Use of foscarnet for cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation from a related donor

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Abstract Foscarnet is an active agent against cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation (HSCT), as well as ganciclovir. We investigated the usefulness of foscarnet in patients who underwent related allogeneic HSCT. Foscarnet was used in 320 patients with a median age of 45 years (range 15–72). The purpose of administration was CMV disease in 65, preemptive use in 248 and prophylaxis in 7. Totally, 194 patients had a history of prior ganciclovir treatment. The reason for foscarnet use was insufficient therapeutic effect of prior ganciclovir in 99, and adverse event including myelosuppression in 95. The response rate in symptom was 52% for the CMV disease patients. Antigenemia disappeared in 77% of the preemptive treatment and improved in 13% of the patients. No outbreak of CMV disease was recognized. The total effectiveness of therapeutic and preemptive use was significantly higher for patients without prior ganciclovir (91 vs. 76%, \( P = 0.001 \)). Adverse events of grade 3 or higher were recognized in 24%, including electrolyte abnormalities in 11%, neutropenia in 8%, and thrombocytopenia in 8%. Renal damage was only observed in 3% of patients. Foscarnet was concluded to be a safe and effective anti-CMV agent and to be a suitable alternative to ganciclovir.

Keywords Cytomegalovirus infection · Foscarnet · Blood and marrow transplantation · Efficacy · Adverse reaction
1 Introduction

Cytomegalovirus (CMV) disease is one of the most important infectious complications after allogeneic hematopoietic stem cell transplantation (HSCT), which influences the outcome of the transplantation. The presence of graft-versus-host disease and steroid therapy are associated with the occurrence of CMV infection or reactivation. Ganciclovir is used as a first-line agent for both prophylaxis and the treatment of CMV disease [1-5]. However, approximately one-third of patients receiving ganciclovir develop drug-induced neutropenia or thrombocytopenia [6-9]. Therefore, ganciclovir is unsuitable for use in patients with poor bone marrow function. Another problem is ganciclovir resistant CMV [10-12].

For such cases, foscarnet is an important alternative agent that demonstrates anti-viral activity against all known herpes viruses including CMV [11, 13-15]. In early studies, the dose-limiting toxicities of foscarnet were found to be nephrotoxicity and neurotoxicity, which were seen in up to 50% of patients [16, 17]. Two randomized controlled trials (RCT) comparing the usefulness of preemptive foscarnet versus ganciclovir have been performed for CMV antigenemia [18, 19]. These studies revealed that the effectiveness of foscarnet was equivalent to that of ganciclovir. Adverse reactions and treatment-related mortality of foscarnet were also the same as those of ganciclovir. Renal dysfunction was only noted in 5% of the patients that received foscarnet [19].

The use of foscarnet has also been reported in cord blood transplantation, which is more complicated by viral infection [20]. These studies including the RCT only involved patients who had received foscarnet as an initial therapy. Therefore, we conducted a nationwide study in Japan of the use of foscarnet against CMV infection after related HSCT to investigate the current status, and compared its efficacy and toxicity in patients with and without prior ganciclovir use.

2 Patients and methods

2.1 Study design

This study is a retrospective survey investigating the use of foscarnet after stem cell transplantation. The subjects of this study were patients who received foscarnet after receiving allogeneic transplantation from a related donor in the period from 1998 to 2008. We performed a questionnaire at institutions carrying out allogeneic stem cell transplants in Japan. Data regarding the presence of CMV disease, CMV antigenemia, the reason for foscarnet use, the dose and duration of foscarnet, the effectiveness of therapy, and adverse events were collected. The obtained data were combined with data from the national registry of the Japan Society of Hematopoietic Cell Transplantation, which was collected by the TRUMP system [21]. This study was approved by the Ethical Committees of the Japan Society of Hematopoietic Cell Transplantation and Hyogo College of Medicine.

2.2 CMV antigenemia assay

Cytomegalovirus antigenemia was measured as described previously [22, 23]. Briefly, peripheral white blood cells were attached to slides by cytocentrifugation and stained with HRP-C7 (Teijin, Tokyo, Japan) or C10/C11 (Biotest, Dreieich, Germany) monoclonal antibodies. The number of positive cells was counted per 50,000 attached cells for HRP-C7 and per 150,000 applied cells for C10/C11. The examination was performed in duplicate, and the mean was used for further analyses.

2.3 Definition of CMV disease and infection

CMV diseases were defined as any organ infections by CMV, ideally proven by histopathologic examinations. They include gastroenteritis, pneumonia, retinitis, hepatitis, encephalitis, and cystitis. Patients who presented with interstitial pneumonia accompanied by CMV antigenemia were also diagnosed with CMV disease (pneumonia). For patients who presented with antigenemia and simultaneous diarrhea, gastrointestinal endoscopy and biopsy were recommended, but those who could not receive such diagnostic procedure were regarded as suspicious CMV disease (gastroenteritis). Both CMV antigenemia and CMV disease were regarded as CMV infection.

2.4 Type of therapy

The administration of anti-viral agents for patients without any CMV disease but accompanied by CMV antigenemia with or without febrile complications was defined as preemptive therapy in this study. Therapy of CMV disease was defined as CMV treatment. The use of anti-viral agents for those without antigenemia or CMV disease was regarded as prophylaxis.

2.5 Statistics

Pairwise comparisons were performed using the \( \chi^2 \) test and Fisher’s exact test for categorical variables, and the Mann-Whitney U test for continuous variables. The Kruskal-Wallis test was used to compare multiple groups. \( P \) values of <0.05 obtained in 2-sided tests were considered statistically significant. Data were analyzed with the STATA version 11 statistical software (STATA Corp, TX, USA).
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3 Results

3.1 Patient characteristics

The background data of 320 patients are shown in Table 1. There were 171 males and 149 females. Their median age was 45 years, and the ages of the patients ranged from 15 to 72 years. The underlying disease of patients was acute myeloid leukemia (AML) in 110, acute lymphoblastic leukemia (ALL) in 59, chronic myelogenous leukemia (CML) in 18, myelodysplastic syndrome (MDS)/myeloproliferative disorder (MPD) in 42, chronic lymphocytic leukemia (CLL) in 2, non-Hodgkin lymphoma (NHL) in 51, Hodgkin lymphoma (HL) in 4, adult T cell lymphoma (ATL) in 16, multiple myeloma (MM) in 10, aplastic anemia (AA) in 6 and 1 each for renal cell carcinoma and virus associated hemophagocytic syndrome. Several demographic data were not available due to the lack of patient entry to the TRUMP system. CMV antibody was positive in both the patient and donor in 189 pairs (59%), in the patient only in 22 cases (7%), and in the donor only in 8 cases (3%), and it was negative in both patient and donor in 4 pairs (1%). Of 289 patients with evaluable data, 113 patients received bone marrow (BM) as a graft, 172 received peripheral blood stem cell (PBSC), and 4 received both BM and PBSC. HLA was matched in 108 of 268 patients but was mismatched in the remaining 160 (155 with serological mismatch and 5 with allele mismatch).

3.2 CMV infection

Foscarnet was administered for CMV disease in 65 patients (20%), including 46 with gastroenteritis, 12 with pneumonia, 2 with retinitis, and one each for hepatitis, encephalitis, and cystitis. Each one other patient developed pneumonia and retinitis accompanied by simultaneous gastroenteritis. On the other hand, 248 (78%) were preemptively treated (only complicated with CMV antigenemia), and 7 (2%) were prophylactically treated. Before foscarnet administration, 194 (61%) patients had received ganciclovir, and one of the patients was treated with cidofovir after ganciclovir use. The reason for changing the anti-viral agent to foscarnet was insufficient therapeutic effect in 99 patients and adverse events due to preceding ganciclovir including myelosuppression in 95 patients. In 126 patients who had not received any anti-viral premedication, foscarnet was used because of poor bone marrow function in 116.

A total of 208 patients (67%) received steroid therapy at the time of foscarnet initiation. The rate of patients under steroid use was 58% for CMV disease, 70% for preemptive foscarnet, and 43% for prophylaxis, but the difference was not significant ($P = 0.08$).

3.3 Dosage of foscarnet

The initial dose of foscarnet ranged from 7 mg/kg to 216 mg/kg (median 88 mg/kg, Fig. 1). The dose was

![Fig. 1 Initial dose of foscarnet. Foscarnet was given at a variety of doses ranging from 7 to 216 mg/kg (median 88 mg/kg). Two peaks at 90 and 180 mg/kg were seen in the histogram.](image-url)
significantly higher in the patients who had received prior ganciclovir (range 10–216 mg/kg, median 91 mg/kg) than those who had not (range 7–180 mg/kg, median 72 mg/kg) \( (P < 0.0001) \). The median dose in the preemptive, treatment, and prophylactic groups was 89, 90, and 63 mg/kg, respectively; i.e., it was significantly lower in the prophylactic use group \( (P = 0.05) \). The initial dose of foscarnet did not have any correlation with creatinine clearance calculated from serum creatinine level and age by the Modification of Diet in Renal Disorder (MDRD) formula \( (r = -0.21) \). The duration of foscarnet use ranged from 1 to 163 days (median 20 days) and was significantly shorter for patients who had received prior ganciclovir than those who had not (median 17 vs. 22 days, \( P = 0.05 \)). As there were two peaks at 90 and 180 mg/kg in the dose of foscarnet administered, 5 dose categories (0–39, 40–79, 80–99, 100–159, and 160–220) were defined, and the efficacy and toxicity of foscarnet were estimated according to this categorization.

### 3.4 Efficacy

Among 65 patients with CMV disease, the symptoms disappeared in 5 (8%) and improved in 28 (44%), no change was seen in 20 (32%), and the symptoms worsened in 10 (16%) (Table 2). One patient was not evaluable with regards to their response, and another patient did not have any symptoms at the initiation of foscarnet because of the effect of prior ganciclovir use. The effectiveness (resolved or improved) was higher in those who did not receive ganciclovir, but the difference was not statistically significant \( (71 \% \text{ vs. } 46 \%, \ P = 0.10) \). When the effectiveness in symptom was compared between HLA-matched and -mismatched transplant, the rate was almost comparable \( (14/25 \% = 56 \% \text{ vs. } 14/29 \% = 48 \%, \ P = 0.60) \). Among 238 evaluable patients who received preemptive CMV therapy, antigenemia was resolved in 183 (77%) and improved in 31 (13%), but was not changed in 17 (7%) and worsened in 7 (3%). No patient developed outbreaks of CMV disease. The effectiveness was higher for those who had not received prior ganciclovir, but the difference was not significant \( (93/99 \% = 93 \% \text{ vs. } 121/139 \% = 87 \%, \ P = 0.13) \).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prior GCV</th>
<th>No prior GCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( % )</td>
</tr>
<tr>
<td>CMV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disappeared</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Improved/decreased</td>
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<td>37</td>
</tr>
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<td>39</td>
</tr>
<tr>
<td>Worsened/increased</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>No symptoms/antigenemia</td>
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<td>-</td>
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<tr>
<td>Unevaluable</td>
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<table>
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<tr>
<th>Antigenemia</th>
<th>Prior GCV</th>
<th>No prior GCV</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( % )</td>
</tr>
<tr>
<td>Preemptive</td>
<td></td>
<td></td>
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<tr>
<td>Disappeared</td>
<td>-</td>
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<tr>
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<td>-</td>
</tr>
<tr>
<td>No antigenemia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>-</td>
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</tbody>
</table>

### Table 2: Response to foscarnet

GCV ganciclovir

\* Symptoms/antigenemia had disappeared after prior GCV
Although the effectiveness in preemptive use was lower in HLA-matched transplant as compared with HLA-mismatched transplant, the difference was not also significant

\[ \frac{64}{75} = 85\% \text{ vs. } \frac{114}{123} = 93\%, \quad P = 0.14. \]

Among the patients who received prior ganciclovir, the effectiveness was significantly higher in the patients in whom an insufficient effect of ganciclovir was seen compared with those who had suffered an adverse reaction to ganciclovir \[ \frac{64}{68} = 94\% \text{ vs. } \frac{57}{71} = 80\%, \quad P = 0.02. \]

The overall effectiveness of treatment and preemptive use was significantly higher in those who had not received prior ganciclovir (91 vs. 76%, \( P = 0.001 \)) because of the low effectiveness in the patients of the CMV disease group who had received prior ganciclovir use. The changing courses of CMV antigenemia are box plotted in Fig. 3a for the patients who received prior ganciclovir and in Fig. 3b for those who did not. After the administration of foscarnet, the CMV antigenemia decreased in both groups \( (P < 0.0001 \) and \( P = 0.01 \), respectively).

The responses to foscarnet according to the 5 dose categories are summarized in Fig. 4. The symptoms of CMV disease improved in around 50% of patients in every dose category. In the CMV disease patients the response rate of
antigenemia was significantly lower for those received foscarnet <40 mg/kg ($P = 0.01$).

3.5 Survival

The overall survival of all patients who received foscarnet was 34% at a median follow-up of 3 years (Fig. 5a). Patients with CMV disease showed significantly lower survival than those who received preemptive or prophylactic therapy (Fig. 5b, $P = 0.0004$). No significant difference in prognosis was found between the patients with and without preceding other anti-viral agents ($P = 0.21$). A total of 170 patients died, and the main causes of death were disease recurrence in 47, bacterial sepsis in 27, acute/chronic graft-versus-host disease in 25, and fungal infection in 10. The cumulative incidence of transplant-related mortality at 1 year was 30% (95% confidence interval 25–35%). Three patients eventually died of CMV disease, and the cumulative incidence of CMV-associated death at 1 year was 1.0% (95% confidence interval 0.3–2.6%).

3.6 Adverse events

Adverse events (irrespective of causal association) of NCI-CTCAE grade 3 or higher are listed in Table 3. The most common adverse event was electrolyte abnormalities, which occurred in 35 patients (11%). The other major toxic events included neutropenia in 27 patients, thrombocytopenia in 26 patients, and bone marrow dysfunction in 11 patients. Renal and hepatic damage developed in 11 and 10 patients, respectively. Adverse events associated with foscarnet included neutropenia in 5 patients; electrolyte abnormalities in 4 patients; thrombocytopenia, renal dysfunction and sensory disturbance in 2 patients each; and bone marrow dysfunction in 1 patient. No patient died of an adverse reaction associated with foscarnet. The total number of patients who developed a grade 3 adverse reaction or higher was 56 (28%) in the patients who received prior ganciclovir and 21 (17%) in those who did not ($P = 0.03$). The rate of adverse events did not differ among the 5 dose categories (Table 4). The duration of foscarnet medication was not different between patients who developed adverse event of grade 3 or more (median 16 days, range 2–121) and those did not (median 20 days, range 1–121).

![Fig. 5 Overall survival (OS) of patients who received foscarnet therapy. a The 3-year OS was 34%. b The prognosis of patients with CMV disease was significantly poorer than those of patients who had received preemptive or prophylactic use ($P = 0.0004$)](image-url)
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Table 4 Adverse effects according to foscarnet dose

<table>
<thead>
<tr>
<th>Dose level (mg/kg)</th>
<th>0–39</th>
<th>40–79</th>
<th>80–99</th>
<th>100–159</th>
<th>160–</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 18 (%)</td>
<td>N= 106 (%)</td>
<td>N= 88 (%)</td>
<td>N= 60 (%)</td>
<td>N= 48 (%)</td>
<td>N= 320 (%)</td>
<td></td>
</tr>
<tr>
<td>Any grade 3 or higher</td>
<td>33</td>
<td>23</td>
<td>17</td>
<td>25</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Grade 3 or higher, possibly by foscarnet</td>
<td>28</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Grade 3 or higher, definitely by foscarnet</td>
<td>0</td>
<td>2.8</td>
<td>3.4</td>
<td>8.3</td>
<td>6.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

range 1–322, \( P = 0.50 \)). The difference was not evident for patients with possible and definite association with foscarnet \((P = 0.84 \text{ and } P = 0.22, \text{ respectively})\). When the adverse events were compared between HLA-matched and -mismatched transplant, the rates were significantly higher in the HLA-matched transplant. Any grade 3 or more toxicity was developed in 36 of 108 HLA-matched and 33 of 160 HLA-mismatched transplant \((P = 0.02)\). Of these, 31 and 24, respectively, were possibly due to foscarnet use \((29 \text{ vs. } 15\%, \ P = 0.009)\).

4 Discussion

The present study demonstrated that foscarnet is effective for patients with CMV infection who are not suitable for ganciclovir therapy. Sixty percent of the patients had a history of prior ganciclovir, but had demonstrated problems of ineffectiveness and/or adverse reactions. The remaining 40% had poor bone marrow function, and therefore foscarnet had been selected as the up-front use. In both situations, most of the patients were preemptively treated, and prophylactic use was seen in <2% of cases in our series.

The initial dose of foscarnet had two convergent doses, which were 90 and 180 mg/kg. The former corresponds to the maintenance dose, and the latter is the initial dose which was used in most prospective studies \([18, 19]\). The dose of foscarnet was significantly higher in patients with secondary therapy. This might have resulted from a higher number of more severe patients with CMV infection being present in the secondary therapy group. On the other hand, no dosage differences were found between the various purpose groups (preemptive/prophylactic/treatment). The lack of a correlation between foscarnet dose and creatinine clearance suggested that foscarnet was used irrespective of the renal function of the patient.

The most important adverse reaction of foscarnet was previously described as renal damage including electrolyte abnormalities. In that study, one-third of patients developed renal insufficiency and/or electrolyte disturbance \([15]\). However, a later study showed that these adverse events occurred less frequently \([19]\). In our series of patients, electrolyte abnormalities were recognized in 11% of patients, and renal insufficiency was found in no >3% of patients, which was consistent with the findings in the literature \([24]\). Thus, foscarnet seems to be a safer drug than was initially predicted.

In the preemptive use of foscarnet, >80% of patients showed CMV antigenemia disappearance in both the initial and secondary therapy groups. Foscarnet was highly effective in this setting, but its efficacy was decreased in CMV disease. The efficacy of foscarnet did not correlate with its dose, which was contradictory to a previous dose-finding study \([25]\). Our findings suggest a need to explore appropriate therapeutic strategies for this agent. Recently, "low-dose" administration of foscarnet at 60 mg/kg/day has been reported to be effective for CMV preemptive treatment \([26, 27]\), which could be an option for future clinical trials. A prospective trial comparing ganciclovir alone and a combination of ganciclovir and foscarnet (half doses of both) was performed for HSCT and organ transplant patients \([28]\). The efficacy was equivalent for both arms, but adverse events were more frequent in the foscarnet combined arm.

In conclusion, our study shows that foscarnet is a safe and effective agent for treating CMV antigenemia after allogeneic HSCT. It remains to be determined how CMV infections should be treated, as well as how to improve the survival of affected patients.

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References


