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The impact of cytomegalovirus infection ≥1 year after primary renal transplantation

Barry J. Browne[a], **Jo-Anne Young**[b], **Ty B. Dunn**[c], and **Arthur J. Matas**[c]

[a]Transplant Services, Balboa Nephrology Medical Group, Inc., San Diego, CA

[b]Department of Medicine, University of Minnesota, Minneapolis, MN, USA

[c]Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Abstract

We studied the impact of a first post-transplant cytomegalovirus (CMV) infection greater than one year after primary kidney transplantation. Risk factors for developing late CMV were acute rejection and donor–recipient CMV status. Of those developing late CMV, 35% were donor (D) positive, recipient (R) negative; however, 23% were D+R+, 22% D−R+, and 15% D−R−. Late CMV was associated with significantly decreased patient and graft survival.

Keywords

cytomegalovirus; renal transplant; infection; post transplant; late

Cytomegalovirus (CMV) infection is associated with significantly decreased kidney transplant recipient and graft survival. Development of potent antiviral agents for prevention and treatment of CMV has lowered (but not eliminated) the incidence of infection; however, in most cases, antiviral agents have reduced the severity and consequences of infection. CMV infection occurs most commonly in the first few post-transplant months; thus, much of the focus on CMV prevention, diagnosis, and treatment is concentrated on this interval. To minimize CMV-related disease, some transplant centers have routinely used antiviral agents as prophylaxis for weeks to months post transplant; others have chosen to do routine surveillance for CMV in the first few months and to institute treatment if CMV viremia is detected (1). Neither strategy addresses delayed CMV infection.

Most studies of late CMV infection describe infection after three months or after six months post transplant (2–16). This is probably because CMV infection is unusual after the first year, and so it is difficult to accumulate a case series. We have encountered primary CMV infections up to 17 yr post transplant. Because our index-of-suspicion has not been high, there was often considerable delay in making the diagnosis.

Herein, we report our experience with late CMV infection (≥1 yr post transplant). We found that, in a large series, 3% of recipients developed their first CMV infection ≥1 yr post transplant. We compare recipients developing late CMV with those developing early infection (<1 yr post transplant) and those remaining CMV infection free.

Corresponding author: Arthur J. Matas, MD, Department of Surgery, MMC 328, 420 Delaware St. SE, Minneapolis, MN 55455, USA. Tel.: 612-625-6460; fax: 612-624-7168; matas001@umn.edu.

Methods

Between January 1, 1985 and July 31, 2007, 2764 recipients had a primary kidney transplant at the University of Minnesota. Of these, we have obtained complete information on both donor and recipient pre-transplant CMV status of 2489 recipients (1601 living donor [LD], 888 deceased donor [DD]) (2118 adult, 372 pediatric recipients), and this group is the subject of this report. Immunosuppressive protocols have been described in detail (17). In short, between January 1985 and July 1996, LD recipients were treated with triple therapy (calcineurin inhibitor [CNI], antimetabolite, and prednisone). After July 1996, LDs were treated with antibody induction in a sequential therapy protocol (antibody, antimetabolite, and prednisone at transplant, with delayed introduction of CNI). After October 1999, we discontinued prednisone after the fifth post-operative day (18). Since 1985, all DDs have been treated with sequential therapy; after October 2000, we discontinued prednisone after the fifth post-operative day. Rejection episodes were confirmed by percutaneous allograft biopsy. Mild to moderate cellular rejection was treated with a steroid taper; severe rejection was treated with antibody.

Viral infection prophylaxis

In 1988, subsequent to a prospective randomized study of placebo vs. acyclovir for CMV prevention, all CMV-seropositive recipients or seronegative recipients with seropositive donors were treated with acyclovir (800 mg [18 mg/kg pediatric] orally five times daily) for CMV prophylaxis (19). All blood products were leukoreduced by filtration and untested for CMV status. Patients with a CMV-negative donor and recipient serostatus did not receive antiviral agents. Oral ganciclovir replaced acyclovir in 1994 and was likewise replaced by valganciclovir in 2001.

CMV surveillance monitoring

Historically, recipients presenting with signs and symptoms of CMV infection were evaluated by a qualitative shell vial assay. In 1996, antigenemia testing replaced shell vial testing on blood but not body fluids or tissues. In 2006, quantitative CMV DNA PCR replaced antigenemia and shell vial testing of blood and body fluids. Tissue biopsy specimens from lung, stomach, duodenum, and colon were tested for the presence of CMV using both shell vial and conventional tube cultures (virology) as well as immunohistochemical staining (pathology).

CMV therapy

Before ganciclovir was available, patients with suspected or diagnosed CMV infection were treated with intravenous acyclovir. After the introduction of ganciclovir in 1988, recipients with CMV infection were treated with a two-wk course of intravenous ganciclovir at induction dosing (renal dose equivalent of 5 mg/kg IV twice daily), followed by six wk of oral maintenance therapy (5 mg/kg per d). In the setting of renal insufficiency, induction ganciclovir doses were reduced to 2.5 mg/kg IV every 12 h at a creatinine clearance of 70 mL/min and further reduced to 2.5 mg/kg daily at a creatinine clearance of 50 mL/min. Treatment usually included reduction of immuno-suppression.

Of note, early in our experience, we did not treat those recipients with asymptomatic CMV viremia. Almost all untreated recipients developed tissue invasive disease, and we now treat asymptomatic CMV viremia with a course of oral valganciclovir.

Clinical information is kept in an IRB-approved database. We studied the outcome of late CMV infection, defined as a first CMV infection after the first post-transplant year. CMV infection was defined as diagnosed CMV (shell vial assay, buffy coat, culture, or tissue

biopsy) and institution of treatment. Primary transplant recipients were grouped based on the timing of first presentation with CMV infection: (i) no CMV infection; (ii) early CMV infection (<1 yr post transplant); and (iii) late CMV infection (≥1 yr post transplant). Actuarial outcome was compared using Kaplan–Meier table analysis. Risk factors for the development of early and late CMV were studied using multivariate analysis. Included in the analysis were donor source (LD vs. DD), acute rejection (yes vs. no), donor (D) and recipient (R) CMV status (D−R−, D−R+, D+R−, D+R+), transplant PRA ≥ 50 (vs. <50), peak PRA ≥ 50 (vs. <50), pre-transplant diabetes (yes vs. no), and age (≥18 vs. <18).

Results

Of the 2489 recipients with complete CMV information, 77 (3.1%) developed late CMV infection (54 LD; 23 DD), 303 (12%) early infection (157 LD; 146 DD), and 2190 (85%) no CMV infection (1390 LD; 719 DD). Characteristics that differed ($p < 0.05$) between the three groups (age at transplant, race, and donor and recipient CMV status) are shown in Table 1. There were no differences in gender, peak and transplant PRA, primary disease, or in the rate of preemptive transplants.

Mean time to CMV infection (±SE) for those with early CMV was 3.4 ± 2.6 months (LD, 3.7 ± 2.7 months; DD, 3.2 ± 2.4 months); for those with late CMV, 54 ± 46 months (LD, 54 ± 45 months; DD, 49 ± 52 months). For the late CMV group, 54 developed infection between one and five yr post transplant, 15 between six and 10 yr, four between 11 and 15 yr, and four after 15 yr.

For those developing either early or late CMV infection, recurrent infection was common—48% of those with early CMV and 33% of those with late CMV. Of those with early CMV, 32% had two episodes, 5% had three episodes, 7% had four episodes, and 4% had greater than four episodes. Of those with late CMV, 24% had two episodes and 2% each had three episodes, four episodes, and greater than four episodes.

Risk factors for the development of early CMV infection (logistic regression) were DD ($p < 0.002$), donor–recipient CMV status (increased risk with R+D− [$p = 0.001$], D+R− [$p < 0.0001$], D+R+ [$p < 0.0001$] vs. D−R−), pre-transplant diabetes ($p = 0.03$), and recipient age ≥18 ($p < 0.004$) (Table 2). When the analysis was independently repeated for LDs and DDs, donor and recipient CMV status, and recipient age remained significant.

For early CMV, there was an association between acute rejection and CMV. However, for 67% of recipients, the rejection episode preceded the CMV infection; for 33%, the CMV infection preceded the rejection. Risk factors for late CMV infection included acute rejection ($p < 0.0001$), donor–recipient CMV status (increased risk with R+D− [$p = 0.03$], D+R− [$p < 0.01$], D+R+ [$p < 0.0001$] vs. D−R−). In contrast to early CMV, acute rejection preceded CMV in almost all cases. Donor source approached significance ($p = 0.08$). When the analysis was repeated for LD and DD independently, acute rejection and donor and recipient CMV status remained significant.

Both early and late CMV infections were associated with decreased actuarial patient survival, graft survival, and death-censored graft survival (Table 3 and Fig. 1). In a multivariate analysis in which both acute rejection episodes and CMV infections were included, late CMV infection was an independent risk factor for worse graft outcome ($p < 0.001$).

Early CMV had its impact in the first transplant year (Table 3). Because developing late CMV (as we defined it) required surviving with graft function for one yr, death and graft loss were censored in the first year for all three groups and actuarial outcome restudied. In

this analysis, late CMV infection was associated with significantly worse patient survival and death-censored graft survival. Interestingly, when only one-yr survivors were considered, there was no significant difference in outcome between the early CMV infection and the CMV-free groups. There was no difference between groups in the causes of graft loss.

Survival from the time of diagnosis of CMV is shown for the early and late CMV groups in Fig. 2. LD recipients with late (vs. early) CMV have significantly worse patient ($p < 0.0001$) and death-censored graft ($p = 0.04$) survival (Fig. 2A). There was no difference for DD recipients (Fig. 2B).

There were no significant differences between groups in cause of graft loss. However, for both LDs ($p = 0.03$) and DDs ($p = 0.008$), there were differences between groups in cause of death. For LDs, infection (all types) was the cause of death for 14% with no CMV, 19% with early CMV, and 46% with late CMV. For DDs, infection was the cause of death for 14% with no CMV, 10% with early CMV, and 35% with late CMV.

Discussion

Traditionally, post-transplant CMV infection is thought to develop from reactivation of latent virus or from primary infection from virus transmitted with the allograft. The risk is highest in the first few months after transplantation (when immunosuppressive doses are highest) and is increased by the treatment of an acute rejection episode (20). As a consequence, most transplant programs have developed protocols for early CMV prophylaxis or aggressive surveillance with rapid institution of treatment. Most such protocols end within the first six post-transplant months.

Case series of late CMV infection have previously been published (2–16). In most, late infection has been defined as primary infection occurring greater than six months post transplant, and studies in all types of solid organ transplant (heart, liver, lung, kidney) have suggested that CMV infection frequently emerges once prophylaxis has been discontinued (2–16). However, Arthurs et al. (15) reported primary infection occurring at 12 and at 24 months post transplant in D+R− liver transplant recipients who had received three months of CMV prophylaxis. Arthurs et al. (16). also studied late CMV infection in CMV-seronegative recipients of kidney transplants from CMV-seropositive donors (n = 176). All received ganciclovir prophylaxis. None of the recipients developed CMV while taking ganciclovir; however, 51 (29%) recipients developed CMV disease at a median of 61 d after stopping antiviral prophylaxis. Risk factors for developing late CMV were early-onset bacterial and fungal infection and a Charlson comorbidity index ≥3.

In our series, late CMV was defined as disease >1 yr post transplant. Our data suggest that late CMV infection is not a rare event. Of 380 recipients developing CMV, 77 (20%) developed infection ≥1 yr post transplant. Although pre-transplant donor–recipient CMV status was a risk factor for the development of late CMV (Table 1), 15% of cases occurred in D−R− recipients. Of note, late CMV infection was associated with significantly decreased patient and graft survival (Table 3). This may have been because CMV was not initially considered in the differential diagnosis of late post-transplant infection, because a higher percentage of infections were primary infections, or because of the immune status of the recipients. In addition, 34% of those with late CMV had recurrent infections. When the data were censored for patient death, it appears as if those with late CMV infection have better long-term outcome (Table 3). However, this is an artifact of the small numbers and the way the analysis was carried out. First, to be in this group, one had to survive past one yr, so at one yr, the survival is already higher than those without CMV. Second, 10-yr patient

survival for those with late CMV is poor (most of the losses were because of death). So, when the data are death-censored, it looks better.

We conclude that CMV infection must be considered in the differential diagnosis for transplant recipients presenting with signs and symptoms of infection greater than one yr post transplant.

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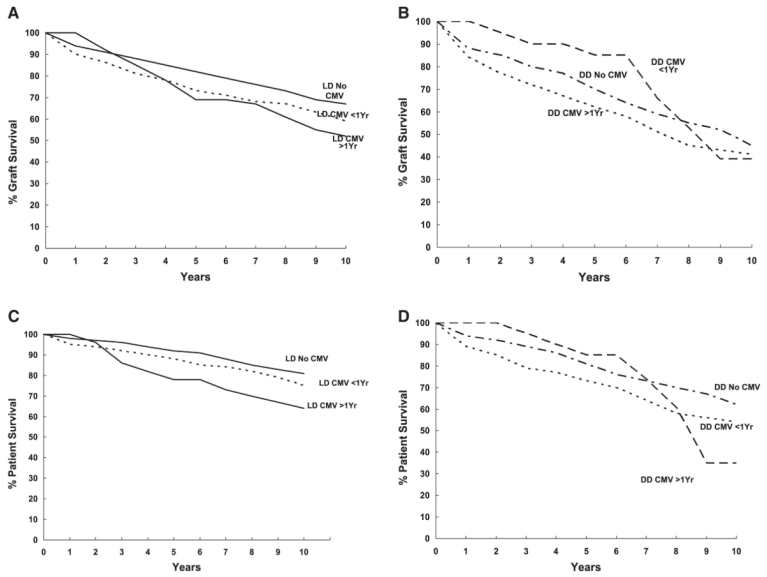

Fig. 1.

The impact of cytomegalovirus infection on actuarial patient and graft survival: (A) living donor (LD) graft survival; (B) deceased donor (DD) graft survival; (C) LD recipient survival; (D) DD recipient survival.

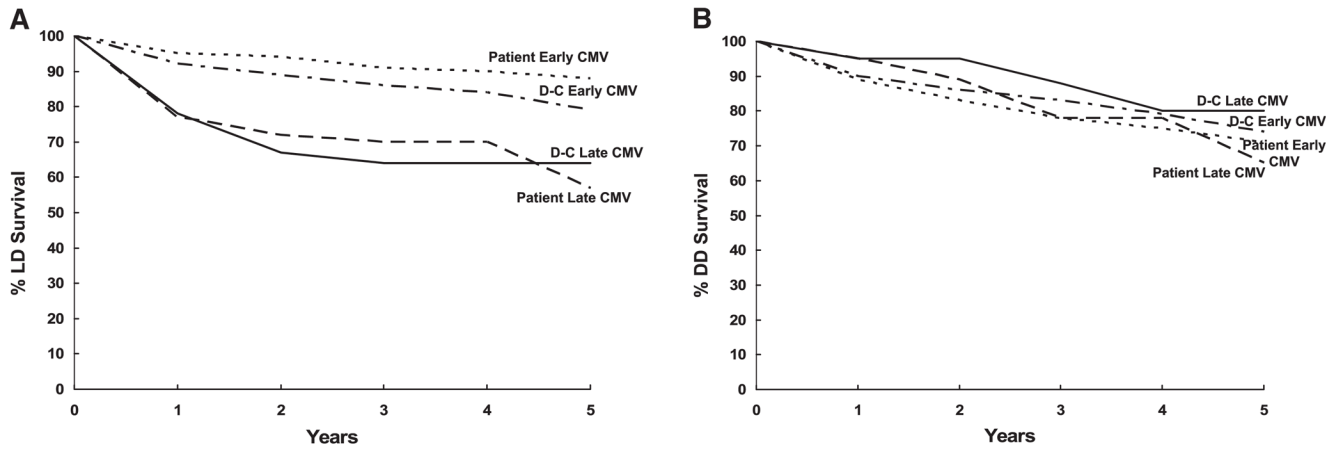

Fig. 2.

Actuarial recipient and death-censored graft survival after cytomegalovirus (CMV) diagnosis for early vs. late CMV infection: (A) living donor; (B) deceased donor.

Table 1

Characteristics of those with no cytomegalovirus (CMV) infection, early infection, and late infection

	No CMV	Early CMV	Late CMV
Mean age at transplant (yr)	37 ± 14	42 ± 15	38 ± 13
Range (yr)	61–77	4–72	7–63
Percentage of white *	90	85	91
CMV status at transplant *			
Percentage of D−R−	35	5	15
Percentage of D−R+	21	12	22
Percentage of D+R−	16	53	35
Percentage of D+R+	28	30	23

* $p < 0.05$.

Table 2

Significant risk factors for the development of early and late cytomegalovirus (CMV) infection

	Factor	p-value
Early CMV	Deceased donor	<0.002
	Acute rejection therapy	<0.0001
	Pre-transplant diabetes	0.03
	Recipient age ≥18	<0.004
	Donor–recipient CMV status *	
Late CMV	Acute rejection	<0.0001
	Donor–recipient CMV status **	

* Increased risk with R+D− (p = 0.001), D+R− (p < 0.0001), D+R+ (p < 0.0001) vs. D−R−.

** Increased risk with R+D− (p = 0.03), D+R− (p < 0.01), D+R+ (p < 0.0001) vs. D−R−.

Table 3

Actuarial outcome

	1 yr	3 yr	5 yr	10 yr	p-value
Living donor					
Percentage of recipient survival					
Early CMV	95	92	88	75	0.004
Late CMV	100	86	78	64	
No CMV	97	94	91	79	
Percentage of graft survival					
Early CMV	90	81	73	59	0.05
Late CMV	100	90	69	52	
No CMV	94	88	82	67	
Percentage of D-C[a] graft survival					
Early CMV	94	84	80	68	0.003
Late CMV	100	90	80	69	
No CMV	96	93	89	80	
Deceased donor					
Percentage of recipient survival					
Early CMV	90	79	72	54	0.01
Late CMV	100	95	85	35	
No CMV	92	89	81	62	
Percentage of graft survival					
Early CMV	84	72	62	41	0.03
Late CMV	100	90	85	38	
No CMV	88	80	64	45	
Percentage of D-C[a] graft survival					
Early CMV	91	84	77	62	0.02
Late CMV	100	95	95	88	
No CMV	92	88	82	68	

CMV, cytomegalovirus.

[a]Death-censored.