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THERAPEUTIC USE OF GANCICLOVIR FOR INVASIVE CYTOMEGALOVIRUS INFECTION IN CADAVERIC RENAL ALLOGRAFT RECIPIENTS

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ABSTRACT

Between November 1987 and September 1989, 419 cadaveric renal transplants were performed at our university. Of the patients 36 (8.6%) had invasive cytomegalovirus infection documented by gastric or duodenal mucosal biopsy in 23 (64%), bronchoalveolar lavage in 12 (33%), allograft biopsy or nephrectomy specimen in 5 (14%) and/or liver biopsy in 1 (3%). Cytomegalovirus severity was defined as mild in 27 patients, moderate in 6 and severe in 3. Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)-guanine] was begun once the diagnosis was confirmed by histology or culture at a median of 56 days from transplantation (range 28 to 133 days). Duration of ganciclovir therapy was a minimum of 7 days or until fever was absent for 5 consecutive days (mean 12.2 ± 3.5 days, range 4 to 21). Ganciclovir was well tolerated and side effects were limited to de novo neutropenia (7 patients), thrombocytopenia (2) and rash (1). Initial clinical improvement was observed in all patients. Two patients had recurrent cytomegalovirus infections that responded to a second course of ganciclovir. The 1-year actuarial patient survival was 100%. At a mean followup of 12.7 ± 6.2 months 19 patients retained allograft function with a mean serum creatinine of 2.5 mg./dl. (range 1.2 to 4.6). Ganciclovir appears to be a safe and effective drug for the treatment of tissue invasive cytomegalovirus infection in cadaver renal transplant recipients. Prompt institution of this drug at diagnosis of invasive cytomegalovirus may lower the mortality rate formerly associated with this disease.

KEY WORDS: cytomegaloviruses, kidney transplantation, cadaver, ganciclovir

Renal transplant recipients with tissue invasive cytomegalovirus infection have had as much as a 25% risk of dying, even when immunosuppression is decreased or stopped.[1] Until recently, there was no effective therapy for this group of patients. Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)-guanine] is metabolized by viral kinases within infected host cells to yield 2'-nor-2'deoxyguanine, a potent inhibitor of herpesvirus deoxyribonucleic acid polymerase.[2] Although previous studies have reported its usefulness for life or sight-threatening cytomegalovirus infections in immunocompromised hosts,[3-10] the optimum use of ganciclovir in cadaver renal transplant recipients with tissue invasive cytomegalovirus has not yet been established. We report our experience with the use of ganciclovir in treating tissue invasive cytomegalovirus infection following cadaver renal transplantation. The results suggest that this drug is well tolerated and is effective in arresting the progress of invasive cytomegalovirus to life-threatening disease with little or no drug-related morbidity.

MATERIALS AND METHODS

Patients. Of 419 cadaveric renal allograft recipients who underwent transplantation at our university between November 1987 and September 1989, 36 (8.6%) had tissue invasive cytomegalovirus infection, including 25 men and 11 women (mean age 42.1 ± 11.5 years, range 18 to 71). Cytomegalovirus serology was determined by solid phase fluorescence immunoassay of IgG antibodies to cytomegalovirus. Immunoassay titers of less than 20 were considered negative, 20 to 30 equivocal and more than 30 seropositive. In 16 of the 36 patients (44%) an allograft from a cytomegalovirus seropositive donor was transplanted into a seronegative recipient. Nine cases (25%) were seropositive to seropositive, 5 (14%) were seronegative to seropositive and 4 (11%) were seronegative to seronegative. Cytomegalovirus serology was not available from 2 donors. Prophylactic acyclovir was given to all patients at either low dose (200 mg. twice daily in 28) or high dose (up to 3,200 mg./24 hours based on renal function in 8).[11]

Immunosuppression. A standard immunosuppressive regimen including cyclosporine (15 to 17.5 mg./kg. orally before transplantation, subsequently tapered to maintain whole blood high performance liquid chromatography levels of 100 to 200 ng./ml.), prednisone (tapered to 0.1 mg./kg. by 3 months) and azathioprine (3 to 5 mg./kg. preoperatively tapered by 1 mg./kg. per day to a maintenance dose of 1 mg./kg. per day) was used in all patients. A total of 8 patients (22%) received prophylactic OKT3 (5 mg. daily for 10 to 14 days). Rejection episodes were defined clinically by an increase in serum creatinine accompanied by fever, decreased urinary output, graft tenderness and/or weight increase and were confirmed by a core needle biopsy. Rejection was treated with increased steroid therapy and/or a 10 to 14-day course of OKT3.

Definitions of cytomegalovirus infection. Cytomegalovirus infection was clinically suspected in patients with unexplained fever 38.3C or greater for more than 2 days, leukopenia (white blood count less than 4,000/mm.^{3}), thrombocytopenia (platelet count less than 100,000/mm.^{3}) and/or diffuse pulmonary infiltrates. Cultures of blood, urine and pharyngeal washings were performed in all patients. When clinically indicated, the presence of tissue invasive cytomegalovirus was sought by bronchoalveolar lavage, upper gastrointestinal endoscopy with biopsy, liver biopsy, lumbar puncture, bone marrow examination and/or renal allograft biopsy. The diagnosis of tissue invasive

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cytomegalovirus required histological documentation of cytomegalic inclusion bodies and/or positive tissue cultures for cytomegalovirus. An increase in serum antibody titer and/or seroconversion was considered insufficient for the diagnosis of tissue invasive cytomegalovirus. Only those patients with invasive cytomegalovirus infection as defined by these criteria were considered as candidates for therapy with ganciclovir.

Categories of cytomegalovirus severity. Disease severity was based on 6 clinical features defined previously by Peterson et al: 1) prolonged fever (temperature 38.3C or greater for more than 7 days), 2) diffuse pulmonary infiltrates, 3) gastrointestinal bleeding, 4) pancreatitis, 5) transplant nephrectomy and 6) development of another systemic infection.[1] Patients with severe cytomegalovirus infection had at least 3 of these 6 features, patients with moderate disease had 2 of these features and mild cytomegalovirus disease was defined by the presence of no more than 1 of these features.

Ganciclovir therapy. Ganciclovir was made available with informed consent to patients with proved tissue invasive cytomegalovirus on a compassionate release basis. The protocol was approved by the local Institutional Review Board. Immediately after the diagnosis of tissue invasive cytomegalovirus was established, ganciclovir was administered intravenously at 2.5 mg./kg. every 12 hours if the calculated creatinine clearance was more than 50 ml. per minute, 2.5 mg./kg. every 24 hours for a creatinine clearance of 25 to 50 ml. per minute and 1.25 mg./kg. every 24 hours for a creatinine clearance of less than 25 ml. per minute. Hemodialysis patients received 1.25 mg./kg. after each dialysis and every 24 hours. Patients on peritoneal dialysis were given 1.25 mg./kg. every 48 hours. Treatment lasted for a minimum of 7 days and was continued until the patient was afebrile for 5 consecutive days. Duration of ganciclovir therapy was extended if persistent symptoms or evidence of widely disseminated infection were present. Baseline and serial complete blood counts, serum electrolyte determinations and renal function tests were performed daily in all patients. Liver function tests were done twice weekly or daily for patients with hepatitis. End points used to evaluate the outcome of cytomegalovirus infection included patient survival, resolution of clinical symptoms, reversal of chest radiographic, hematologic and liver function abnormalities, and elimination of the virus from the affected tissue or body fluid as determined histopathologically or by culture.

Statistical analysis. Actuarial patient and graft survival rates were determined by life-table analysis using BMDP statistical software. Potential risk factors were studied for their effects on cytomegalovirus severity and treatment outcome, and were compared by chi-square analysis.

RESULTS

Diagnosis of tissue invasive cytomegalovirus infection. A total of 36 patients with clinically suspected cytomegalovirus infection had tissue invasive cytomegalovirus a mean of 60.6 days (median 55.8, range 28 to 133) after transplantation. Cytomegalovirus infection was clinically suspected because of unexplained fever in 32 patients (89%), leukopenia in 21 (58%), thrombocytopenia in 6 (17%) and/or diffuse pulmonary infiltrates in 9 (25%). Of the patients 27 (75%) had mild, 6 (17%) had moderate and 3 (8%) had severe infection (table 1). There were no lethal infections. The pattern of cytomegalovirus tissue involvement was stomach/duodenal mucosa in 26 patients (72%), lung in 14 (39%), allograft in 5 (14), liver in 1 (3%) and multiple sites in 11 (31%). Biopsies were considered positive for cytomegalovirus based on viral culture or histology/immunomicroscopy. Tissue diagnosis was accompanied by positive viral blood cultures in 17 patients (46%), urine cultures in 19 (53%) and pharyngeal washings in 2 (5%). A total of 8 patients (22%) underwent treatment for concurrent infections, including esophageal or gastric candidiasis (4), Pneumocystis carinii pneumonia (1), pseudomonal pneumonia (1), pseudomonal allograft pyelonephritis (1) and Escherichia coli urosepsis (1).

Management of immunosuppression during cytomegalovirus infection. Azathioprine was discontinued or temporarily withheld in 31 patients, decreased in 4 and continued without change in dosage in 1 following the diagnosis of cytomegalovirus infection. Cyclosporine was stopped in 6 patients with nonfunctioning allografts at cytomegalovirus diagnosis. In the remainder cyclosporine was either temporarily withheld (6, mean 7 days) or continued with (4) or without (20) dosage reduction. Prednisone dosage was lowered in 23 patients and continued without change in the remaining 13.

Outcome of ganciclovir therapy. A total of 36 patients with documented tissue invasive cytomegalovirus infection was treated for 12.2 ± 3.5 days (range 4 to 21) and followed for an average of 12.7 months. One patient refused further therapy after 4 days but showed no evidence of residual or recurrent disease. Ganciclovir was well tolerated by all 36 patients. Side effects were limited to transient, de novo leukopenia (white blood count less than 4,000) in 7 patients, thrombocytopenia (less than 100,000) in 2 and rash in 1, none of whom required discontinuation of the drug. Serum creatinine was unaltered by ganciclovir in patients with functioning grafts (mean 4.1 ± 1.6 mg./dl. before and 3.8 ± 1.9 after ganciclovir therapy). Following the initial course of treatment with ganciclovir, all 36 patients had complete resolution of symptoms (fever, fatigue, malaise, cough and abdominal discomfort) associated with cytomegalovirus. A total of 18 patients had positive baseline cultures for cytomegalovirus from at least 1 body fluid with at least 1 followup culture after ganciclovir treatment. The figure summarizes the virological data of these patients before and after ganciclovir therapy. The overall virological responses for patients with initial viremia and/or viruria are summarized in table 2. Viral blood cultures were negative 7.5 ± 3.6 days after starting ganciclovir in 11 of 11 patients (100%) who had positive blood cultures before therapy. Of the 13 patients with initially positive urine cultures 11 (85%) became negative at 8.1 ± 4.8 days and 2 remained positive. All 9 patients with initially positive cultures for blood and urine were cleared after ganciclovir. Tissue sampling was repeated in 7 patients after ganciclovir therapy. In 1 patient with cytomegalovirus pneumonia repeat bronchoalveolar lavage was negative for cytomegalovirus 68 days after ganciclovir. Two stomach biopsies were rendered negative 8.0 ± 9.9 days after treatment and 4 duodenal biopsies were negative at 29.3 ± 20.9 days.

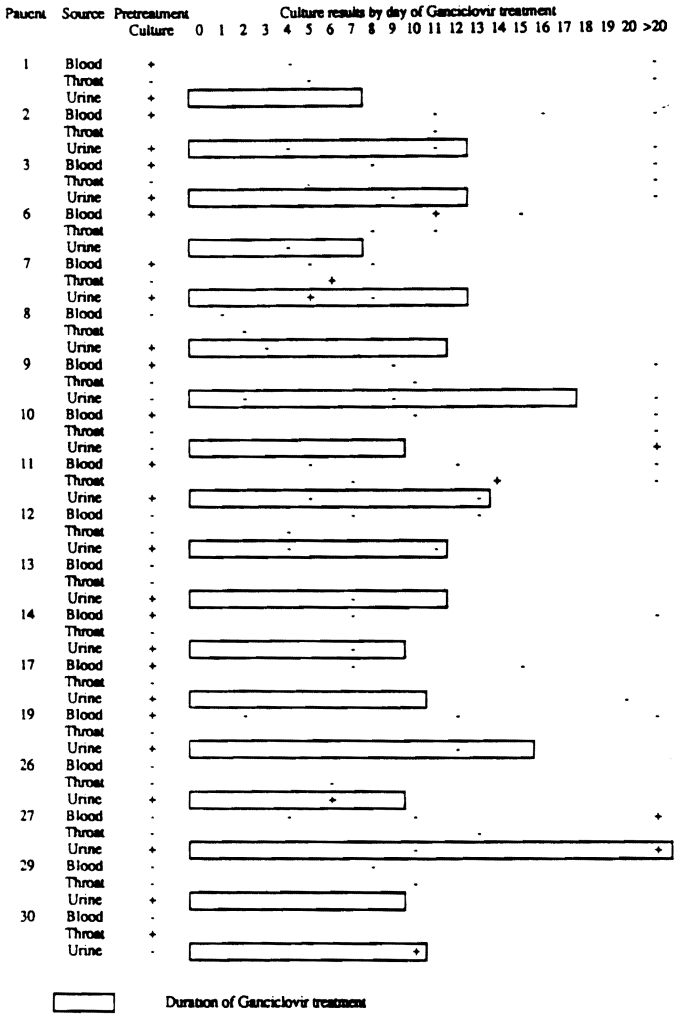
Factors potentially influencing cytomegalovirus severity and outcome. There was no correlation between cytomegalovirus severity and recipient age (more than 45 or 45 or less years), interval to cytomegalovirus onset after transplantation, prior rejection, OKT3 use, use of low dose versus high dose prophylactic acyclovir, or donor/recipient cytomegalovirus serology status (table 3). Graft survival, however, was higher in inverse proportion to disease severity, with 17 of 27 grafts (63%) still functioning in patients originally having mild, 3 of 6 (50%) in those with moderate and 0 of 3 (0%) in those with severe disease ($p < 0.02$).

Graft losses. There was a total of 17 graft losses in this series; 4 were lost at the onset of cytomegalovirus infection (primary graft nonfunction in 2 and chronic rejection in 2). The remaining 13 graft losses occurred at a median of 5 weeks (range 10 days to 16 months) following invasive cytomegalovirus infection. One patient underwent allograft nephrectomy after immunosuppression was withheld for transverse myelitis 2 months after treatment with ganciclovir. Concurrently, he had benign cerebrospinal fluid and no evidence of ongoing cytomegalovirus infection. One patient lost the graft to rejection concurrent with acute pancreatitis (with negative cytomegalovirus evaluation) 2 months after treatment, and 1 patient had recurrent oxalosis and graft failure 1 year after ganciclovir.

TABLE 1. *Categories of clinical severity of cytomegalovirus disease*

Category*	No. Pts. (% of total)	No. Pts. (%) in Each Clinical Category With					
		Prolonged Fever†	Diffuse Pulmonary Infiltrates	Gastrointestinal Bleeding	Pancreatitis	Transplant Nephrectomy	Other Systemic Infection
Lethal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe	3 (8)	2 (67)	3 (100)	0 (0)	2 (67)	3 (100)	2 (67)
Moderate	6 (17)	4 (67)	2 (33)	0 (0)	1 (17)	3 (50)	2 (25)
Mild	27 (75)	0 (0)	4 (15)	0 (0)	0 (0)	3 (11)	4 (15)
Totals	36	6 (17)	9 (25)	0 (0)	3 (8.3)	9 (25)	8 (22)

* Lethal—fatal illness, severe—3 or more clinical features, moderate—2 clinical features, mild—no more than 1 clinical feature.
† Temperature 38.3C or greater for more than 7 hospital days.



Results of viral cultures for cytomegalovirus before, during and after ganciclovir therapy. Patients 10 and 30 had asymptomatic urinary shedding, which was not treated. Patient 27 had recurrent cytomegalovirus in allograft 60 days after initial treatment and was successfully retreated with 14-day course of ganciclovir. Patient 29 had recurrent cytomegalovirus gastritis at 50 days, which was successfully retreated with 19-day course of ganciclovir.

Two patients had primary graft nonfunction and the remaining 8 grafts were lost to rejection.

Cytomegalovirus and rejection episodes. A total of 29 patients (81%) with invasive cytomegalovirus infections had been previously treated for rejection with either increased steroid therapy alone in 18 (50%), OKT3 (5 mg. daily for 10 days) alone in 2 (6%), or OKT3 and steroids in 9 (25%). Prophylactic OKT3 was used in an additional 8 patients. Overall, 19 of the 36 patients (53%) received an average 13.2-day course (range 6 to 19 days) of OKT3 before contracting cytomegalovirus. Of 7 patients who had cytomegalovirus without prior rejection 6 (86%) still have functioning allografts, compared to only 13 of 29 (45%) treated for rejection before cytomegalovirus infection occurred. Of the 13 graft losses that occurred after cytomegalovirus infection (median time 5 weeks) 10 (83%) were due to either acute (2) or chronic (8) rejection.

Patient and graft survival. The overall 1-year actuarial patient and graft survival rates were 100% and 56%, respectively, with a mean followup of 12.7 ± 6.2 months. As indicated previously, survival was significantly better for allografts not treated for rejection before the onset of invasive cytomegalovirus infection (86% versus 45%, $p < 0.05$). Those grafts still functioning have a mean serum creatinine of 2.5 mg./dl. (range 1.2 to 4.6). The 1-year actuarial patient and graft survival rates for all cadaveric renal transplants (419) performed at our institution during the same period were 95% and 80%, respectively.

DISCUSSION

Cytomegalovirus infection is a serious and potentially lethal complication in immunocompromised patients. Renal transplant recipients with cytomegalovirus infection have had mortality rates as high as 25% with even higher death rates (up to 100%) reported for patients with cytomegalovirus pneumonitis.[1, 12, 13] Until recently, the only therapeutic approach for this group of patients was to withhold immunosuppression and provide supportive care. Ten years ago the reported incidence of overt cytomegalovirus in renal transplant recipients was 40 to 50%.[1, 14, 15] In this earlier era aggressive use of certain agents, such as prophylactic antilymphocyte preparations, was associated with the development of severe cytomegalovirus infection.[16] Despite ongoing refinements in immunosuppressive protocols, the incidence of cytomegalovirus infection in renal transplant recipients (cadaveric and living related) has been recently reported to be as high as 29%.[11] A successful approach to reducing the incidence of overt cytomegalovirus in renal transplant patients has been the use of prophylactic acyclovir.[11] However, a finite number of patients will still have cytomegalovirus infection despite acyclovir prophylaxis. The severity of subsequent cytomegalovirus is not lessened by prophylactic acyclovir in these patients.[11] Attempts to treat established cytomegalovirus disease with intravenous acyclovir[11] as well as other antiviral agents[17-20] have been unsuccessful.

Ganciclovir selectively inhibits the replication of herpes group viruses and is much more potent than acyclovir in vitro.[2] This drug has been used to treat severe cytomegalovirus infection in patients with the acquired immunodeficiency syndrome (AIDS), with initial clinical improvement observed in 73 to 77%.[3-5] However, these patients experience significant relapse rates (up to 80%) with up to 100% mortality[3] often due to disseminated cytomegalovirus. Early experience with the use of ganciclovir for life or sight-threatening cytomegalovirus infection in bone marrow[4-7] and solid organ allograft recipients[8-10] has been encouraging, with response rates ranging from 36 to 70%. These patients have responded better to ganciclovir than those with AIDS[7] with less frequent relapse. The use of

TABLE 2. *Effect of ganciclovir on cytomegalovirus viremia and viruria*

Culture Site	Before Ganciclovir		After Ganciclovir					Mean Days (± SD) to Neg. Culture if Initially Pos.
				Initial Culture Neg.		Initial Culture Pos.		
	Total Obtained	No. Cultures Pos. (%)	Total No. Obtained	Remained Neg. No. (%)	Became Pos. No. (%)	Became Neg. No. (%)	Remained Pos. No. (%)	
Blood	33	17 (52)	22	11 (100)	0 (0)	11 (100)	0 (0)	7.5 ± 3.6
Urine	31	19 (61)	16	1 (33)	2 (67)	11 (85)	2 (15)	8.1 ± 4.8

TABLE 3. *Influence of potential risk factors on severity of cytomegalovirus infection*

	Total No. (%)	Cytomegalovirus Severity			P Value (chi-square)
		Mild No. (%)	Moderate No. (%)	Severe No. (%)	
Pt. age (yrs.):					
Less than 45	23 (64)	18 (78)	4 (17)	1 (5)	0.52
45 or more	13 (36)	9 (70)	2 (15)	2 (15)	
Prophylactic acyclovir:					
Low dose	28 (78)	21 (75)	5 (18)	2 (7)	0.85
High dose	8 (12)	6 (75)	1 (12.5)	1 (12.5)	
Days to cytomegalovirus onset after transplantation:					
Less than 40	6 (17)	39 (50)	2 (33)	1 (17)	0.45
40–100	25 (69)	19 (76)	4 (16)	2 (8)	
100 or more	5 (14)	5 (100)	0 (0)	0 (0)	
Prior rejection:					
Yes	29 (81)	21 (72)	5 (17)	3 (11)	0.64
No	7 (19)	6 (86)	1 (14)	0 (0)	
Prior OKT3:					
Yes	19 (53)	14 (74)	4 (21)	1 (5)	0.63
No	17 (47)	13 (76)	2 (12)	2 (12)	
Graft loss:					
Yes	17 (47)	11 (64)	3 (18)	3 (18)	0.15
No	19 (53)	16 (84)	3 (16)	0 (0)	
Serologic status of donor/recipient:*					
Neg./neg.	4 (11)	3 (75)	1 (25)	0 (0)	
Neg./pos.	5 (14)	4 (80)	1 (20)	0 (0)	0.18
Pos./neg.	16 (44)	11 (69)	3 (19)	2 (12)	
Pos./pos.	9 (25)	8 (89)	1 (11)	0 (0)	

* Serologic status defined by cytomegalovirus FIAX antibody (IgG) titer: less than 20—negative, more than 30—positive. Serologic status was unknown in 2 donors.

ganciclovir for the treatment of cytomegalovirus in renal allograft recipients has been reported for small numbers of patients with severe disease.[7-10] Erice et al treated 5 renal transplant recipients with severe cytomegalovirus (pneumonitis, retinitis and gastritis) with improvement observed in 4.[7] However, allograft outcome was not reported. In another study 4 kidney transplant recipients with invasive cytomegalovirus received ganciclovir with a 90% patient survival rate; however, allograft outcome again was not reported.[8] Harbison et al treated 3 kidney transplant recipients with severe cytomegalovirus with clinical improvement in 2 but only 1 retained graft function.[10] Snydman noted only a 59% clinical response in 17 renal allograft recipients but the majority of these patients (12 of 17) had cytomegalovirus pneumonitis.[9] A virological response occurred in 47% of the patients. Two patients with established generalized cytomegalovirus died despite ganciclovir therapy, 1 after multiple courses of the drug. Only 3 of the 6 patients with cytomegalovirus pneumonitis responding to ganciclovir retained allograft function. The results of these initial reports suggest that ganciclovir therapy instituted after the onset of severe cytomegalovirus infection may not represent the optimum use of this drug.[7-10]

In our series ganciclovir was begun in all patients with a diagnosis of tissue invasive cytomegalovirus infection, regardless of the category of disease severity (table 1). Viremia resolved in 100% of the patients and viruria in 85% (overall 92%). Viral shedding in the urine continued asymptomatically in 2 patients but neither had recurrence of invasive disease. Persistent viruria has been reported in up to 70% of the patients treated with ganciclovir,[9] with no adverse impact on clinical outcome. Treatment of cytomegalovirus with ganciclovir was accomplished with only modest reductions in immunosuppression (usually azathioprine). The most common side effect observed was leukopenia in 7 patients (19%), followed by thrombocytopenia in 2 (5%) and skin rash in 1. Leukopenia and thrombocytopenia were transient and did not require cessation of ganciclovir therapy. De novo anemia was not observed. In patients with a functioning graft, renal function was likewise not adversely affected by ganciclovir, with mean serum creatinine of 4.1 mg./dl. before and 3.8 mg./dl. after therapy.

There were no deaths in this series, with an actuarial 1-year patient survival rate of 100%. All patients had clinical improvement with course 1 of ganciclovir despite concurrent infections in 8 (22%). Relapses occurred in 2 patients within 9 weeks of the initial course of ganciclovir but both were successfully retreated. The overall virological clearance rate of 92% compares favorably with other reported series and usually occurred within 1 week of treatment. Although the natural history of viral shedding without treatment of cytomegalovirus is not well documented, these results suggest that ganciclovir has an antiviral effect in vivo.

The overall graft survival of 56% in this series is similar to that reported previously in cytomegalovirus infected patients.[3-10] However, this series differs from these earlier reports in several major respects. The definition of cytomegalovirus (and therefore the use of ganciclovir) was restricted to patients with absolute proof of tissue invasive disease, not merely seroconversion and/or viral shedding. All of our patients received acyclovir prophylaxis, which has recently been shown to lower the incidence (but not the severity) of clinical cytomegalovirus in renal transplant recipients.[11] Thus, our patients acquired cytomegalovirus despite acyclovir prophylaxis and, therefore, they may be regarded as a high risk group. Whether the patients had received low dose or high dose prophylactic acyclovir had no influence on the severity of cytomegalovirus infection ($p = 0.85$). Of the patients in our series 81% had been treated for rejection before acquiring cytomegalovirus. More than 50% of the patients had received OKT3 either as prophylaxis for or treatment of rejection. Therefore, this population was already at higher risk of graft loss even had cytomegalovirus infection not occurred.

These results have led us to a more aggressive approach in patients with proved tissue invasive cytomegalovirus infections. We believe that most are able to tolerate ganciclovir with only a modest (25 to 50%) decrease in the dose of azathioprine. In our experience cyclosporine can be continued at therapeutic doses and steroid doses may be tailored individually. We have continued to decrease or withhold immunosuppression in patients with moderate or severe infections and those with nonfunctioning allografts. The efficacy of ganciclovir in the treatment of tissue invasive cytomegalovirus infection in renal transplant recipients would best be studied in a controlled trial. Our initial experience with ganciclovir suggests that early, aggressive treatment of invasive cytomegalovirus infection can be accomplished with little or no reduction in immunosuppression, thus, affording the opportunity for graft salvage and optimum patient survival (100% in our series). We observed no

progression of cytomegalovirus infection to life-threatening disease with this approach. Reservation of ganciclovir treatment only for patients with severe cytomegalovirus has met with poor results.[6-10] The optimum use of this drug will require further study and enthusiasm for its use must be tempered by recent observations of the emergence of cytomegalovirus strains resistant to ganciclovir.[21] However, the limited toxicity and prompt, uniform eradication of symptomatic disease observed in our series indicate that ganciclovir is a valuable addition to the therapeutic armamentarium in the management of cadaveric renal transplant recipients with tissue invasive cytomegalovirus infection.

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