and 1 adult received only CMV-seronegative blood products.

RESULTS

Fourteen patients (39%) developed 25 episodes of CMV disease. Six had a single episode, 5 had 2 episodes, 2 had 3 episodes, and 1 had 4 episodes. The first, second, and third episodes of CMV disease occurred at a mean of 48 ± 23, 131 ± 68, and 173 ± 19 days, respectively, after transplantation. The types of CMV disease were: 20 (80%) enteritis, 2 (8%) hepatitis, 2 (8%) pneumonitis, and 1 (4%) syndrome. Table 1 shows the relationship between donor/recipient CMV serologic status and the frequency of CMV disease.

Table 1. Incidence of CMV Disease after Small Bowel Transplantation

Donor/Recipient CMV Status (n = 38)	Patients (n = 14) (%)	Episodes (n = 25)
D−/R− (16)	0	0
D−/R+ (8)	4 (50)	6
D+/R+ (3)	2 (75)	3
D+/R− (11)	8 (73)	16

Univariate and multivariate analyses to study risk factors for CMV disease were performed using Cox's proportional hazards model. Factors analyzed included age, type of transplantation, donor and recipient serologic status, use of ganciclovir prophylaxis, blood products transfused, the cumulative blood level of FK 506, and cumulative doses (adjusted to weight) of OKT3, azathioprine, and pulse and maintenance doses of steroids. Multivariate analysis showed that the factors associated with a first episode of CMV disease were: CMV-seronegative recipient of a CMV-seropositive graft (relative risk [RR] 6.4, 95% confidence interval [CI] 1.7 to 24.7, $P = .007$), the cumulative blood level of FK 506 (RR 2.3, 95% CI 1 to 5.2, $P = .04$), the cumulative dose of pulse of steroids (RR 2.6, 95% CI 1 to 6.9, $P = .06$) and the cumulative dose of maintenance steroids (RR 5.2, 95% CI 1.1 to 23.1, $P = .03$). The only 2 factors independently associated with recurrent CMV disease were CMV-seronegative recipient of CMV-seropositive graft (RR 10.1, 95% CI 1.9 to 52.5, $P = .006$) and the cumulative doses of steroid boluses (RR 15.1, 95% CI 1.6 to 125.4, $P = .01$).

DISCUSSION

This study showed that SBx transplantation is associated with a high incidence of CMV disease. Although the morbidity associated with CMV infection is quite variable, 2 factors have been associated with an elevated incidence of CMV disease: primary CMV infection after transplantation and the type and amount of immunosuppression given. Primary CMV infection occurred in 73% of CMV-seronegative recipients who received grafts from CMV-seropositive donors, and accounted for 64% of episodes of disease. This contrasts with the lack of infection and disease in seronegative recipients of seronegative grafts. However, the morbidity of CMV infection was also high in secondary infections, because 55% of CMV-seropositive recipients developed disease. The multivariate analysis showed that the cumulative FK 506 levels, and amount of steroid given in boluses and for maintenance, were also risk factors for CMV disease. This suggests that the

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increased immunosuppression that many of these patients required also played an important role in the high incidence of CMV disease after SBx. Because long courses of ganciclovir prophylaxis were not sufficient to prevent CMV disease, new strategies are needed. Avoiding transplantation of CMV-seropositive grafts into CMV-seronegative recipients and new approaches to prevent overimmunosuppression are 2 potential alternatives to decrease the incidence of CMV disease in SBx.

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