Original Article

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Oral valganciclovir *versus* intravenous ganciclovir as preemptive treatment for cytomegalovirus infection after living donor liver transplantation: A randomized trial

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Summary **It is unclear whether valganciclovir (VGCV) is effective compared with intravenous ganciclovir (GCV) for preemptive therapy of cytomegalovirus (CMV) infection in living donor liver transplantation (LDLT). A randomized trial was conducted to compare the efficacy of oral VGCV with intravenous GCV for preemptive treatment of CMV infection after LDLT. Patients who developed CMV infection within 6 months after LDLT at Tokyo University Hospital were randomly assigned to the VGCV or GCV group and received either oral VGCV 900 mg/day or intravenous GCV 5 mg/kg twice daily, respectively. The primary endpoint was the treatment success rate. Secondary endpoints were recurrence of CMV infection within 1 year after finishing the treatment, and safety and tolerability of the treatment. Twenty-two patients with CMV infection after LDLT fulfilled the inclusion criteria and were randomly assigned to the oral VGCV group (*n* = 11) or the intravenous GCV group (*n* = 11). Treatment success rates were 82% (9 of 11) and 91% (10 of 11) in the VGCV and GCV groups, respectively. One patient in the VGCV group developed recurrence, whereas no patients in the GCV group developed recurrence. All the patients completed the treatment protocol, and no patients in either group dropped out of the study. In conclusion, oral VGCV and intravenous GCV are safe, feasible options for preemptive treatment of CMV infection after LDLT.**

Keywords: Cytomegalovirus, preemptive treatment, living donor liver transplantation, valganciclovir, ganciclovir

1. Introduction

Cytomegalovirus (CMV) is one of the most common infectious complications after living donor liver transplantation (LDLT). Three etiologies of CMV infection in LDLT recipients are proposed; viral transmission *via* the donor graft, viral transmission *via* transfusion from a sero-positive donor, and reactivation of dormant CMV in the recipients (*1*). Approximately 23% to 85% recipients after liver transplantation develop CMV infection, and 15% to 40% (*1-3*) of them develop CMV-related disease, such as interstitial pneumonia, hepatitis, and enteritis. CMV infection is also reported to be the cause of other infectious complications, such as acute rejection, poor survival rate, increased graft loss, increased length of hospital stay, and high cost. Therefore, the establishment of optimal strategies, including the most effective antiviral agents and the most effective administration route for preventing CMV infection or disease after LDLT is in high demand.

Two strategies are currently acceptable for the prevention of CMV-related morbidity or mortality after liver transplantation; universal prophylaxis (*4-6*) and preemptive treatment (*7-9*). It is controversial whether either strategy is superior to the other, because both strategies have limitations: universal prophylaxis is

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associated with the risk of late-onset CMV disease (*10*) and ganciclovir (GCV) resistance, and preemptive treatment requires frequent monitoring of CMV by sensitive methods such as polymerase chain reaction or CMV pp65 antigenemia.

We selected the preemptive treatment strategy to prevent CMV-related complications from 1996 to November 2006 using intravenous GCV. Although intravenous GCV has been the gold standard for treating CMV infection and disease in liver transplant recipients, it is somewhat inconvenient for patients because it requires frequent hospitalization and long-term intravenous catheter access (*11*).

Valganciclovir (VGCV), which has an oral bioavailability of 60%, was recently shown to be effective for the treatment of CMV infection in solid organ recipients (*12*). If treatment with oral VGCV as an alternative to intravenous GCV is equally effective in treating CMV infection after liver transplantation, it might benefit patients, with regard to both convenience and cost.

Although earlier studies reported the efficacy of VGCV for the treatment of CMV infection in liver transplant recipients, these studies were not randomized controlled trials. In addition, although VGCV was clinically effective and well tolerated in a multicenter trial of high-risk solid organ transplant recipients, a subgroup analysis in this trial revealed that tissue-invasive CMV disease occurred more frequently in liver transplant recipients on VGCV *versus* oral GCV (*13*). Therefore, we conducted a prospective, randomized, open-label, single center trial for a head-to-head comparison of VGCV with GCV for preemptive treatment of CMV infection after LDLT.

2. Patients and Methods

2.1. *Study design*

This study was conducted in accordance with tenets of the Declaration of Helsinki. The study compared the efficiency of VGCV with GCV for preemptive treatment of CMV infection after LDLT. Eligibility criteria included age 20 and over, LDLT recipients who were able to receive an oral drug at the onset of CMV infection, acceptable bone marrow function profile (platelet count $\geq 5 \times 10^4$/mL, hematocrit level $\geq 18\%$, and neutrophil $\geq 10^3$/mL), and adequate renal function. Exclusion criteria were history of CMV infection before LDLT, the presence of CMV disease, severe diarrhea, malabsorption state, and other postoperative complications. Patients with a history of drug allergy to GCV, VGCV, acyclovir, or valacyclovir were also excluded. The study protocol was approved by the institutional review board of Tokyo University Hospital. The protocol was explained to eligible patients, and written informed consent was obtained from all patients before enrollment.

Enrolled patients were stratified according to postoperative day at onset of CMV infection (≥ 30 *versus* < 30), preoperative model for end-stage liver diseases score (≥ 15 *versus* < 15), CMV pp65 antigen-positive cell counts/50,000 white blood cells at the diagnosis of CMV infection (≥ 10 *versus* < 10), and the presence or absence of the history of acute rejection after LDLT. Patients were randomly assigned to either the VGCV or GCV group.

This study was registered as UMIN ID: C000000295.

2.2. *Immunosuppression and CMV surveillance*

Our immunosuppressive regimens (methylprednisolone plus tacrolimus) after LDLT are described elsewhere (*14*). No CMV-specific prophylaxis was administered. After LDLT, recipients in both groups underwent surveillance for CMV infection using the CMV pp65 antigenemia assay, which was measured at the Mitsubishi Kagaku Bio-Clinical Laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan). CMV pp65 antigenemia was routinely measured twice a week for 1 month, once a week for the next 3 months, and twice a month thereafter until 6 months after LDLT. When CMV disease was clinically suspected, the CMV pp65-antigenemia assay was checked accordingly.

2.3. *Definition of CMV infection and disease*

CMV infection was defined as positive results of the CMV pp65 antigenemia assay, which was defined as $\geq$ 5 antigen-positive cells/50,000 white blood cells. CMV disease was defined by the involvement of visceral and end-organs with the presence of compatible symptoms and signs as well as positive CMV pp65 antigenemia assay results or isolation of CMV in biopsy specimens. Deterioration of CMV infection was defined as follows: when CMV pp65 antigen-positive cell counts/50,000 white blood cells at 2 weeks after enrollment were elevated to more than 50 or more than three times, or when CMV pp65 antigenemia assay results remained positive for 3 weeks after enrollment. Recurrence of CMV infection was diagnosed when CMV pp65 antigenemia assay became negative and then was again positive.

2.4. *Preemptive treatment of CMV infection*

In the VGCV and GCV groups, patients received oral VGCV at 900 mg/day or intravenous GCV at 5.0 mg/kg every 12 hours as induction therapy for up to 1 week after CMV pp65 antigenemia turned negative, respectively. Thereafter, oral VGCV 900 mg/day was administered as maintenance treatment in both groups for an additional week. VGCV and GCV doses during the induction period were adjusted based on the

individual renal function calculated by Cockcroft-Gault creatinine clearance, as described previously (*12*).

2.5. *Outcome measures*

The primary endpoint was the treatment success of CMV infection after LDLT, which was defined in each group as a negative CMV pp65 antigenemia assay result within 2 weeks after enrollment, which was sustained for 1 month. Secondary endpoints included recurrence rate of CMV infection for 1 year after LDLT, and the safety and tolerability of the treatment.

2.6. *Statistical analysis*

All analyses were performed on an intention-to-treat basis. Statistical analysis was performed using computer software JMP 5.1 (SAS Inc., Cary, NC). Continuous data were analyzed by one-way analysis of variance and *t*-tests. *p* values of less than 0.05 and 0.01 were considered statistically significant for *t* tests and analysis of variance, respectively. The categorical data between the two groups were compared using Fisher's exact test or Mann-Whitney *U*-test. Confidence intervals (95% CIs) were calculated for differences in proportions for categorical data. Recurrence-free and overall survival curves were analyzed by the Kaplan-Meier method. Recurrence rates and survival rates were compared between the groups by the log-rank test and one-tailed and two-tailed analyses were used to analyze the primary and secondary endpoints, respectively.

3. Results

Between December 2005 and December 2008, 75 recipients underwent LDLT and were followed up for 1 year after LDLT. Of the 75 recipients, 34 (45%) developed CMV infection during the study period. Of these 34, 12 were excluded because of the presence of severe postoperative complications (n = 6) and unavailable informed consent (n = 6). Accordingly, the remaining 22 recipients were enrolled in the study. The recipients were randomly assigned to either the VGCV (n = 11) or GCV (n = 11) group for preemptive treatment of CMV infection, and were followed up for 1 year after LDLT (Figure 1).

3.1. *Baseline characteristic*

All baseline characteristics were similar in both groups (Table 1). The 22 recipients comprised 15 men and 7 women with a median age of 53 and 51 (range, 21-64) years, respectively. The median model for end-stage liver disease score was 16 (range: 7-27). The indications included virus-related cirrhosis with or without hepatocellular carcinoma (n = 14), cholestatic disease (n = 3), fulminant hepatic failure (n = 2), and cryptogenic liver cirrhosis (n = 3). Patients developed CMV infection at a mean of 31 ± 13.8 and 30 ± 5.6 days after LDLT in the VGCV and in GCV groups, respectively. CMV pp65 antigen-positive cells/50,000 white blood cells at the onset of CMV infection were 7.1 ± 4.6 in the VGCV group and 9.2 ± 6.6 in the GCV group. None of the patients in either group had a history of acute rejection at the onset of CMV infection.

3.2. *Primary and secondary endpoints*

Preemptive VGCV and GCV treatment of CMV infection after LDLT was successful in 9 of 11 (82%) patients in the VGCV group and in 10 of 11 (91%) patients in the GCV group (hazard ratio, 0.70; 95% CI, 0.15 to 2.24). Mean time until the results of the CMV pp65 antigenemia assay were negative after the initiation of treatment was 9.4 ± 4.9 days in the VGCV group and 8.2 ± 5.1 days in the GCV group (p = 0.59). CMV recurrence within 1 month after starting treatment was detected in 1 of 11 (9%) patients in the VGCV group and in 0 of 11 patients in the GCV group. The patient developed recurrence of CMV infection at 23 days after finishing the CMV treatment.

The time-course of pp65-antigenemia is depicted in Figure 2. During the first 30 days after LDLT, there was no difference in the recurrence-free survival rates between treatment groups (Figure 3; p = 0.55). As for CMV detection in the blood after completion of treatment, the median interval between discontinuation of study drug and retreatment of CMV infection was 96 ± 58 days (range: 55-137) for patients who received VGCV and 75 ± 37 days (range: 23-124) for patients who received GCV. At Day 180, clinical success was achieved in 6 of 11 VGCV-treated patients (55%) and in 9 of 11 (82%) GCV treated patients; by Day 365 clinical success was achieved in the same 55% and 82%, respectively. None of the patients in either group developed CMV disease. In both groups, the overall 1-year survival rate after LDLT was 100%. The 1- and 3-year patient survival rates with CMV infection were 96% and 96%, *versus* 95% and 95% without CMV in December 2009.

3.3. *Allograft rejection*

Acute rejection was detected in 1 of 11 patients (9%) in the VGCV group at 2 weeks after CMV infection. None of the patients in either group developed chronic rejection during the study period.

3.4. *Safety and tolerability of preemptive treatment*

None of the patients in either group dropped out of the study after initiation of the CMV treatment. Only 1 of 11 patients (9%) in the GCV group developed severe neutropenia, in whom the neutrophil counts decreased

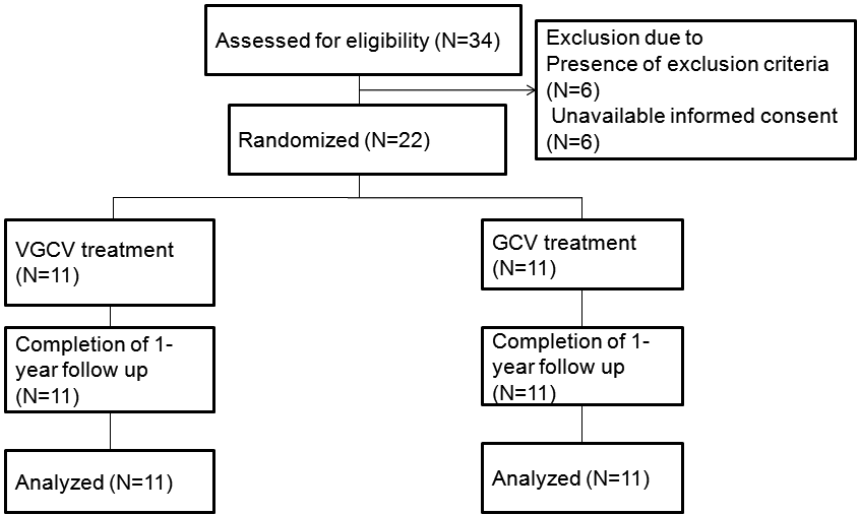

Figure 1. Study design.

Table 1. Baseline characteristics of patients in the two groups

Variable	VGCV group (n = 11)	GCV group (n = 11)	p-Value
Age (years)	51.1 ± 9.6	53 ± 11.8	0.70
Sex			
Men	6	9	0.36
Women	5	2	
MELD score	16 ± 7	17 ± 5	
≥ 15	6	7	0.67
< 15	5	4	
Primary liver disease			
Viral hepatitis	11	10	
Cryptogenic cirrhosis	2	0	
Fulminant hepatitis	0	2	
PBC	0	3	
Others	1	1	
Onset of CMV infection (days after LDLT)	30 ± 6	31 ± 14	0.83
≥ 30	5	4	
< 30	6	7	
CMV pp65 antigenemia			
≥ 10	6	6	1.00
< 10	5	5	
Acute rejection			
Present	3	2	0.10
Absent	8	9	
HLA-A,B,DR mismatch	3.5 ± 1.2	2.9 ± 1.1	0.22
Donor age	43 ± 11	39 ± 13	0.44

Some values are expressed as Mean ± Standard Error of the Means. (Abbreviations: LDLT, living donor liver transplantation; MELD, model for end-stage liver diseases; PBC, primary biliary cirrhosis; HLA, human leukocyte antigen.)

from 2.0×10^9/L to $< 0.5 \times 10^9$/L during treatment. Deterioration of renal function was observed in 1 of 11 (9%) patients in the VGCV group and in 2 of 11 (18%) patients in the GCV group. All of these adverse events were treated conservatively.

4. Discussion

To our knowledge, this study is the first randomized controlled trial comparing the effectiveness of oral VGCV with intravenous GCV for preemptive treatment of CMV infection after LDLT. Kalil *et al*. (*13*) reported that VGCV was not the preferred option as a first-line agent for CMV preemptive or universal prophylaxis in solid organ transplant recipients. In contrast, the success rate of preemptive treatment of CMV infection in our series, defined by the results of the CMV pp65 antigenemia assay, was similar in the VGCV and GCV groups (82% and 91%, respectively). In addition, none of the patients in either group developed CMV disease. This finding was acceptable compared with our previous reports, in which 5 of 75 (7%) LDLT recipients developed CMV disease during intravenous preemptive GCV treatment against CMV infection after LDLT. A

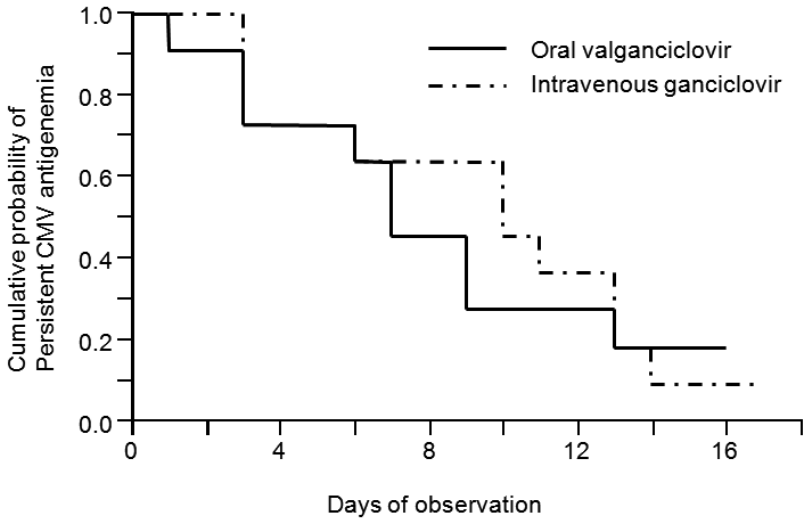

Figure 2. Kaplan-Meier curves showing cumulative probability of persistent CMV antigenemia (cutoff level, 5 copies/1 × 10^5 peripheral blood leukocytes) in patients treated with either oral valganciclovir or intravenous ganciclovir. There were no differences between groups. Straight lines denote the valganciclovir treatment arm and dotted lines represent the intravenous ganciclovir treatment arm.

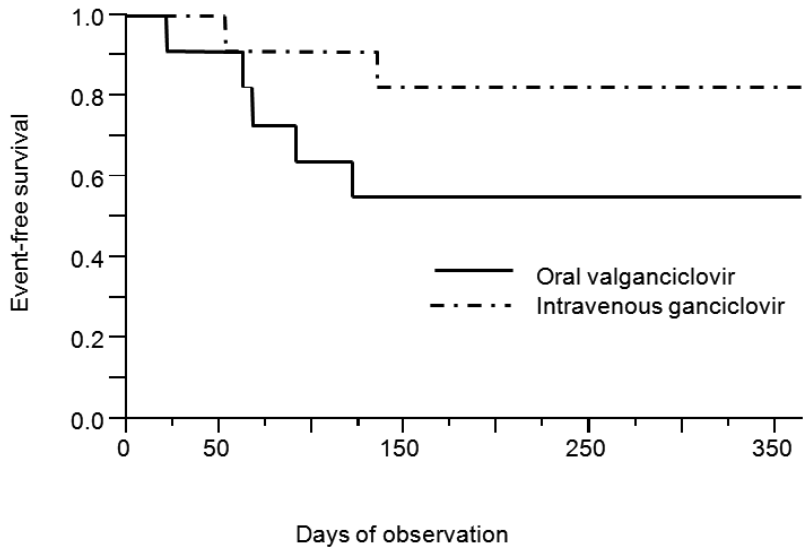

Figure 3. Kaplan-Meier estimates of event-free survival within the first year after living donor liver transplantation in both study groups. Events were defined as the recurrence of CMV antigenemia positive. There was no significant difference between patients treated with oral valganciclovir (straight line; $n = 11$) and patients treated with intravenous ganciclovir (dotted line; $n = 11$) ($p = 0.57$).

negative CMV pp65 antigenemia assay was obtained in 82% and 91% within 2 weeks, and in 91% and 100% within 1 month after the initiation of the treatment with VGCV and GCV, respectively. Although we observed a trend toward a higher proportion of recurrent CMV infection during the first year after LDLT in the VGCV group compared with GCV group (32% *versus* 18%), this difference was not statistically significant.

Both oral VGCV and intravenous GCV use for preemptive treatment of CMV infection after LDLT were well tolerated. There was no difference in the adverse event profiles between the two groups, which were comparable with those of previous studies (*13,15-17*). Patients treated with preemptive VGCV did not experience an increased incidence of adverse effects, such as leucopenia, neutropenia, and impaired renal function, compared with patients in the GCV group. Furthermore, the rate of discontinuation of the treatment due to these adverse effects in the present study was lower than that in previous reports, although the reason for this difference is unknown.

Our study has several limitations. First, the study is limited by the small sample size. To evaluate a hypothesized success rate of preemptive GCV treatment for CMV infection after LDLT of 65% with a one-tailed type I error of 5% and a statistical power of 80% would require 50 patients in each group in order to show that VGCV is not inferior compared to GCV.

Second, our preoperative examination did not include serologic CMV antibody status of either the recipients or donors; therefore we had no information on high-risk recipients with recipient-negative and donor-positive CMV serostatus. With regard to this point, however, CMV is endemic in Japan (81.7% of adults were CMV IgG positive (*18*), which suggests that almost all of the recipients in the present study were likely CMV IgG-positive (*19*). Third, this study was a not a multi-center, double-blinded study. Therefore, caution is required in applying the results of the present study to recipients with different immunosuppressive protocols or characteristics, which might lead to different outcomes. Further randomized controlled trials are necessary to establish optimal treatment strategies for CMV infection after LDLT.

In conclusion, both oral VGCV and intravenous GCV are safe, feasible options for preemptive treatment of CMV infection after LDLT.

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