Reduced dose of foscarnet as preemptive therapy for cytomegalovirus infection following reduced-intensity cord blood transplantation


Abstract: Although foscarnet is a promising alternative for the treatment of cytomegalovirus (CMV) infection, its toxicity can be significant in patients with advanced age. We retrospectively reviewed medical records of 123 patients (median age of 55; range, 17-79) who received reduced-intensity cord blood transplantation (RI-CBT). Patients preemptively received reduced-dose foscarnet 30 mg/kg twice daily when CMV antigenemia exceeded 10/50,000. Sixty-three patients developed CMV antigenemia on a median of day 34, and 29 received foscarnet preemptively. The median level of CMV antigenemia at the initiation of foscarnet was 30. Median duration of foscarnet administration was 24 days. Adverse effects included electrolyte abnormalities (n=19), renal impairment (n=13), and skin eruption requiring discontinuation of foscarnet (n=1). Preemptive therapy of foscarnet was completed in 18 patients. Seven patients died during foscarnet use without developing CMV disease. The remaining 3 developed CMV enterocolitis 5, 14, and 17 days after initiation of foscarnet. All of them were successfully treated with ganciclovir or foscarnet. Reduced dose of foscarnet is beneficial to control CMV reactivation following RI-CBT; however, it has considerable toxicities in RI-CBT recipients with advanced age. Further studies are warranted to minimize toxicities and identify optimal dosages.

Reduced-intensity stem cell transplantation (RIST) represents an attractive treatment for elderly patients and those with organ dysfunction who have advanced hematologic malignancies. Although RIST from a human leukocyte antigen (HLA)-identical sibling is promising, only 30% of the patients have such an identical donor. The value of cord-blood transplantation (CBT) using myeloablative preparative regimens was confirmed for adult patients (1-3). We and other groups recently demonstrated the feasibility of reduced-intensity cord-blood transplantation (RI-CBT) for adult patients (4, 5).

Cytomegalovirus (CMV) infection is a serious complication after CBT (6, 7) as well as after conventional allogeneic hematopoietic stem cell transplantation (allo-SCT) (8, 9). The preemptive use of ganciclovir decreased the incidence of CMV disease, leading to longer survival after allo-SCT (10-12), while management of CMV infection following RI-CBT remains to be established. Myelosuppression of ganciclovir is a possible concern in CBT recipients; however, little information is available about the effects of ganciclovir on cord blood-derived myeloid progenitors (13).

Foscarnet reversibly inhibits DNA polymerase of CMV (14) and lacks significant hematotoxicity (15, 16). Preemptive use of foscarnet at a dose of 60-90 mg/kg twice daily against CMV infection shows comparable efficacy with ganciclovir in allo-SCT (7, 8). These studies suggest that foscarnet might be a promising alternative in the management of CMV infection following RI-CBT. However, patients enrolled in these studies (17-18) with median age of 39-42 years were younger than most RI-CBT recipients. Renal toxicity of foscarnet can be significant when nephrotoxic drugs, such as cyclosporine, tacrolimus, and amphotericin

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B, are concomitantly given to RI-CBT recipients. Optimal dosages of foscarnet remain unknown in RI-CBT.

When patients receive foscarnet at a dose of 60 mg/kg, its peak plasma concentration achieves 600 μmol/L (19). An in vitro experiment demonstrated that complete inhibition of CMV replication was obtained with 300-400 μmol/L of foscarnet (14). There is no human pharmacokinetic data at reduced dose of foscarnet. In theory, however, foscarnet at a dose of 30 mg/kg twice daily might be sufficient to prevent CMV reactivation following allo-SCT. We reduced the dose of preemptive foscarnet to 30 mg/kg to ameliorate its toxicities. We reviewed clinical courses of patients who had received a reduced dose of foscarnet as preemptive therapy against CMV infection following RI-CBT.

Patients and methods

Patients and transplantation procedures

Between January 2002 and August 2004, 123 consecutive patients with hematologic diseases and solid tumors underwent RI-CBT at Toranomon Hospital. All patients had incurable diseases by conventional treatments and were not candidates for conventional allo-SCT because of the lack of HLA-identical sibling or a suitable unrelated donor, age over 50, and/or organ dysfunction (generally attributable to previous intense chemotherapy and/or radiotherapy). All patients provided written informed consent in accordance with the requirements of the Institutional Review Board.

Unrelated donors for patients without HLA-identical sibling donors were sought via the Japan Marrow Donation Program (20). If no appropriate donor was identified, the Japan Cord Blood Bank Network (21) was searched. Preparative regimens and prophylaxis of graft-versus-host disease (GVHD) are shown in Table 1. Supportive managements were reported previously (5). Fluconazole was administered for prophylaxis against fungal infections.

Engraftment was defined as white blood cell counts >1.0 x 10^9/L or absolute neutrophils >0.5 x 10^9/L for 2 consecutive days. CMV-specific immunoglobulin M (IgM) antibodies in the cord-blood units were not examined. Anti-CMV high-titer intravenous immunoglobulin was not regularly administered. All packed red blood cells and platelets were transfused using leukocyte-depleting filters. When patients were seronegative for CMV, they received CMV-seronegative red blood cells and platelets. Serum creatinine and electrolytes were monitored every other day during administration of foscarnet.

Patients' characteristics of RI-CBT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>55 (17-79)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>70/53</td>
</tr>
<tr>
<td>Primary diseases</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>15</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>35</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Adult T-cell leukemia</td>
<td>15</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>13</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>27</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>2</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>6</td>
</tr>
<tr>
<td>Risk of underlying diseases (high/low)</td>
<td>93/20</td>
</tr>
<tr>
<td>Preparative regimen</td>
<td></td>
</tr>
<tr>
<td>Flud 125 mg/m² + L-PAM (50-100 mg/m²) + TBI (2-8 Gy)</td>
<td>111</td>
</tr>
<tr>
<td>Flud 150 mg/m² + BU 8 mg/kg + TBI (4-6 Gy)</td>
<td>8</td>
</tr>
<tr>
<td>Flud 150 mg/m² + BU 8 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>Flud 150 mg/m² + L-PAM 340 mg/m²</td>
<td>2</td>
</tr>
<tr>
<td>Number of infused nucleated cells, median (range)</td>
<td>2.8 x 10^7/kg (0.7-5.2)</td>
</tr>
<tr>
<td>Number of infused CD34+ cells, median (range)</td>
<td>0.74 x 10^7/kg (0.01-3.9)</td>
</tr>
</tbody>
</table>

HLA match
- 6/6: 2
- 5/6: 20
- 4/6: 101

GVHD prophylaxis
- Cyclosporine: 89
- Tacrolimus: 34

RI-CBT: reduced-intensity cord blood transplantation; Flud: fludarabine; L-PAM: melphalan; BU: busulfan; TBI: total body irradiation; HLA: human leukocyte antigen; GVHD: graft-versus-host disease.

CMV infection and management

CMV infection was defined as isolation of CMV or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. Failure of preemptive therapy was defined as development of CMV disease. CMV disease was diagnosed as follows:
CMV enterocolitis was diagnosed by gastrointestinal symptoms with histological demonstration of CMV on biopsy materials obtained by endoscopy; CMV pneumonia was diagnosed when either a bronchoalveolar lavage or a lung biopsy was positive for CMV infection in a patient with characteristic signs, symptoms, and chest radiographic findings; CMV retinitis was diagnosed by characteristic retinal opacities without other likely explanation for the retinal findings.

CMV pp65 antigenemia was monitored weekly after engraftment. Briefly, $1.5 \times 10^7$ peripheral blood leukocytes were attached to slides using a cytcoat and fixed with cold acetone. From one-third to one-half of the centrifuged cells were fixed on the slides. The cells were incubated with monoclonal antibody HRP-C7 (Teijin, Tokyo, Japan) raised against immediate-early antigen, and stained by the direct immunoperoxidase method. These cells were analyzed under a light microscope and results were presented as the number of positive cells per 50000 cells (22, 23). If CMV antigenemia exceeded 10/50000, patients preemptively received foscarnet $30 \text{mg/kg}$ intravenously twice daily. Initiation of foscarnet with less than 10 positive cells was optional in the patients who received more than $0.5 \text{mg/kg}$ of prednisolone. The doses were adjusted for renal function (24, 25). Foscarnet was discontinued when 2 consecutive results of antigenemia were negative. When CMV disease was diagnosed during preemptive foscarnet therapy, we increased the dose to $60 \text{mg/kg}$ twice or 3 times daily, or initiated ganciclovir $5 \text{mg/kg}$ twice a day.

Clinical toxicities were judged by experienced physicians based on the clinical presentation, laboratory results, concomitant events such as sepsis, hypotension, and nephrotoxic drug exposure. Toxicities of foscarnet were evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (26).

Results

Patient characteristics

Patient characteristics are shown in Table 1. Ninety-eight patients (80%) achieved primary engraftment on a median of day 20 (range, 11–53). Fifty-two patients (42%) died of transplant-related causes within 100 days of transplant. Underlying diseases progressed in 16 patients and 5 became fatal. Of the 98 patients who achieved engraftment, 28 developed grade II–IV acute GVHD at a median onset of day 22 (range, 11–45). As of March 2004, the median follow-up of the surviving patients was 8.5 months (range, 3.9–31). Overall survival rates were 86% and 53% at day 30 and 100, respectively.

CMV infection and efficacy of preemptive use of foscarnet

Sixty-three patients developed CMV antigenemia on a median of day 34 (range, 1–22 to 87), and 29 patients received preemptive administration of foscarnet. The median level of CMV antigenemia at the initiation of foscarnet was 30 (range, 2–867). The other 34 patients did not receive foscarnet administration because of antigenemia below 10/50000. No patients developed CMV diseases before engraftment. All patients treated were in the hospital for the full course of foscarnet. One patient was given amphotericin B during foscarnet therapy and none received aminoglycoside. Median duration of foscarnet was 24 days (range, 6–85). Eighteen patients successfully completed preemptive therapy (Table 2). One patient discontinued foscarnet because of skin eruption. Seven patients died during foscarnet use without CMV disease. The causes of death included progression of primary diseases ($n=2$), pneumonia ($n=1$), invasive aspergillosis ($n=1$), lung tuberculosis ($n=1$), acute GVHD ($n=1$), and sepsis ($n=1$). The remaining 3 patients developed CMV enterocolitis 5, 14, and 17 days after initiation of foscarnet. One patient was successfully treated with ganciclovir. The other 2 died of concomitant bacterial pneumonia and septic shock, while CMV enterocolitis improved with foscarnet or ganciclovir. The antigenemia levels rose despite preemptive therapy before CMV disease developed in 1 of the 3 patients. However, this patient did not receive the increased dose of foscarnet owing to impaired renal function. Antigenemia levels did not rise during preemptive therapy in the other 2 patients.

Toxicity of foscarnet

Twenty-four patients developed adverse events associated with foscarnet (Table 2) and it was discontinued in a patient because of grade 2 skin eruption. However, fatal adverse events were not documented in any patients.

Nineteen patients developed grades 3–4 electrolyte abnormalities that were asymptomatic and reversible. Renal impairment was observed in 13 grade 1 in 5 and grade 2 in 8. The dose of foscarnet was reduced in 3, and their renal impairments were reversible. Other grades 3–4 toxicities, including myelosuppression, oral and/or penile ulceration, nausea, seizures, and thrombophlebitis, were not documented in any of our patients.

Discussion

The present study suggests that CMV infections after RI-CBT in patients with advanced age could be controlled.
with reduced dose of foscarnet. CMV antigenemia was detected in 63 patients, of whom 29 received foscarnet as preemptive therapy. Three patients progressed to CMV disease; the rate of preemptive treatment failure was 10%. All of the 3 improved with foscarnet or ganciclovir, and no patients who received the 60 mg/kg daily of foscarnet died of CMV disease in the present study. There are few reports on CMV infections after CBT, and little is known about the clinical courses (6). In contrast, more data are available on CMV infections after myeloablative bone marrow transplantation, where the rates of preemptive treatment failure are 4.9–10.5% with ganciclovir and 4.9–50% with foscarnet (17, 18). The results are comparable with our observation and suggest the possibility that dose reduction of foscarnet is unlikely to increase CMV disease after RI-CBT.

In the present study, only 1 of 29 patients discontinued foscarnet, suggesting that RI-CBT recipients with advanced age can tolerate our foscarnet regimen. However, elevated creatinine by 100% or more and some electrolyte disturbance were observed in 11 (38%) and 19 (66%), respectively. Although the precise mechanism of nephrotoxicity associated with foscarnet has not been ascertained, the effect appears to be due to acute tubular damage (27). While renal toxicity by foscarnet in post-transplant patients was reportedly dose-dependent (28), the frequency of adverse events with low-dose foscarnet was comparable with those in previous reports (17, 18). The observation suggests some possibilities. First, concomitant use of nephrotoxic drugs can aggravate renal insufficiency (15) and might have affected the severity of renal toxicity in our study. However, as only 1 patient used amphotericin B and none used aminoglycoside, the effect of concomitant nephrotoxic drugs is unlikely. Second, different creatinine clearance by patients might have affected the severity of renal toxicity (29), as more than 80% of administered foscarnet is excreted in the urine. In our study and the previous reports, creatinine levels at the initiation of foscarnet were comparable, suggesting that creatinine clearance is unlikely to have affected the results. Third, the advanced age in our study could explain the observation. The median age of our patients was more than 10 years older than those of the previously studied patients (17, 18). To our knowledge, this is the first investigation on foscarnet administration in post-transplant patients with advanced age. Thus, further investigation into the foscarnet-related toxicities and its pharmacokinetics in patients with advanced age is necessary to allow a proper interpretation.

While the present study provided novel information on foscarnet use following RI-CBT, we need to take its limitations into consideration. It is a small-sized, retrospective study; unrecognized biases might have affected the results. We might have underestimated the toxicity of foscarnet. Nephrotoxicity, even when not severe enough to warrant discontinuation of foscarnet, may have led to clinicians giving lower doses of concomitant nephrotoxic drugs. However, it has demonstrated that reduced dose of foscarnet is beneficial to control CMV reactivation following RI-CBT. These observations provide a rationale for continuing our clinical trials on preemptive use of foscarnet following RI-CBT, focusing on minimizing toxicities and identifying optimal dosages. While resistance for antiviral drug is a potential concern (30), we had not conducted resistance genotyping analysis for polymerase mutations on breakthrough viral isolates. Further investigation is requested for it. Furthermore, phase III clinical trials comparing ganciclovir with reduced dose of foscarnet are needed.

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