Impact of Prophylaxis vs Pre-emptive Approach for Cytomegalovirus Infection in Kidney Transplant Recipients

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ABSTRACT

Cytomegalovirus (CMV) is the most common viral infection during the post-transplant period, and it is one of the major causes of morbidity and mortality in kidney transplantation. In this study, the incidence and impact of pre-emptive and prophylactic approaches and long-term effects on graft and patient survival of CMV infection were investigated. Among 493 adult kidney transplant recipients, pretransplant CMV IgG-negative patients and patients with a follow-up shorter than a month were excluded. The patients were divided into 2 groups: pre-emptive group (n = 187, regular screening and acyclovir 400 mg twice daily for 6 months), and prophylaxis group (n = 275, valganciclovir 450 mg/d for 3 months). The pre-emptive group was screened for CMV with either pp65 antigenemia or CMV DNA. There were 462 patients, and mean follow-up was 37.7 months. There were more CMV infections in the pre-emptive group than in the prophylaxis group (n = 56, 30.1% vs n = 12, 4.4%, respectively; $P < .001$). Late CMV infections were significantly more frequent in the prophylaxis group (10 of 12, 83.3%) than in the pre-emptive group (8 of 56, 14.3%, $P < .001$). In multivariate analysis, valganciclovir prophylaxis was associated with a lower CMV infection (relative risk [RR]: 0.18, 95% confidence interval [CI] 0.08 to 0.39, $P < .001$). Delayed graft function was the only independent risk factor for graft loss during the follow-up on multivariate Cox regression analysis (RR: 2.66, 95% GA 1.17 to 6.04, $P = .02$). Valganciclovir prophylaxis was more protective against CMV infection than the pre-emptive approach. Neither prophylaxis/pre-emptive approaches nor CMV infection had negative effect on graft and patient survival.

CYTOMEGALOVIRUS (CMV) infection is the most frequent viral infection after kidney transplantation and causes significant morbidity and mortality [1]. The incidence of symptomatic CMV infection is between 20 and 60% in kidney transplant recipients without preventive strategies [2]. The severity of CMV infection depends on donor and recipient serostatus before transplantation, transplanted organ type, and immunosuppressive treatment [3,4].

Currently, there are 2 different approaches to screen and treat CMV infection: universal prophylaxis or pre-emptive treatment. Universal prophylaxis has some disadvantages, such as increased cost, drug side effects, development of viral resistance, and late CMV infection. On the other hand, a pre-emptive approach needs frequent monitoring and may be inadequate to prevent rejection, allograft dysfunction, opportunistic infection, and mortality due to asymptomatic CMV replication. In this retrospective study, the incidence and risk factors of CMV infection and its impact on graft and patient survival were investigated in prophylaxis and pre-emptive groups.

MATERIALS AND METHODS

In this retrospective study, 493 recipients transplanted between 2009 and 2013 were evaluated. Patients who were CMV IgG-negative at the time of transplantation (n = 8) or had follow-up

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duration shorter than 1 month (n = 23) were excluded. Patients were divided into 2 groups. In the pre-emptive group, acyclovir (400 mg/d) was given during the first 6 months, and patients were screened with CMV pp65 antigenemia or CMV DNA polymerase chain reaction (PCR) testing. In the prophylaxis group, valganciclovir (450 mg/d) was given during first 100 days, then acyclovir was given until the end of month 6.

CMV IgG was identified with chemiluminescence microparticle immunoassay (Architect i2000sr, Abbott, Chicago, Ill, United States). Semiquantitative Cina kit (Argene Biosoft, Varilhes, France) was used for pp65 antigenemia test. Real-time PCR (Abbott m2000rt, Abbott, Chicago, Ill, United States) was used for CMV DNA detection.

CMV infection was defined as isolation of CMV or determination of antigen or genome. CMV disease was defined as demonstration of CMV antigen or genome in the tissue with the disease sign or symptoms. The cutoff values to begin pre-emptive treatment was over 50 positive cells from 200,000 leukocytes for antigenemia and over 3000 IU/mL for CMV DNA. If the patient was clinically symptomatic for CMV infection, the treatment was initiated with any positive value regardless of a cutoff. Demographic, clinical, and laboratory data were collected retrospectively. The data were analyzed with SPSS 22.0 (Statistical Package for the Social Sciences, SPSS Inc, Chicago, Ill, United States).

RESULTS

Mean age was 40.5 ± 11.9 years, and 285 of 462 (61.6%) were male patients. In all, 323 patients received a living donor organ, and mean donor age was 48.2 ± 13.5 years. Induction treatment consisted of anti-thymocyte globulin (ATG) in 403 (87.8%) and interleukin 2 receptor antagonists in 49 (10.6%) patients. Maintenance immunosuppression involved corticosteroids, mycophenolate mofetil or mycophenolate sodium, and calcineurin inhibitor or mammalian target of rapamycin inhibitors. At the end of the follow-up (37.7 ± 18.3 months), 417 patients had a functioning allografts, graft failure occurred in 26 patients, and 19 patients died.

Patients were divided into 2 groups: pre-emptive (n = 187) and prophylaxis (n = 275) groups. There were significant differences between 2 groups as shown in Table 1. The most striking difference was organ source. Nearly all patients in the pre-emptive group received organs from living donors. Half of the patients in the prophylaxis group received organs from deceased donors. This imbalance originated from our center policy. After the routine use of valganciclovir, the pre-emptive approach with use of acyclovir continued in living donor transplants, whereas valganciclovir was used in only deceased donor transplants. After the accumulating experience, valganciclovir prophylaxis was preferred in all recipients. Other differences between 2 groups, such as older age, longer dialysis duration, more frequent and higher doses of ATG in prophylaxis, are linked to more deceased donor transplants in the prophylaxis group.

Despite this high-risk profile of the prophylaxis group, CMV infection was significantly lower compared with the pre-emptive group (n = 12, 4.4% in prophylaxis group and n = 56, 30.1% in pre-emptive group, $P < .001$). Recurrent CMV infection occurred in 4 patients who were all in the pre-emptive group. CMV viremia appeared earlier in the pre-emptive group (14.7 ± 32.3 weeks in pre-emptive group, 39.9 ± 48.5 weeks in prophylaxis group, $P < .001$). Ten of 12 CMV-infected patients in the prophylaxis group had late-onset CMV infection, and 8 of 56 patients (14.3%) in the pre-emptive group had late-onset CMV infection ($P < .001$).

Follow-up duration in the pre-emptive and prophylaxis groups were 46 ± 16 and 32 ± 17 months, respectively. During follow-up, 5 patients died in the pre-emptive group, and 14 patients died in prophylaxis group ($P = .20$). Number of graft losses were similar in the pre-emptive (n = 8) and prophylaxis (n = 18) groups ($P = .27$). Kaplan-Meier graft survival curve is shown in Fig 1.

Multivariate Cox regression analysis (adjusted with donor age, delayed graft function, dose of ATG) showed that longer time on dialysis (relative risk [RR]: 1.00, 95% confidence interval [CI] 1.00 to 1.01, $P = .03$), deceased donor transplantation (RR: 0.07, 95% CI 0.01 to 0.38, $P = .002$), and use of valganciclovir (RR: 0.37, 95% CI 0.15 to 0.86, $P = .02$) were associated with CMV infection. In subgroup analysis excluding donor source, valganciclovir (RR: 0.18, 95% CI 0.08 to 0.39, $P < .001$) was the only significant factor decreasing the incidence of CMV infection.

Eleven of 68 patients with CMV infection had CMV disease. Main presentations were fever, leukopenia, and flulike symptoms. Only 1 patient had tissue-invasive CMV disease who presented as CMV pneumonitis with CMV

Table 1. Comparative Data for Pre-emptive and Prophylaxis Groups

	Pre-emptive Group (n = 187)	Prophylaxis Group (n = 275)	*P* Value
Age, y (range)	36.6 ± 10.9 (18–71)	43.2 ± 11.9 (18–67)	<.001
Time on dialysis, mo (range)	25.3 ± 35.1 (1–216)	75.2 ± 66.6 (1–276)	<.001
Pre-emptive transplant, n (%)	61 (32.6)	39 (14.1)	<.001
Living donor, n (%)	185 (98.9)	138 (50.2)	<.001
ATG induction n (%)	135 (72.2)	267 (98.1)	<.001
Cumulative ATG dose (mg)	290 ± 196	549 ± 305	<.001
CMV infection/disease, n (%)	56 (30.1)	12 (4.4)	<.001
Creatinine at 1 y (mg/dL)	1.33 ± 0.4 (0.6–3.76)	1.36 ± 0.76 (0.6–7.8)	.082
Proteinuria at 1 y (g/d)	0.25 ± 0.7 (0.01–8.9)	0.31 ± 0.84 (0.01–12)	.05
Follow-up duration (mo)	46.1 ± 16 (2.8–75.3)	32 ± 17.6 (1.2–81.2)	<.001

Abbreviations: ATG, anti-thymocyte globulin; CMV, cytomegalovirus.