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ORIGINAL ARTICLE

Oral valganciclovir as preemptive therapy is effective for cytomegalovirus infection in allogeneic hematopoietic stem cell transplant recipients

Katsuto Takenaka · Tetsuya Eto · Koji Nagafuji · Kenjiro Kamezaki · Yayoi Matsuo · Goichi Yoshimoto · Naoki Harada · Maki Yoshida · Hideho Henzan · Ken Takase · Toshihiro Miyamoto · Koichi Akashi · Mine Harada · Takanori Teshima · for Fukuoka Blood and Marrow Transplant Group (FBMTG)

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Abstract Between March 2007 and January 2008, the safety and efficacy of oral valganciclovir (VGC) preemptive therapy for cytomegalovirus (CMV) infection was evaluated in ten consecutive patients who received allogeneic hematopoietic stem cell transplantation (HSCT). Patients were screened once or twice per week after engraftment using CMV pp65 antigenemia assay. When more than 2 CMV antigen-positive cells per 50,000 leukocytes were detected, preemptive therapy with oral VGC was initiated at a dose of 900 mg twice daily for 3 weeks. Nine patients (90%) completed the 3-week VGC treatment except for one patient who developed febrile neutropenia. There was no other significant toxicity. CMV antigen-positive cells were rapidly decreased in all nine patients and became undetectable by the end of the VGC treatment. None of the patients developed CMV disease. CMV infection relapsed in four of the ten patients (40%) after the VGC treatment. These observations suggest that preemptive therapy with VGC is effective for preventing CMV disease in allogeneic HSCT patients. Further studies with a large number of patients will be necessary to determine the optimal initial- and maintenance-dose of VGC.

Keywords Allogeneic hematopoietic stem cell transplantation · Cytomegalovirus infection · Preemptive therapy · Valganciclovir

K. Takenaka (✉) · K. Nagafuji · K. Kamezaki · G. Yoshimoto · N. Harada · K. Akashi · M. Harada
Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: takenaka@intmed1.med.kyushu-u.ac.jp

T. Eto · Y. Matsuo · M. Yoshida · H. Henzan · K. Takase
Department of Hematology, Hamanomachi General Hospital, Fukuoka, Japan

T. Miyamoto · T. Teshima
Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

M. Harada
Department of Internal Medicine, National Hospital Organization Omuta National Hospital, Omuta, Japan

1 Introduction

Despite improvement in the treatment of cytomegalovirus (CMV) infection and CMV disease with ganciclovir (GCV) and/or foscarnet, CMV disease is still a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT) [1–4]. Major risk factors for CMV disease include CMV seropositivity before transplantation, development of graft-versus-host disease (GVHD), unrelated donor transplantation, and T cell depleted transplantation [3, 5–7]. In addition, new transplantation modalities such as nonmyeloablative conditioning regimens consisting of intensive immunosuppression increase the risk of late-onset CMV infection and CMV disease [2, 8]. Therefore, extended prevention of CMV disease may be required, especially for high-risk recipients, not only those within 100 days after HSCT but also those in the later period after HSCT [8–10]. Currently, the prevention of CMV disease involves general prophylaxis and preemptive therapy. Preemptive therapy is based on the early detection of CMV infection by virus surveillance, by monitoring with either CMV antigenemia assay or PCR techniques and followed by immediate treatment with anti-CMV drugs

[4, 11–13]. Intravenous GCV (IV-GCV) and/or foscarnet are commonly used for preemptive therapy and are effective for decreasing the incidence of early CMV disease [11, 13, 14]. However, these antiviral treatments are given intravenously and often require hospitalization, as well as high costs and IV-related complications.

Valganciclovir hydrochloride (VGC) is an oral valine-ester GCV prodrug with a tenfold higher bioavailability than oral GCV, and it is rapidly hydrolyzed to GCV after oral administration. VGC and IV-GCV have similar efficacy in the treatment of CMV retinitis in HIV-infected patients and in preemptive CMV treatment in solid organ (heart, renal, and renal-pancreas) transplant patients [15–19]. Recently, several studies have shown the efficacy of VGC for preemptive therapy in allogeneic HSCT patients [20–23]. We evaluated the safety and efficacy of oral VGC as preemptive therapy for CMV reactivation in ten allogeneic HSCT patients.

2 Patients and methods

2.1 Patients

This was a prospective multicenter study with VGC. The study patients were adults who had received an allogeneic bone marrow or peripheral blood stem cell transplant. Patients were eligible when they screened for CMV infection using CMV pp65 antigenemia assay and more than two CMV antigen-positive cells were detected. Patients unable to take oral medication, and those who impaired renal function (serum creatinine level >2.0 mg/dL) were ineligible. Patients, who developed CMV disease, had received antiviral agents other than acyclovir and who developed more than stage 2 gastrointestinal GVHD were also ineligible. Ten consecutive patients who received allogeneic HSCT at Kyushu University Hospital and Hamanomachi General Hospital between March 2007 and January 2008 were included in the study (Table 1). This study was approved by Institutional Review Board of each institute and a written informed consent was obtained from each participating patient.

Eight patients had acute myeloid leukemia, one had myelodysplastic syndrome, and one had non-Hodgkin's lymphoma. The median age of the patients at the time of transplantation was 56 years (range 33–63). They received bone marrow grafts from an HLA-matched sibling donor ($n = 1$), a matched unrelated donor ($n = 8$), or an HLA-1 locus mismatched unrelated donor ($n = 1$). All of the patients were CMV seropositive before transplantation. Nine patients received myeloablative preparative regimens including total body irradiation/cyclophosphamide (Cy) in five patients and busulfan (BU)/Cy in four patients.

Table 1 Patient characteristics

Number of patients	10
Median age, years (range)	56 (33–65)
Diagnosis	
Acute myeloid leukemia	8
Myelodysplastic syndrome	1
Non-Hodgkin's lymphoma	1
Stem cell source	
HLA-identical sibling bone marrow	1
HLA-matched unrelated bone marrow	8
HLA-mismatched unrelated bone marrow	1
CMV serologic status	
Donor + /Recipient +	9
Donor −/Recipient +	1
Preparative regimens	
TBI/Cy	5
Bu/Cy	4
Flu/Bu/TBI	1
GVHD prophylaxis	
Taclorimus + MTX	9
CSP + MTX	1
Acute GVHD prior to CMV reactivation	
Grade I	1
Grade II	7
Grade III	2
PSL treatment at the time of starting VCG	8

Bu busulfan, *CMV* cytomegalovirus, *CSP* cyclosporine, *Cy* cyclophosphamide, *Flu* fludarabine, *GVHD* graft-versus-host disease, *TBI* total body irradiation, *MTX* methotrexate, *PSL* prednisolone, *VGC* valganciclovir

The remaining patient received a fludarabine-based reduced-intensity conditioning regimen. GVHD prophylaxis consisted of taclorimus/short-term methotrexate (MTX) ($n = 9$) or cyclosporine/short-term MTX ($n = 1$). Patients who developed grade II–IV acute GVHD were given methylprednisolone (mPSL) or prednisolone (PSL) at a dose of 1 or 2 mg/kg. Acyclovir was administered orally (1,000 mg/day) or intravenously (500 mg/day) from days −7 to 35 as a prophylaxis against herpes simplex infection.

2.2 CMV antigenemia assay

CMV antigenemia assay was determined as previously described [7, 24]. In brief, peripheral blood leukocytes isolated from 3 mL of EDTA-treated blood were applied to slides by centrifugation and fixed with cold acetone. The slides were stained using a direct immunoperoxidase technique that employed the peroxidase-conjugated monoclonal antibody HRP-C7 (Teijin, Tokyo, Japan) against the CMV pp65 antigen. CMV antigen-positive cells were counted under a light microscope and the results were

expressed as the number of CMV antigen-positive cells per 50,000 leukocytes.

2.3 Definition of CMV infection and CMV disease

A positive test for CMV antigenemia was defined as the presence of one or more CMV antigen-positive cells per 50,000 leukocytes. CMV infection was considered in patients with a positive test for CMV antigenemia. CMV disease was diagnosed according to published recommendations [25]. Patients with clinical manifestations of CMV disease, such as interstitial pneumonia and gastroenteritis in the presence of CMV infection, were examined histopathologically and immunochemically from biopsy specimens.

2.4 Preemptive therapy with VGC for CMV infection

Monitoring with CMV antigenemia assay was performed at least once per week after engraftment until day 100 after HSCT and once every other week thereafter. Preemptive therapy with VGC for CMV infection was initiated at the time of the first detection of more than two CMV antigen-positive cells per 50,000 leukocytes. VGC was administered orally at a dose of 900 mg twice daily for 3 weeks. The dose was adjusted for patients with impaired renal function according to the manufacturer's recommendation. Acyclovir for the prophylaxis against herpes simplex infection was discontinued when VGC treatment was started. Supplemental immunoglobulin was administered only when a total IgG level was less than 400 mg/dL.

2.5 Endpoints and definitions

The primary endpoint was the rate of complete response of the VGC preemptive therapy to the CMV infection. The efficacy of VGC was monitored weekly using a CMV antigenemia assay. A complete response was defined as the conversion from positive to negative CMV antigenemia test results at the completion of the treatment. Patients who persistently showed positive test results for CMV antigenemia after 3 weeks of preemptive therapy or developed CMV disease during the period of preemptive therapy were considered a treatment failure.

The secondary endpoints included the safety of preemptive therapy, the incidence of CMV disease during VGC treatment, and the incidence of a recurrent CMV reactivation after the completion of VGC treatment. The patients were monitored with the CMV antigenemia assay for 5 weeks after the completion of the VGC treatment. At least once per week, a safety analysis was conducted. The analysis included the monitoring of blood counts, liver and renal function tests, and documenting other unexpected side effects. The incidence of CMV disease was evaluated for the entire period of the study. The incidence of recurrent reactivation of CMV infection after the VGC preemptive therapy was based on the conversion from negative CMV antigenemia to positive CMV antigenemia test results with more than two CMV antigen-positive cells per 50,000 leukocytes during the 5-week follow-up period.

3 Results

3.1 CMV infection and VGC preemptive therapy

Forty-seven patients received allogeneic bone marrow/peripheral blood stem cell transplants at these two institutes during the study period. Thirty-one patients showed positive CMV antigenemia test results after transplantation. Ten patients were enrolled into this study, but the remaining 21 patients were not enrolled mostly by their inability to take oral medication. Ten enrolled patients were given preemptive therapy with VGC for CMV infection (Table 1). All patients were CMV seropositive before transplantation, and nine donors were also CMV seropositive. In these patients, more than 2 CMV antigen-positive cells per 50,000 leukocytes were detected after a median of 69 days (range 22–252) following transplantation. The median number of CMV antigen-positive cells at the initiation of VGC therapy was 5 per 50,000 leukocytes (range 3–59). All of the patients developed acute GVHD prior to CMV infection after a median of 23 days (range 11–135). The severity of acute GVHD was grade I in one patient, grade II in seven, and grade III in two. Eight patients received mPSL or PSL for the treatment of acute GVHD. Preemptive therapy with VGC was started within five days after the detection of CMV antigen-positive cells. Nine patients completed 21 days of VGC treatment, whereas one patient failed to complete the therapy because of the development of grade 4 neutropenia and subsequent febrile neutropenia. Patients were followed at least 5 weeks after the completion of VGC preemptive therapy. The median follow-up was day 122 (range 41–355).

3.2 Response to VGC preemptive therapy

All patients showed negative test results for CMV antigenemia within 3 weeks after the initiation of the VGC treatment. In nine patients, CMV antigen-positive cells became negative within 2 weeks (Fig. 1). The remaining patient, who had 60/50,000 CMV antigen-positive cells at the time of initiation of VGC treatment, took 3 weeks to clear CMV antigen-positive cells. None of the patients required other anti-CMV agents. None of the patients developed CMV disease during the preemptive therapy or

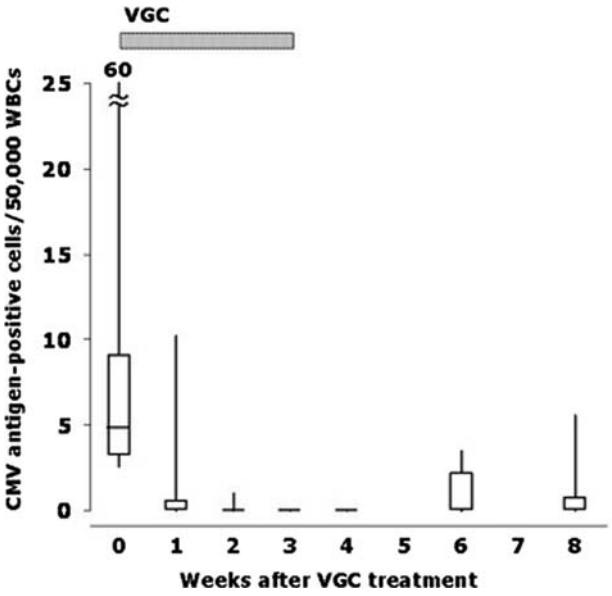

Fig. 1 Time course of the number of cytomegalovirus (CMV) antigen-positive cells after valganciclovir treatment. CMV antigenemia was reduced during treatment with valganciclovir. The *box plots* display the median, the 25th and 75th percentiles (*box*), and the smallest and largest values (*longitudinal line*). One patient discontinued valganciclovir on day 18 due to grade 4 neutropenia

in the subsequent 5 weeks after the completion of the VGC treatment.

CMV infection relapsed in four of the ten patients within 3–5 weeks after the completion of the preemptive VGC therapy. These four patients were successfully treated with IV-GCV.

3.3 Toxicity

Nine patients completed a 21-day course of VGC treatment, but one patient discontinued VGC due to grade 4 neutropenia. Due to impaired renal function (serum creatinine level, 1.68 mg/dL), this patient received a reduced VGC dose of 450 mg once per day for the first week. Renal function improved with the reduced dose, and the VGC dosage was increased to 450 mg twice per day in the second week of treatment. However, this patient developed grade 4 neutropenia (absolute neutrophil counts 0.17×10^9/L) after 17 days of treatment and then developed febrile neutropenia. The VGC was discontinued, and the patient immediately received granulocyte-colony stimulating factor (G-CSF) and antibiotic therapy. Neutrophil counts recovered to more than 1.0×10^9/L, and neutropenia resolved after five days. Recurrent CMV reactivation was not observed in this patient during the follow-up period. None of the patients developed thrombocytopenia (platelet count $<30 \times 10^9$/L)(Fig. 2).

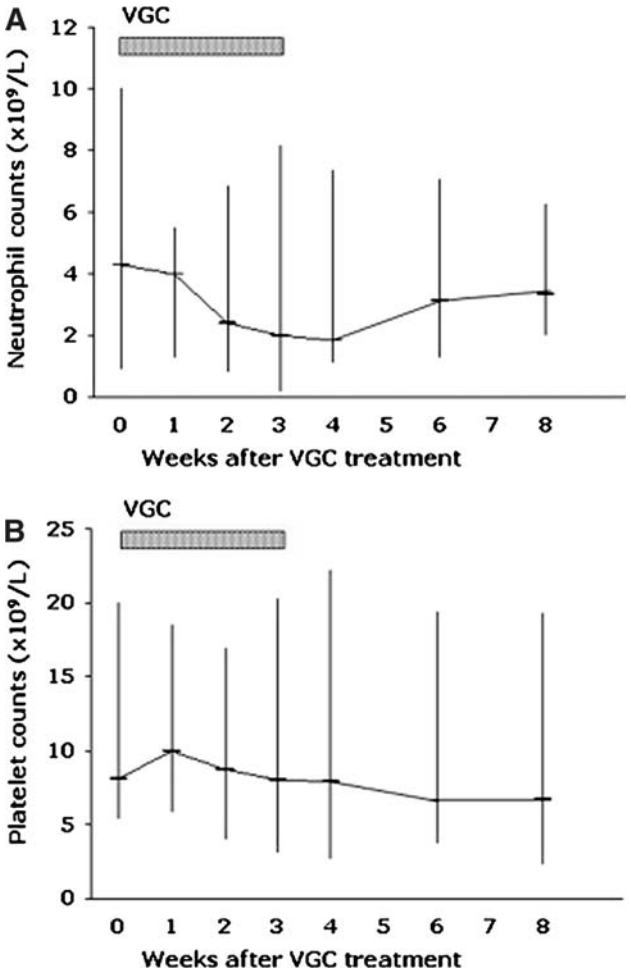

Fig. 2 Time course of neutrophils and platelets during valganciclovir treatment. Time course of neutrophil (**a**) and platelet numbers (**b**) during treatment with valganciclovir. The bar graph displays the median (*horizontal line*), and the smallest and largest values (*longitudinal line*). One patient discontinued valganciclovir on day 18 due to grade 4 neutropenia

Table 2 Adverse events other than hematological toxicities related to valganciclovir

Adverse events		No. of cases
Gastrointestinal		
Diarrhea	Grade 1	1/10
Hepatic		
AST/ALT	Grade 1	3/10

None of the patients experienced renal toxicity during the VGC treatment. Three patients developed grade 1 liver dysfunction, and one patient had grade 1 diarrhea (Table 2). However, none of these complications required discontinuation of the VGC.

4 Discussion

Effective preemptive therapy with IV-GCV reduced the incidence of early CMV disease to 5–10%; however, the risk of late CMV disease beyond day 100 after transplantation has increased over the past few years. Therefore, extended CMV monitoring beyond day 100 is currently recommended, especially in high-risk patients [2, 8]. There is a need for an effective oral anti-CMV drug that can be used for outpatient care. Oral VGC could be a useful alternative to IV-GCV in patients who require preemptive therapy for CMV infection. This study demonstrated the efficacy and safety of preemptive VGC therapy for CMV infection after allogeneic HSCT. There are four published studies that have shown the safety and the efficacy of VGC as preemptive therapy after allogeneic HSCT [20–23]. Although dosage and duration of the drug varied between studies, VGC therapy resulted in a rapid decrease of the viral load in all of the patients. In this study, we administered a dose of 900 mg twice daily for 3 weeks, and corroborated the efficacy and the tolerability of preemptive VGC therapy.

We demonstrated that VGC at a dose of 900 mg twice per day was effective and resulted in a rapid clearance of CMV antigen-positive cells in all patients. No CMV disease developed during the preemptive therapy or the subsequent 5 weeks after the completion of treatment. VGC was well tolerated as 90% of the patients completed the entire treatment course. However, four of the ten patients developed a recurrent CMV reactivation after the discontinuation of VGC treatment, and they were all successfully treated with IV-GCV. Because a guideline for preemptive VGC therapy has not been established for patients that have received allogeneic HSCT, further studies will be necessary to determine the optimal initial- and maintenance-dose of VGC.

We, and four other groups, have obtained good results with VGC starting-doses of 900 mg twice per day [20–23]. This dose was based on observations from previous pharmacokinetics studies in HIV-infected patients and liver transplant recipients. A VGC dose of 900 mg results in an area under the concentration-time curve for GCV similar to that of 5 mg/kg IV-GCV [26, 27], which is the recommended standard dose for preemptive CMV therapy [28, 29]. One of the concerns of using VGC after allogeneic HSCT is the absorption of oral VGC in patients suffering from severe gastrointestinal GVHD. Recently, Einsele et al. [30] conducted a randomized crossover clinical trial of IV-GCV and VGC in patients with or without intestinal GVHD. The results showed that patients without intestinal GVHD who took VGC were exposed to more GCV when compared to those administered IV-GCV. This was also true in patients with grade I and II intestinal GVHD. Thus, VGC may be as effective even in patients developing a mild form of intestinal GVHD as in patients without intestinal GVHD. However, a higher exposure of VGC may increase the toxicity of the drug, and the absorption of VGC was not evaluated in patients with severe intestinal GVHD. Recently, Candoni et al. [22] examined the efficacy of a lower dose of VGC. Preemptive therapy with 900 mg/day VGC was as effective for clearing CMV antigen-positive cells and preventing CMV disease as the standard dose of 1800 mg/day. These findings suggest that the initial dose of VGC could be reduced to 900 mg/day as preemptive therapy in low-risk patients.

The effective duration for preemptive VGC therapy is currently unclear. In the previous studies, patients received VGC for 2 weeks and then it was either discontinued or continued at a maintenance dose of variable duration dependant upon a negative CMV test result. Different from previous studies, we continued an initial dose of VGC for 3 weeks. The dosage and duration of VGC therapy likely affects the incidence of hematological toxicity such as neutropenia. In a study by Busca et al. [21], in which VGC was administered at a dose of 1,800 mg/day for 2 weeks, followed by 900 mg/day for an additional 2 weeks, 4 of the 15 patients failed to complete the 3-week scheduled therapy due to neutropenia and/or thrombocytopenia. In our study, only one of the ten patients failed to complete treatment. Thus, hematologic toxicity may be a significant problem after a 3 week treatment with VGC.

In our study, four of the ten patients treated with VGC developed recurrent CMV reactivation 3–5 weeks after the discontinuation of VGC. This was somewhat similar to the 10–53% recurrence rates in previous studies [20–23]. Thus, careful monitoring after the completion of VGC therapy is recommended. We continued an initial dose of VGC for 3 weeks. However, when considering hematological toxicity and frequent recurrence of CMV antigenemia, the duration of treatment and/or maintenance should be decided by monitoring CMV.

As previously reported [20–23], we found neutropenia to be the main toxic effect of VGC. One patient, who had impaired renal function before the preemptive therapy that required a dose reduction, discontinued the drug on day 17 due to grade 4 neutropenia. In high-risk patients, especially outpatient should be closely monitored, although any other toxicity profile different from IV-GCV was not observed in this study.

Our study demonstrated that the oral VGC preemptive therapy at a dose of 900 mg daily seemed to be as effective as conventional IV-GCV at a dose of 10 mg/kg daily to clear CMV antigen-positive cells. However, as shown in Fig. 1, CMV antigen-positive cells seem to decrease in numbers much faster after VGC treatment than those observed after standard dose of IV-GCV treatment.

Furthermore, hematological toxicities were considerable. Although pharmacokinetic data was not available in this study, these observations coincide with the previous pharmacokinetic study in HSCT recipients that showed the exposure of GCV after administration of 1800 mg daily VGC was significantly higher compared with 10 mg/kg IV-GCV even in patients without gastrointestinal GVHD [30]. Careful monitoring of neutrophil counts will be useful to improve the safety of VGC in HSCT recipients, especially with reduced renal function. Kanda et al. [14] showed the efficacy of response-oriented preemptive therapy using a low initial dose of IV-GCV that resulted in a successful reduction of the total dose of IV-GCV and decreased hematological toxicities. A lower dose of VGC could be also used as preemptive therapy by close CMV monitoring. Similar studies with a large number of patients will be required to define the optimal treatment schedule for preemptive VGC therapy.

Despite a limited number of patients, our results suggest that oral VGC is an effective alternative to IV-GCV for preemptive therapy to prevent CMV disease in allogeneic HSCT patients. Studies with a larger number of patients will be necessary to assess the efficacy and long-term effect of this preemptive therapy.

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