Intravenous Cidofovir for Compassionate Use in AIDS Patients with Cytomegalovirus Retinitis

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We report the compassionate use of intravenous cidofovir for the treatment of cytomegalovirus retinitis in 51 patients with AIDS who were receiving highly active antiretroviral therapy (HAART). After a median of 9 doses, 49 patients showed no retinitis activity. However, treatment was stopped in 17 patients because of adverse reactions and in 5 patients for other reasons. Two deaths were considered related to the drug. Iritis developed in 21 patients (41.2%), a frequency higher than that reported during the pre-HAART era. Patients with iritis had median CD4 cell counts—both at nadir and at the initiation of cidofovir therapy —approximately 3 times higher than those for patients without iritis ($P = .003$ and $P = .05$, respectively). Our study confirms the efficacy of cidofovir therapy for AIDS-associated cytomegalovirus retinitis. Our data suggest that the risk of iritis may be higher for patients with better immunological status, probably because of their enhanced ability to mount an inflammatory response.

Cidofovir is a nucleotide analogue with prolonged antiviral activity against cytomegalovirus (CMV) that can be infused every 2 weeks, thus obviating the need for a central venous catheter [1]. The efficacy of iv cidofovir has been established by 3 randomized studies carried out in the era before highly active antiretroviral therapy (HAART) was available [2–4]. We report the results of compassionate-use iv cidofovir for treatment of CMV retinitis in patients with AIDS who are receiving HAART.

Patients and Methods

From 22 April 1997 to 31 March 1998, 61 AIDS patients with CMV retinitis were treated with iv cidofovir in Spain. In return for supplies of the agent, physicians were asked to provide information about patient characteristics, retinitis, and cidofovir treatment. We obtained information on 51 patients from 20 hospitals.

Cidofovir was infused at a dose of 5 mg/kg body weight. The dose was reduced to 3 mg/kg when serum creatinine levels increased by 0.3–0.4 mg/dL above baseline or when 2^+ proteinuria developed. For induction, the dosing interval was once a week for 2 weeks; for maintenance, the dosing interval was once every other week. To minimize the risk of nephrotoxicity, patients were given 2 L of normal saline and 4 g of probenecid. Laboratory evaluation, including complete blood count, serum biochemical profile, and urinalysis, was performed and reviewed within 24–48 h before each cidofovir infusion. Ophthalmologic examinations were performed at the end of induction (or reinduction) therapy and at least once a month thereafter. We assessed the efficacy of treatment by observing the progression of CMV retinitis with indirect ophthalmoscopy and by monitoring mortality. Safety was assessed by recording serious systemic, ocular, or analytical adverse events.

Results

In our study cohort ($n = 51$), the male-to-female ratio was 1 : 4, the median age was 34 years, and the median CD4 cell count at the initiation of cidofovir therapy was 97×10^6/L. Forty-nine patients were receiving HAART during cidofovir treatment. Thirty-one had bilateral CMV retinitis. Patients had been treated with other anti-CMV agents for a median of 31.8 weeks and had relapsed a median of 1 time (range, 0–5 relapses). Reasons for cidofovir use included relapse of retinitis ($n = 22$), drug intolerance ($n = 12$), failure of induction ($n = 8$), and problems related to venous access ($n = 8$). The patients received a median of 9 doses of cidofovir during a median period of 18.7 weeks. Of the 51 patients receiving cidofovir therapy, 49 patients did not show any evidence of retinitis activity, 1 patient did not achieve remission, and 1 patient relapsed.

Adverse events considered to be possibly associated with cidofovir and/or probenecid are shown in table 1, and reasons for withdrawal of cidofovir are shown in table 2. A total of 21 patients developed iritis after receiving iv cidofovir; only 2 of them were receiving rifabutin concomitantly. A Kaplan-Meier survival analysis shows that iritis developed in 50% of patients

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Table 1. Adverse events considered to be possibly associated with cidofovir and/or probenecid therapy.

Adverse events	No. (%)
Iritis	21 (41.2)
Proteinuria (2^+, 3^+)	11 (21.6)
Renal insufficiency (Cr, > 0.6 mg/dL)	9 (17.6)
Ocular hypotony	8 (16.7)
Nausea and vomiting	8 (16.0)
Neutropenia (<1.0 cells $\times$ 10^9/L)	7 (13.7)
Cutaneous hypersensitivity	4 (7.8)
Anemia (Hct decrease $\geqslant$6%)	1 (2.0)

NOTE. Cr, creatinine; Hct, hematocrit.

who received at least 10 doses of cidofovir and in 71% of patients who received at least 12 doses (figure 1). The iritis was always observed in eyes where CMV was involved and was relieved with topical steroids and mydriatics. Five patients sustained recurrent episodes. We did not find any significant association between iritis and age, sex, risk factors for HIV infection, severity of retinitis, proteinuria, or renal insufficiency. The median of nadir CD4 cell counts was 24×10^6/L for patients with iritis and 7.5×10^6/L for patients without iritis ($P = .003$). The median of CD4 cell counts at the initiation of cidofovir therapy was 143×10^6/L for patients with iritis and 43×10^6/L for patients without iritis ($P = .05$). The median values of viral load at the initiation of cidofovir therapy were 2.5 $\log_{10}$ copies/mL for patients with iritis and 4.2 $\log_{10}$ copies/mL for patients without iritis ($P = .06$). Seven patients died during cidofovir therapy, 2 of them as a consequence of acute renal failure. Both patients had concomitant medical conditions and were being treated with drugs that contributed to the renal insufficiency.

Discussion

Our study found reduced CMV retinitis relapse and mortality rates in comparison to those found in randomized clinical trials, probably because almost all of the patients in our study cohort were receiving HAART during cidofovir therapy [5]. The safety assessment demonstrated a frequency of adverse events within

Table 2. Reasons for withdrawal of cidofovir therapy.

Reason	No. (%)
Toxicity related	17 (33.3)
Renal insufficiency	7
Ocular hypotony	4
Hypersensitivity to probenecid	2
Proteinuria (3^+)	1
Proximal tubulopathy	1
Iritis and ocular hypotension	1
Iritis	1
Other	5 (9.8)
Relapse	1
Failure of reinduction	1
Patient refusal	2
Immunological recovery	1

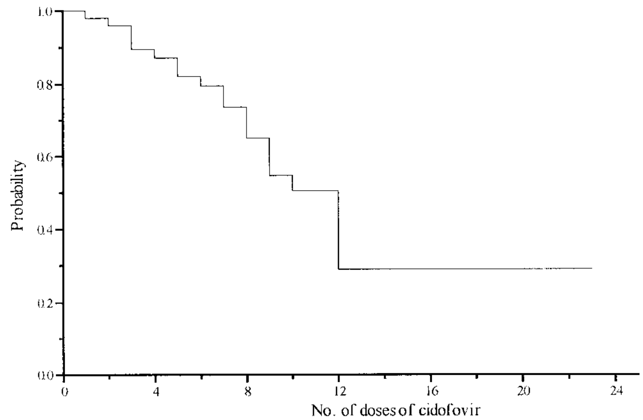

Figure 1. Kaplan-Meier survival curve showing cumulative probability of freedom from iritis.

the range reported in these trials, with the exception of iritis, which complicated the course of 41.2% of the patients in our study, versus 4.9%–6.8% in randomized trials [2–4]. The type of inflammation did not fit the characteristics of the vitritis associated with immune reconstitution [6, 7] or HIV-induced iridocyclitis [8].

A high proportion of iritis has also been reported in 2 recently published retrospective cohort studies of iv cidofovir for the treatment of CMV retinitis. In the first study, iritis developed in 26% of 43 treated patients [9]. In the second one, iritis was observed in 44% of 18 treated patients [10]. The reason for the higher frequency of iritis in cohort studies is not entirely understood. An association between severe CMV retinitis and the development of iritis has been found, suggesting that breakdown of the blood-ocular barrier in these patients may promote higher intraocular levels of cidofovir, leading to toxicity [9]. It has also been found that renal insufficiency may contribute to an increased risk of iritis [10]. In our study, the severity of CMV retinitis and the frequency of renal insufficiency were the same for patients who developed iritis and for patients who did not.

It has been suggested that protease inhibitors may increase the risk of intraocular inflammation with cidofovir, either by a drug interaction or by enhanced inflammatory responses. Of the 2 published retrospective studies, 1 found an association between protease inhibitor use and iritis [9]. In our study, almost all patients were treated with protease inhibitors, and the duration of this therapy before the initiation of cidofovir was the same for patients who developed iritis and for patients who did not. However, we found that patients with iritis had better immunological and virological status. They had median CD4 cell counts—both at nadir and at the initiation of cidofovir therapy—approximately 3 times higher than those of patients without iritis. Their median viral load at the initiation of cidofovir therapy was 1.7 $\log_{10}$ copies/mL lower.

We believe that these are important findings because they suggest that the risk of developing iritis during cidofovir iv therapy may be higher for patients with better immunological status, because such patients may be better able to mount a local inflammatory response. A matter of concern is the finding that 2 of our patients died of acute renal failure during cidofovir therapy. It must be mentioned, however, that both of them had concomitant medical conditions and/or were treated with drugs that without any doubt contributed to the renal insufficiency. Furthermore, both patients were receiving indinavir, a drug that can cause acute renal failure [11].

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