Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir

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Summary:

Cytomegalovirus (CMV) disease can be prevented by administration of ganciclovir prophylactically post-transplant. However, up to 30% of patients discontinue use of ganciclovir as a result of profound neutropenia and may subsequently develop CMV infections while unprotected. To prevent reactivation of CMV, we administered foscarnet to 39 adults unable to receive ganciclovir due to delayed engraftment or ganciclovir-induced neutropenia. Twenty-four (62%) of the patients had received T cell-depleted marrow transplants. Foscarnet sodium 60 mg/kg i.v. daily was continued until the neutropenia resolved, at which time ganciclovir was resumed. CMV prophylaxis commenced at a median of 28 days following transplantation. Median time to initiation of foscarnet was day 60 post-transplant, and the median duration of treatment was 22 days. Foscarnet was well-tolerated. Six (15%) patients had CMV detected while receiving prophylaxis, and CMV-related mortality was 5%. Foscarnet is a safe and effective agent for prevention of CMV disease in allogeneic transplant recipients unable to receive ganciclovir.

Keywords: BMT; foscarnet; ganciclovir; cytomegalovirus; allogeneic

Infection with cytomegalovirus (CMV) is a life-threatening complication in the first 6 months following allogeneic marrow transplantation.1,2 Historically, CMV infection occurred in 70–80% of allogeneic recipients, and 15% progressed to CMV pneumonia.4 Recent studies have shown that ganciclovir significantly reduces the incidence of CMV infection and CMV disease when given prophylactically.1,2,5 However, 30% of patients receiving ganciclovir prophylaxis develop drug-induced neutropenia.1,2,5 The long duration of this neutropenia, approximately 12 days, places these patients at significant risk for bacterial and fungal infections,1 and 8% also develop CMV disease.2 Foscarnet is a pyrophosphate analogue with in vitro activity against all known human Herpes viruses (CMV, HSV, VZV, EBV, HHV-6).6–7 The dose-limiting toxicities of foscarnet are nephrotoxicity and neurotoxicity.6–9 However, it causes little or no myelosuppression. The limited clinical experience to date suggests that foscarnet prophylaxis is less effective than ganciclovir in preventing CMV infection and disease, and significant nephrotoxicity occurs in up to 50% of patients.10–12 To evaluate the safety and activity of foscarnet for CMV prophylaxis, we used this drug as an alternative to ganciclovir for patients who could not receive ganciclovir because of delayed engraftment or ganciclovir-induced neutropenia. The study end-points include CMV excretion, CMV disease, CMV-related mortality, and toxicity.

Patients and methods

Patients

Thirty-nine adults transplanted between November 1991 and November 1994 who received either marrow (38) or blood stem cells (one) from allogeneic donors were enrolled on a non-randomized, open-label, standard practice protocol utilizing foscarnet sodium at our institution. Patients were eligible for the study if they did not engraft by day 28 or if they developed persistent neutropenia while on ganciclovir post-transplant. Patients with documented excretion of CMV immediately prior to transplantation or prior to hematologic recovery and those with biopsy proven CMV disease were ineligible for study participation. Patient demographics are outlined in Table 1. Sixty-two percent of the patients received T cell-depleted marrow transplants. The treatment protocols were approved by the MD Anderson Institutional Review Board, and written informed consent was obtained from each patient.

All patients received a myeloablative regimen with or without total body irradiation as preparation for transplantation (Table 1). Partial T cell depletion was performed as previously reported.13 Graft-versus-host disease prophylaxis regimens included cyclosporine with methylprednisolone and/or methotrexate, or cyclosporine with methylprednisolone and anti-CD5 antibody A chain immunocytogate.14

Infection prophylaxis and CMV monitoring

Ganciclovir was administered at 5 mg/kg i.v. every 12 h beginning day −8 to day −2. Acyclovir was administered at 5 mg/kg i.v. every 8 h starting day −1 and continued until
Table 1  Patient demographics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>34</td>
</tr>
<tr>
<td>(range)</td>
<td>(17–54)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>29/10</td>
</tr>
</tbody>
</table>

Diagnosis
- Chronic myelogenous leukemia: 20
- Acute leukemia: 16
- Other: 3

Donor
- Matched related: 17
- Matched unrelated: 16
- Mismatched related: 6

Preparative regimens
- Thiotepa + busulfan + cyclophosphamide: 12
- Thiotepa + cyclophosphamide + TBI: 24
- Etoposide + cyclophosphamide + TBI: 1
- Cyclophosphamide + TBI: 2
- T cell-depleted transplants: 24

CMV serology (patient/donor)
- +/+
- 22
- +/-
- 13
- –/–
- 4

Engraftment. Upon discontinuation of acyclovir, ganciclovir was resumed at 5 mg/kg i.v. three to five times per week and continued until day 100. Intravenous immunoglobulin (IVIG) 500 mg/kg i.v. was administered weekly until day 100 to all patients. All blood products were CMV-seronegative and/or filtered. Urine and peripheral blooduffy coat cells were collected pre-transplant and at weekly intervals to day 100. The samples were tested for CMV by standard culture and shell vial assay. For diagnosis of CMV disease, bronchoalveolar lavage fluid or tissue biopsies were similarly cultured. Tissue biopsies and autopsy specimens were also examined by light microscopy and immunocytochemistry or by in situ hybridization for CMV. Patients who developed CMV infection or disease were treated with ganciclovir 5 mg/kg i.v. every 12 h or fosfocarnet 60 mg/kg i.v. every 8 h for 14–21 days. IVIG was administered every other day for patients who developed CMV pneumonia. Granulocyte colony-stimulating factor 5 μg/kg/day was administered subcutaneously when patients absolute neutrophil count fell to less than 1.5 × 10^9/L while receiving ganciclovir prophylaxis.

Foscarnet prophylaxis protocol

For prophylaxis, foscarnet sodium (Foscavir: Astra Pharmaceutica Products, Westborough, MA, USA) was administered at 60 mg/kg i.v. over 2 h daily. Doses were modified for renal insufficiency with adjustments according to the guidelines in the package insert. Outpatients received foscarnet via an Intermate pump (Baxter Healthcare, Roundlake, IL, USA). Patients received i.v. hydration if daily oral fluid intake was less than 2 l. Foscarnet was continued until the absolute neutrophil count was greater than 1.5 × 10^9/L for 3 days after growth factor discontinuation or until day 100. When neutropenia resolved and foscarnet was stopped, ganciclovir was resumed at 5 mg/kg i.v. five times per week until day 100. Serum creatinine was monitored daily. Serum calcium, phosphorous and magnesium levels were monitored at least three times weekly. Toxicity was graded using the NCI common toxicity criteria.

Definitions and analysis

Ganciclovir-induced neutropenia was defined as an absolute neutrophil count less than 1.5 × 10^9/L for 2 consecutive days despite the use of filgrastim 5 μg/kg/day s.c. Engraftment was defined as an absolute neutrophil count greater than 0.5 × 10^9/L for 3 consecutive days. CMV infection (excretion) was defined as recovery of virus from the blood, urine or throat. Disease caused by CMV was defined as recovery of the virus from a visceral site (lung, gastrointestinal tract) or by bronchoalveolar lavage in patients with pulmonary findings consistent with CMV pneumonitis. Minimum follow-up at the time of the analysis was 6 months. CMV-related mortality was calculated by the method of Kaplan and Meier.

Results

Foscarnet prophylaxis

Nine patients (23%) received foscarnet as initial prophylaxis because of delayed engraftment. The other 30 patients were switched from ganciclovir to foscarnet for ganciclovir-induced neutropenia. The median ANC in patients with ganciclovir-induced neutropenia was 0.6 × 10^9/L. Prophylaxis for CMV was initiated at a median of 28 days (range 16–51) following transplantation. Foscarnet was started at a median of 60 days (range 21–91) post-transplant and continued for a median of 22 days (range 7–71).

Toxicity of foscarnet

Renal toxicity was mild (Table 2). There was no significant difference in the median increase in creatinine in patients receiving amphotericin B in comparison to those who did not. Nausea and vomiting, which is not well reported, occurred in 15% of patients despite aggressive anti-emetic treatment. No seizures occurred in patients receiving prophylactic foscarnet. In the three patients with significant tremors, serum calcium and magnesium levels were within

| Table 2  Toxicity |
|-------------|----------------|
| Nephrotoxicity | 1.5 mg/dl (0.8–2.2) |
| Baseline creatinine (range) | 1.6 mg/dl (0.8–2.4) |
| Maximal creatinine (range) | (3.3 mg/dl) |
| Median creatinine increase | 0 (0) |
| Dialysis (%) | 6 (15) |
| Gastrointestinal toxicity | 0 (0) |
| Nausea and vomiting (%) | 3 (8) |
| Neurotoxicity (%) | 3 (8) |
| Seizure | 2 (5) |
| Worsening tremor | 2 (5) |
| Headache | 2 (5) |
normal limits. Foscarnet was discontinued in only two patients (5%), both due to renal toxicity: one of these was receiving amphotericin B at 1 mg/kg/day and the other patient had liver failure.

**Prophylaxis failures**

Six of the 39 patients (15%) had CMV detected by culture, shell vial assay, biopsy or autopsy while receiving prophylaxis with either ganciclovir or foscarnet; four had CMV infection and two had disease. The actuarial risks of CMV infection at day 100 and day 180 post-transplantation are 13% (95% CI 2–27%) and 20% (95% CI 6–33%), respectively (Figure 1). Patient characteristics are included in Table 3. Five of 13 patients who were CMV seropositive pretransplant with CMV seronegative donors failed prophylaxis. Five of the six patients who had received ganciclovir at a dose of 5 mg/kg three times per week. The two patients with CMV disease identified at autopsy had no detectable excretion of CMV prior to death. Of the four patients with CMV infection, two were receiving daily foscarnet at the time of CMV detection and the other two were receiving ganciclovir. All were treated with high-dose foscarnet or ganciclovir and then placed on maintenance therapy with no recurrence of CMV infection.

**Table 3** Prophylaxis failures

<table>
<thead>
<tr>
<th>No.</th>
<th>BMT type</th>
<th>Detected (day)</th>
<th>Site</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MUD</td>
<td>53</td>
<td>Blood</td>
<td>Ganciclovir</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Sibling</td>
<td>65</td>
<td>Blood</td>
<td>Foscarnet</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>MUD</td>
<td>67</td>
<td>Blood, urine</td>
<td>Ganciclovir</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>Sibling</td>
<td>40</td>
<td>Blood</td>
<td>Foscarnet</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>MUD</td>
<td>60</td>
<td>Lungs, adrenals*</td>
<td>Ganciclovir</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>MUD</td>
<td>90</td>
<td>Liver, lungs, kidneys*</td>
<td>Foscarnet</td>
<td>Died</td>
</tr>
</tbody>
</table>

*Identified at autopsy.

Ganciclovir 5 mg/kg i.v. every 12 h; Foscarnet 60 mg/kg i.v. every 8 h.

**Survival**

Thirty-two of the 39 patients (82%) were alive at day 100. Actuarial survivals at day 100 and day 180 post transplantation are 79% (95% CI 67–92%) and 54% (95% CI 38–70%), respectively (Figure 2). Six of the seven patients who died had received T cell-depleted marrow transplants. The causes of death included disseminated CMV with or without fungal infection (two patients), disseminated Aspergillus (two patients), graft failure (one patient), relapse (one patient), and adenovirus (one patient). The two patients with disseminated CMV disease at autopsy had steroid-refractory GVHD; however, the primary causes of death were CMV pneumonitis and CMV hepatitis.

**Discussion**

CMV continues to be a serious complication following allogeneic BMT. Several randomized controlled studies have shown that ganciclovir prophylaxis decreases the incidence and severity of CMV disease. These benefits are offset by the drug-associated neutropenia which occurs in 30–60% of patients. In the study by Winston et al., 8% of patients who discontinued prophylactic ganciclovir secondary to neutropenia developed serious CMV disease and
the incidence of infection was not assessed. In high-risk patients, an alternative to ganciclovir would be beneficial. Previous studies utilizing foscarnet for CMV prophylaxis suggest it is effective in clearing CMV infection and reducing the risk of CMV disease. In our experience, using foscarnet for patients unable to receive ganciclovir prophylaxis, only 15% developed CMV infection and 5% developed CMV disease.

The small sample sizes in the other studies published made it difficult to evaluate the efficacy of foscarnet. The relatively low rate of infection seen in our study is comparable to rates reported by Goodrich et al and Winston et al in their evaluations of ganciclovir prophylaxis. This is despite the fact that in our study 62% received T cell-depleted marrow grafts and almost half were unrelated donor marrow recipients, a subset of patients at higher risk for complications from CMV. This is significant because in the Goodrich study, patients were not eligible if they received T cell-depleted transplants. In the Winston study, only 39% and 18% of the patients were T cell depleted or matched unrelated donor recipients, respectively. In addition, patients were eligible for the ganciclovir prophylaxis studies only if they had engrafted, while 23% of our patients experienced delayed engraftment and therefore required foscarnet as initial prophylaxis. It should be noted that the two patients engrafting CMV while receiving ganciclovir received a prophylactic regimen of ganciclovir 5 mg/kg/day only for three weeks, which is known to be inadequate. The overall survival in our investigation was 82% at day 100, as compared to 88% and 70% reported by Goodrich and Winston. Thus, our results are comparable despite the high-risk nature of the population.

Our strategy of administering foscarnet in patients with delayed engraftment or ganciclovir-induced neutropenia differed from any study published to date. The dose of foscarnet (60 mg/kg/day) used in our study was based on supporting literature in the acquired immune deficiency (AIDS) population which demonstrated efficacy with tolerable toxicity at this dose. Small studies in the BM population employed higher doses of foscarnet. The lower dose of foscarnet was chosen in order to avoid the serious nephrotoxicity reported by Reusser et al and Ringden et al.

The prophylactic foscarnet regimen used in this study was well-tolerated. Two previous studies suggest that the incidence of foscarnet-induced nephrotoxicity approaches 25% in patients receiving cyclosporine with a subset requiring dialysis. We maintained at least 21 per day of hydration in our patients which may have minimized the nephrotoxicity. The study by Bacigalupo et al that reported tolerable nephrotoxicity also used normal saline hydration prior to each dose. A lack of intravenous hydration may have contributed to the enhanced nephrotoxicity seen in these other studies. Reusser et al concluded that the concomitant use of foscarnet with amphotericin B results in increased renal toxicity. There was no statistically significant difference in nephrotoxicity between patients receiving amphotericin B concomitantly and those not receiving amphotericin B in our study. Therefore, foscarnet was tolerable in this high-risk patient population receiving multiple nephrotoxic drugs including amphotericin B, aminoglycosides and cyclosporine. The gastrointestinal and neurological complications were also acceptable in our investigation. Only 5% of patients required drug discontinuation for toxicity.

Foscarnet was successfully given in an ambulatory setting via an Intravenous pump. As mentioned previously, care was taken to maintain adequate hydration either orally or via intravenous fluids. The ability to administer this agent in an outpatient setting makes it an acceptable alternative to ganciclovir.

Our goal in this investigation was not to compare foscarnet to ganciclovir but rather to evaluate the efficacy and tolerability of foscarnet in high-risk patients where maintenance of CMV prophylaxis is critical. We conclude that foscarnet is an effective and safe alternative to ganciclovir for CMV prophylaxis in high-risk allogeneic marrow recipients. However, randomized, comparative studies between ganciclovir and foscarnet are necessary to evaluate better the prophylactic and treatment roles of these agents in specific BM populations.

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13 Champlin R, Giffin S, Przepiorka D et al. Selective depletion of CD8-positive T-lymphocytes for allogeneic bone marrow transplantation: engraftment, graft-versus-host disease and
