Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment

Yuki Asano-Mori¹, Yoshinobu Kanda¹²*, Kumi Oshima¹², Takuro Watanabe¹, Eriko Shoda¹, Toru Motokura¹, Mineo Kurokawa¹² and Shigeru Chiba¹²

¹Department of Hematology & Oncology, University of Tokyo Graduate School of Medicine and Hospital, Tokyo, Japan; ²Department of Cell Therapy & Transplantation Medicine, University of Tokyo Hospital, Tokyo, Japan

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Objectives: We investigated the pharmacokinetics of ganciclovir in 12 haematopoietic stem cell transplantation (HSCT) recipients to evaluate the validity of a 50% reduction in the ganciclovir dosage for mild renal impairment.

Patients and methods: Ganciclovir at 5 mg/kg/day was pre-emptively infused in patients with estimated CLCr > 70 mL/min (Group A), whereas the dose was reduced to 2.5 mg/kg/day in patients with CLCR between 50 and 70 mL/min (Group B).

Results: The peak concentration was significantly higher in Group A (P < 0.01). However, the decrease in the plasma ganciclovir concentration was slower in Group B (P = 0.09), and the AUC of all patients in both groups was distributed within a narrow range (25.6 ± 4.77 μg·h/mL), when two patients with exceptionally high AUC values were excluded.

Conclusions: A 50% reduction in ganciclovir appeared to be appropriate for patients with mild renal impairment. Measuring the ganciclovir concentration at 4 h after starting infusion may be adequate for evaluating AUC.

Keywords: cytomegalovirus, CMV, antigenaemia, antiviral therapy

Introduction

Ganciclovir is the mainstay of antiviral agents in pre-emptive therapy against cytomegalovirus (CMV) disease after allogeneic haematopoietic stem cell transplantation (HSCT). Ganciclovir is mainly excreted from the kidney and about 90% of the administered dose is recovered unchanged in the urine after intravenous (iv) administration. Therefore, total body clearance correlates well with CLCr. In HSCT settings, patients frequently develop renal impairment caused by the use of nephrotoxic drugs. A 50% reduction of ganciclovir is recommended in the drug information leaflet for patients with mild renal impairment of CLCR between 50 and 70 mL/min in order to achieve an unchanged AUC. However, the pharmacokinetic profiles of ganciclovir have not yet been fully evaluated in such patients. Therefore, we investigated the validity of this dose reduction by serial evaluation of the plasma ganciclovir concentration.

Patients and methods

Twelve patients (nine men and three women) aged between 23 and 61 years were enrolled in a 12 h pharmacokinetic study of intravenous ganciclovir after ethical approval. The median age and weight were 50.5 years (range 23–61) and 57.5 kg (range 36.7–80.0), respectively. All patients provided informed consent to participate in this study. The underlying disease was acute leukaemia in three patients, chronic myelogenous leukaemia in three patients, myelodysplastic syndrome in two patients and pancreatic cancer in four patients. Five patients received a graft from an HLA-matched relative and seven received a graft from an alternative donor defined as an HLA-mismatched relative or a matched unrelated donor. We calculated CLCr weekly, based on a 24 h urine collection. Patients were classified into two groups according to CLCr evaluated within 1 week before the initiation of ganciclovir administration: Group A included seven patients with CLCr ≥ 70 mL/min (mean 98.1 mL/min, range 74.9–142.0 mL/min) and Group B included five patients.
Pharmacokinetics of ganciclovir in HSCT recipients

<table>
<thead>
<tr>
<th></th>
<th>Group A (CL&lt;sub&gt;CR&lt;/sub&gt; ≥ 70 mL/min)</th>
<th>Group B (CL&lt;sub&gt;CR&lt;/sub&gt; 50–70 mL/min)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0.5</td>
<td>6.56 (4.39–11.33) µg/mL</td>
<td>4.92 (2.90–10.80) µg/mL</td>
<td>0.37</td>
</tr>
<tr>
<td>C1</td>
<td>9.20 (5.50–19.03) µg/mL</td>
<td>4.75 (3.32–6.61) µg/mL</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C2</td>
<td>4.76 (2.72–12.09) µg/mL</td>
<td>2.38 (2.30–2.73) µg/mL</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C4</td>
<td>2.58 (1.25–6.30) µg/mL</td>
<td>1.57 (1.37–1.80) µg/mL</td>
<td>0.17</td>
</tr>
<tr>
<td>C6</td>
<td>1.69 (0.79–4.89) µg/mL</td>
<td>1.15 (0.90–1.30) µg/mL</td>
<td>0.29</td>
</tr>
<tr>
<td>C8</td>
<td>1.22 (0.40–3.99) µg/mL</td>
<td>0.91 (0.64–1.09) µg/mL</td>
<td>0.57</td>
</tr>
<tr>
<td>C12</td>
<td>0.62 (0.23–2.88) µg/mL</td>
<td>0.58 (0.39–0.81) µg/mL</td>
<td>0.94</td>
</tr>
<tr>
<td>LogC4/C1</td>
<td>–0.66 (–0.73–0.48)</td>
<td>–0.42 (–0.68–0.33)</td>
<td>0.09</td>
</tr>
<tr>
<td>AUC</td>
<td>29.8 (20.2–111.0) µg·h/mL</td>
<td>24.6 (22.5–28.3) µg·h/mL</td>
<td>0.57</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>3.57 (3.36–7.94) h</td>
<td>5.76 (5.05–8.87) h</td>
<td>0.03</td>
</tr>
<tr>
<td>CL&lt;sub&gt;TOT&lt;/sub&gt;</td>
<td>3.04 (0.73–4.31) mL/min/kg</td>
<td>1.66 (1.50–1.81) mL/min/kg</td>
<td>0.12</td>
</tr>
</tbody>
</table>

CL<sub>CR</sub>, creatinine clearance; AUC, area under the concentration curve; t<sub>1/2</sub>, elimination half-life; CL<sub>TOT</sub>, total body clearance.

C0.5–C12 represent plasma ganciclovir concentrations at 30 min, and 1, 2, 4, 6, 8 and 12 h after start of infusion, respectively. The values of each parameter are reported as the median and range.

The peak plasma concentration (C<sub>max</sub>) ranged from 3.32 to 19.03 µg/mL. The C<sub>max</sub> in Group A was significantly higher than that in Group B (9.20 versus 4.75 µg/mL, P < 0.01). There was a borderline significance in the decline ratio between the two groups (0.66 versus 0.42, P = 0.09). Total body clearance in Group B was lower than that in Group A (1.66 versus 3.04 µL/min/kg, P = 0.12). Also, the elimination half-life in Group B was significantly longer than that in Group A (5.76 versus 3.57 h, P = 0.03). There was no significant difference in AUC between the two groups (29.8 versus 24.6 µg·h/mL, P = 0.57). The AUCs of the patients in both groups were distributed within a narrow range (25.6 ± 4.77 µg·h/mL, Figure 1b), when we excluded two patients with exceptionally high AUC values (48.18 and 110.99 µg·h/mL). The CL<sub>CR</sub> values of these two patients were 74.9 and 87.2 mL/min, respectively. Among the serial ganciclovir concentration measurements, C4 most strongly correlated with AUC (r² = 0.95, Figure 1c).

Results

The median pharmacokinetic parameters and the concentration versus time profile are shown in Table 1 and Figure 1(a). The peak plasma concentration (C<sub>max</sub>) ranged from 3.32 to 19.03 µg/mL. The C<sub>max</sub> in Group A was significantly higher than that in Group B (9.20 versus 4.75 µg/mL, P < 0.01). There was a borderline significance in the decline ratio between the two groups (0.66 versus 0.42, P = 0.09). Total body clearance in Group B was lower than that in Group A (1.66 versus 3.04 µL/min/kg, P = 0.12). Also, the elimination half-life in Group B was significantly longer than that in Group A (5.76 versus 3.57 h, P = 0.03). There was no significant difference in AUC between the two groups (29.8 versus 24.6 µg·h/mL, P = 0.57). The AUCs of the patients in both groups were distributed within a narrow range (25.6 ± 4.77 µg·h/mL, Figure 1b), when we excluded two patients with exceptionally high AUC values (48.18 and 110.99 µg·h/mL). The CL<sub>CR</sub> values of these two patients were 74.9 and 87.2 mL/min, respectively. Among the serial ganciclovir concentration measurements, C4 most strongly correlated with AUC (r² = 0.95, Figure 1c).

Pharmacokinetic parameters were calculated by non-compartment modelling using WinNonlin software (version 4.0; Pharsight Corporation). CL<sub>CR</sub> was normalized to 1.73 m² body surface area and AUC was calculated using the linear trapezoidal rules with extrapolation to infinity by standard techniques. The decline ratio was calculated as Log C4/C1 for the evaluation of the decrease in plasma ganciclovir concentration in the distribution phase and early elimination phase, whereas the elimination half-life was calculated from the terminal portion of the slope after C4. The differences between groups were compared using the Wilcoxon (Mann–Whitney)-test. P values of less than 0.05 were considered statistically significant. The relationship between the total AUC and plasma ganciclovir concentration at each point after starting infusion was investigated by calculating correlation coefficients r² using linear regression analysis after logarithmic transformation because they did not fit a normal distribution.
The results demonstrated that a 50% reduction in the ganciclovir dosage was appropriate for HSCT recipients with mild renal impairment of CL\textsubscript{CR} between 50 and 70 mL/min. In addition to the significant difference in the elimination half-life, we observed a difference in the decline ratio (Log C4/C1) between the two groups with a borderline significance, which might indicate that renal excretion had started within 4 h of infusion. AUC was not significantly different from that in patients with normal renal function, probably due to the prolonged elimination in patients with mild renal impairment, although the small sample size might be responsible for the lack of significant difference. When we excluded two patients whose AUC values were exceptionally high, the AUC ranged within 25.6 ± 4.77 \( \mu \text{g} \cdot \text{h/mL} \), which was similar to the values reported previously. An exceptionally high AUC was observed in two patients with CL\textsubscript{CR} values between 70 and 90 mL/min. The reason for the high AUC is not clear, but it may suggest that the dose of ganciclovir should be reduced in patients with CL\textsubscript{CR} values between 70 and 90 mL/min after confirming that the AUC is significantly high in such patients. Drug interaction is also a possible explanation for the high AUC, but these two patients were not being given drugs that are known to interact with ganciclovir. Also, the exceptionally high AUC might result from a transient renal dysfunction, which could not be detected even by a weekly CL\textsubscript{CR} examination.

The role of clinical pharmacokinetic monitoring in solid organ transplantation as well as in HSCT is unclear. Previous studies failed to show a significant correlation between the ganciclovir concentration and its efficacy or toxicity. A possible explanation for this lack of correlation is the small number of patients in these studies, since a significant correlation between the cumulative dose of ganciclovir and the incidence of neutropenia has been shown in large-scale clinical studies. However, it is difficult to perform a large-scale study with pharmacokinetic monitoring because of the need for repeated blood sampling from patients. In this study, C4 most strongly correlated with AUC, with \( r^2 \) values of 0.95, although we should confirm this in a larger study. Another limitation of pharmacokinetic monitoring of ganciclovir is that only the intracellular phosphorylated ganciclovir is active and it is not known how its concentration relates to the plasma concentrations. Nevertheless, a prospective study with monitoring of C4 is warranted to evaluate the role of pharmacokinetic monitoring in HSCT.

In conclusion, a recommended reduction of ganciclovir dosage by 50% appeared to be appropriate for HSCT recipients with mild renal impairment. Measurement of the plasma ganciclovir concentration C4 could be an accurate predictor of AUC. Further studies are necessary to validate these findings in a larger number of patients and to clarify the relationship among plasma concentrations, AUC and responses.

**Transparency declarations**

None to declare.

**References**


