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Clinical Trial Report

Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: A monocenter observational study with clinical and JC virus load monitoring

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A monocenter observational study was conducted to determine the clinical and virological effects of cidofovir added to highly active anti-retroviral therapy (HAART) in AIDS-associated progressive multifocal leukoencephalopathy (PML). Exposure to other anti-viral drugs or late initiation of cidofovir were exclusion criteria. Of the 53 consecutive patients with virologically proven PML admitted at the NeuroAIDS Unit of Bicêtre Hospital between May 1996 and July 2000 and having received HAART with or without cidofovir, 46 met the inclusion criteria. Cidofovir was initiated in most cases on compassionate grounds. The 22 patients treated with HAART only (HAART group) were compared to the 24 patients treated with HAART and cidofovir (CDV group). Survival, neurological outcome assessed by the expanded disability status scale (EDSS), and monitoring of the JC virus (JCV) load in CSF were investigated prospectively. At baseline (date of initiation or intensification of HAART), both groups were similar regarding CD4 cell count, plasma HIV load, CSF JCV load, EDSS, and demographic features. Both groups had similar response to HAART in terms of plasma HIV load and CD4 cell count. At month 6, CSF-JCV load was below the detection level in 8 out of 24 (33%) patients from the CDV group and 7 out of 18 (39%) patients from the HAART group ($P = 0.71$). One-year cumulative probability of being alive was 62% in the CDV group and 53% in the HAART group ($P = 0.72$). However, an additional benefit with respect to survival was observed in patients who were given cidofovir after adjustment to the following baseline variables (CSF-JCV load, CD4 cell count, and EDSS). Despite the addition of cidofovir to HAART, no significant benefit had been observed in neurological outcome, particularly in patients with an early worsening. *Journal of NeuroVirology* (2001) **7,** 375–381.

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Highly active anti-retroviral therapy (HAART), defined as an optimal combination of multiple anti-retroviral drugs (including at least 2 nucleoside reverse transcriptase inhibitors, 1 nonnucleoside reverse transcriptase inhibitor, and/or at least 1 protease inhibitor), was widely available in France by the spring of 1996. The extensive use of aggressive HAART regimen had a positive impact on the natural history of AIDS-associated progressive multifocal leukoencephalopathy (PML). Many reports (Cinque *et al*, 1998, Clifford *et al*, 1999, Gasnault *et al*, 1999,

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De Luca *et al*, 2000b) including 2 large cohort studies (Dworkin *et al*, 1999, Tassie *et al*, 1999) have shown a significant survival increase on HAART. Nevertheless, this survival benefit is observed only in approximately one half of the patients. Those with high JC virus (JCV) load in cerebrospinal fluid (CSF) and/or low CD4+ cell count at baseline and those who have a rapid clinical progression still have a bad outcome (De Luca *et al*, 2000b, Taoufik *et al*, 2000). Moreover, as we previously reported, HAART is not associated with a significant neurological recovery, and many PML patients who survive are left with a severe persistent functional disability (Gasnault *et al*, 1999).

Cidofovir is a nucleoside analogue with clinical effectiveness against CMV and other Herpesviridae. It has demonstrated a significant inhibitory effect on polyomavirus replication *in vitro* (Andrei *et al*, 1997) and therefore has become a potential candidate for PML treatment. Anecdotal reports (Blick *et al*, 1998, Sadler *et al*, 1998, Brambilla *et al*, 1999, De Luca *et al*, 1999, Meylan *et al*, 1999) and a preliminary open study (De Luca *et al*, 2000a) have suggested a benefit for cidofovir as add-on treatment to HAART in AIDS-associated PML.

The aim of the current study was to analyze the clinical and virological effects of cidofovir added to HAART in AIDS-associated PML patients.

Results

Baseline characteristics

Of the 53 patients screened during the study period, 46 were included and classified into 2 groups according to their treatment. The HAART group consisted of the 22 patients treated with HAART only, and the CDV group included the 24 patients treated with HAART and cidofovir. Among the 7 patients excluded, 3 were started on cidofovir later than 3 months after baseline, and 4 were not given cidofovir but received topotecan (1) or alpha-interferon (3). The baseline characteristics of the 46 patients are summarized in Table 1 per treatment group. PML was the first AIDS-defining event in 34 patients without any significant difference between the CDV and HAART groups. Only 8 patients (4 in each of the 2 groups) received HAART before PML clinical onset. Overall, the median CD4+ lymphocyte count was 77 cell/μL with an interquartile range (IQR) from 23 to 133 and no difference between the groups. Plasma HIV load (median = 5.01 $\log_{10}$ copies/mL, IQR = 4.52–5.35) was similar in the 2 groups and above 200 copies/mL at baseline in all patients, including the HAART-experienced patients. No significant difference between the 2 groups was observed concerning CSF JCV load and EDSS score.

Cidofovir treatment and adverse effects

The 24 patients included in the CDV group were started on cidofovir with a mean delay of 1.5 months after baseline (range 0.5–2.8). The mean number of cidofovir cycles was 9.8 ranging from 1 to 30. Three patients received fewer than 3 cycles but were considered for this study in an intent-to-treat view.

Nausea and vomiting related to probenecid were observed in one quarter of patients. Five World Health Organization grade-3 toxicity events were observed in 4 patients. In one case, a severe leukoneutropenia was treated with filgrastim and this did not require cidofovir interruption. Three patients, including 2 cotreated with indinavir, experienced a reduction of the creatinine clearance. These patients completely recovered after drug discontinuation. One patient developed a unilateral anterior uveitis, which reverted after cidofovir interruption. This patient had a recent history of homolateral cataract surgery and had been previously reported (Labetoulle *et al*, 2000).

HIV load and CD4+ responses to HAART

HAART administered after PML diagnosis was effective on the long-term in reducing plasma HIV load. By

Table 1 Baseline characteristics in 46 AIDS-associated PML patients per treatment group

Variables	*HAART group* (n = *22)*	*Cidofovir group* (n = *24)*	P*
Sex (men:women)	22:0	18:6	0.02[a]
Age (years) [median (IQR)]	38 (35–51)	36 (32–44)	0.51[c]
Transmission category [number (%)]			0.93[b]
H/B sexuals	8 (36.4)	7 (29.2)	
Injecting drug users	8 (36.4)	10 (41.7)	
Heterosexuals	6 (27.3)	7 (29.2)	
PML as first AIDS-defining event [number (%)]	19 (86.4)	15 (62.5)	0.10[a]
HAART prior to PML [number (%)]	4 (18.2)	4 (16.7)	0.89[b]
CD4+ count (cell/μL) [median (IQR)]	92 (51–156)	66 (21–137)	0.35[c]
Plasma HIV RNA ($\lg_{10}$ copies/mL) [median (IQR)]	5.01 (4.56–5.43)	5.01 (4.51–5.63)	0.98[d]
CSF JCV DNA ($\lg_{10}$ copies/mL) [median (IQR)]	4.41 (3.34–5.18)	4.69 (3.79–5.63)	0.35[d]
EDSS score [mean (range)]	6.2 (3.5–8.5)	6.1 (3.0–8.5)	0.91[c]

PML = progressive multifocal leukoencephalopathy; IQR = interquartile range; HAART = highly active antiretroviral therapy; CSF = cerebrospinal fluid; JCV = JC virus; EDSS = expanded disability status scale.
[a]Fisher's exact test; [b]chi-square test; [c]Student's *t*-test; [d]Mann–Whitney *U*-test.

M3, the proportion of patients with HIV-load below the detection level (200 copies/mL) in plasma was above 70% and similar in both groups. The median increment of CD4+ lymphocyte count from baseline to M3 was 58 cells/μL (IQR = 29–141) in the CDV group and 25 cells/μL (IQR = 4–87) in the HAART group ($P = 0.15$).

JCV monitoring in CSF

The JCV-DNA was measured from CSF samples collected at baseline for the 46 patients and during follow-up between M1 and M12 in 30 patients, with a mean of 2 samples ranging from 1 to 5. The median time to JCV clearance, determined by the Kaplan–Meier method, was 6.9 months (95% Cl = 5.5–8.8) and was similar for both groups (log-rank, $P = 0.62$). The proportion of patients with a JCV load below the detection level (500 copies/mL) in CSF does not significantly differ at M6, 33% (8/24) in the CDV group and 39% (7/18) in the HAART group ($P = 0.71$). However, JCV load was not monitored during the follow-up in 4 patients in the HAART group, although alive with a survival time exceeding 18 months.

Survival analysis

By the end of the study (31 December 2000), a total of 23 deaths were reported (12 in the CDV group and 11 in the HAART group). All deaths were related to PML. The overall median survival time, determined with the Kaplan–Meier method, was 20.9 months (95% Cl = 0–48.9). Figure 1 shows that patients treated with cidofovir and HAART had the same survival time as patients on HAART alone (log-rank, P = 0.72). The cumulative proportion of patients surviving after 1 year was 62% in the CDV group and 53% in the HAART group.

None of the following variables affected survival in the univariate Cox regression model (age at baseline, HIV-transmission groups, a previous AIDS-defining event, HAART before PML onset, and plasma HIV load at baseline) as well as the use of cidofovir (RH = 0.86, 95% Cl = 0.38–1.95, $P = 0.72$). Baseline variables significantly associated with a

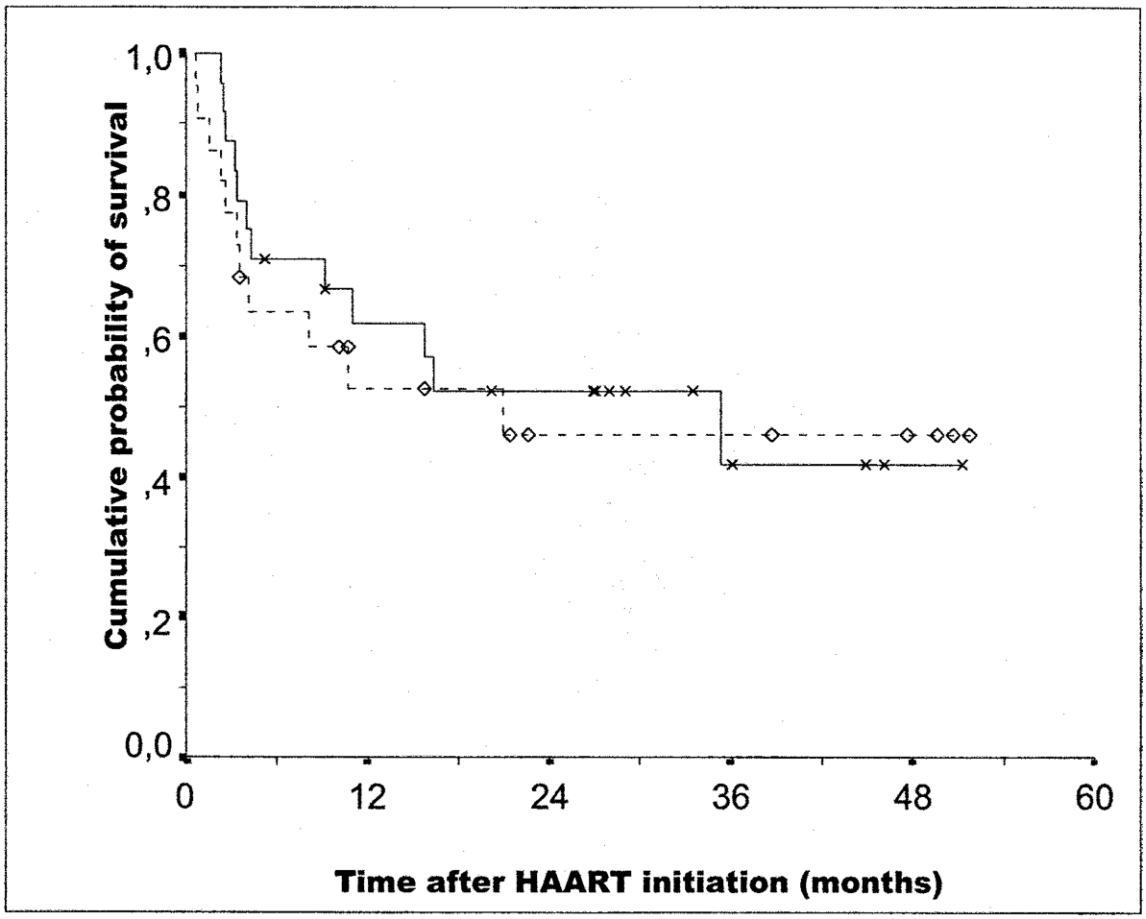

Figure 1 Kaplan–Meier survival estimates for AIDS-associated progressive multifocal leukoencephalopathy patients by treatment received after diagnosis. Solid line, HAART plus cidofovir ($n = 24$). Dashed line, HAART only ($n = 22$). No significant difference by log rank test ($P = 0.72$).

Table 2 Evolution of EDSS score in AIDS-associated PML patients per treatment group from baseline up to M12

	HAART group		*Cidofovir group*		P
EDSS score	n	*mean (95% Cl)*	n	*mean (95% Cl)*	*Mann–Whitney* U-*test*
Baseline	21	6.19 (5.57–6.81)	24	6.15 (5.60–6.69)	0.89
M2	19	6.40 (5.33–7.46)	24	7.40 (6.74–8.05)	0.18
M4	14	5.39 (3.95–6.84)	18	7.14 (6.32–7.96)	0.04
M6	13	4.89 (3.45–6.32)	17	6.79 (5.89–7.70)	0.03
M12	12	4.38 (2.78–5.97)	15	6.23 (5.37–7.10)	0.02
Changes in EDSS					
delta M2 to Baseline	19	0.29 (−0.38–0.96)	24	1.25 (0.99–1.51)	0.02
delta M4 to M2	14	−0.18 (−0.69–0.34)	18	−0.11 (−0.63–0.41)	0.82
delta M6 to M2	13	−0.42 (−1.13–0.28)	17	−0.41 (−0.96–0.14)	0.99
delta M12 to M2	12	−0.71 (−1.67–0.25)	15	−0.90 (−1.45–0.35)	0.52

CDV = cidofovir, EDSS = expanded disability status scale.

reduced risk of death were a CSF-JCV load below 4.5 $\log_{10}$ copies/mL (RH = 0.17, 95% Cl = 0.06–0.47, $P = 10^{-3}$), an EDSS score below 6.0 (RH = 0.28, 95% Cl = 0.10–0.84, $P = 0.02$) and a CD4 cell count above 75 cells/μL (RH = 0.35, 95% Cl = 0.14–0.87, $P = 0.02$). In the multivariate Cox regression model, a JCV load in CSF below 4.5 $\log_{10}$ copies/mL (RH = 0.14, 95% Cl = 0.05–0.39, $P < 10^{-3}$), an EDSS score below 6.0 (RH = 0.16, 95% Cl = 0.05–0.57, $P = 0.004$), a CD4 cell count above 75 cells/μL (RH = 0.31, 95% Cl = 0.12–0.79, $P = 0.01$) and the use of cidofovir (RH = 0.36, 95% Cl = 0.14–0.94, $P = 0.04$) were independently associated with a reduced risk of death.

The exclusion of the 3 patients who received less than 3 cycles of cidofovir has not modified the overall results of the survival analysis (data not shown).

Neurological monitoring

The mean EDSS score (and its 95% Cl) was similar in both groups at baseline (Table 2). Despite the initiation of cidofovir generally between M1 and M3, a trend to higher EDSS score in the CDV group was noted at M2 ($P = 0.18$), as compared to the HAART group. This trend became significant at M4 ($P = 0.04$), M6 ($P = 0.02$), and M12 ($P = 0.03$). The mean change in EDSS score between baseline and M2 was significantly higher ($P = 0.02$) in the CDV group, as compared to the HAART group. However, by using the M2 value as a reference, the mean changes did not significantly differ between the two groups by M4. Compared to the first clinical presentation, the neurological status of the 23 survivors at the end of the study was as follows: 7 patients improved, 2 worsened, and 2 remained stable in the HAART group; 1 patient improved, 3 worsened, and 8 remained stable in the CDV group.

Discussion

This study shows the good tolerability and the safety of cidofovir added to HAART in AIDS-associated PML patients. As previously reported in a small group of 6 patients (Labetoulle *et al*, 2000), none of the PML patients without previous history of eye disease or surgery developed eye inflammation despite a long exposure to cidofovir. However, a precise ophthalmologic assessment remains necessary in all patients receiving cidofovir.

According to ACTG 363 (Marra *et al*, 2001) and NARC 001 (Clifford *et al*, 1999), the mortality rate at the end of the study was similar (50%) in both the CDV and HAART groups. Nevertheless, the use of cidofovir reduced progression until death by 64%, as compared with HAART, only after adjustment of the following baseline variables (JCV load CSF, CD4 cell count, EDSS). This is in agreement with the results of 2 other studies (De Luca *et al*, 2000a, Berenguer *et al*, 2001). As compared with the Italian experience (De Luca *et al*, 2000a), the cumulative proportion of patients who remained alive after 1 year was similar in the CDV group (62% vs 67%) but differed in the HAART group (53% vs 31%). The better survival rate in our HAART control group may be related to the compassionate approach used in our center for initiation of cidofovir. Indeed, cidofovir was not given to patients with early clinical response to HAART. This observational design without random assignement of treatment is the main limitation of our study.

Prolonged survival in PML after HAART is generally associated with JCV clearance from CSF (Miralles *et al*, 1998, Taoufik *et al*, 1998, Gasnault *et al*, 1999, De Luca *et al*, 2000b, Giudici *et al*, 2000). Our study showed no significant benefit for the addition of cidofovir in terms of JCV-suppression rate as well as in the time required for JCV suppression. This contrasts with a previous published study that reported in a group of 20 patients a more rapid clearance of JCV from CSF on cidofovir (De Luca *et al*, 2000a).

According to the clinical monitoring results, the deterioration of the neurological condition is an early event in the PML course, following the irreversible cerebral destruction caused by the lytic replication of JCV in oligodendrocytes. The addition of cidofovir

to HAART failed, in most patients, to eliminate the occurrence of a clinical disability. These results are in agreement with the compassionate design of the study that led to initiating cidofovir generally between baseline and M3 in patients with rapid clinical deterioration. The mean time between baseline and cidofovir onset was 45 days. This period is probably too long to avoid a severe and extensive destruction of cerebral white matter. However, a clinical stabilization is generally observed following induction of cidofovir in survivors. This might be related to a specific anti-JCV effect of cidofovir concomitantly with the anti-JCV immune reconstitution consecutive to efficient HAART (Taoufik *et al*, 2000).

Overall, our study suggests that the slight additional benefit in terms of survival observed with cidofovir might be counterbalanced by the limited neurological effect with respect to the final functional disability in survivors.

In the absence of a controlled randomized study, the place of cidofovir as an add-on treatment to HAART in AIDS-associated PML remains unclear. A large, multicenter, randomized trial is required to clarify this issue. The design of such trial might ideally include recommendations for an early, simple, and rapid diagnosis of PML based on detection of JCV genome in CSF. Survival, neurological, and virological endpoints are required. A placebo-controlled allocation of cidofovir (or any other potential anti-JCV drug) should be planned in association with an optimized efficient antiretroviral therapy. The initiation of anti-JCV drug as soon as possible following the clinical PML onset (less than 45 days) would be considered as a high priority. Data analysis should be stratified according to the following baseline variables: JCV load in CSF, CD4+ cell count, and EDSS or other neurological scale as the NIH Stroke Scale (Brott *et al*, 1989).

Methodology

This prospective observational study included all the HIV-infected patients diagnosed with PML at the NeuroAIDS Rehabilitation Unit of Bicêtre Hospital between May 1996 and July 2000, who were given an optimal antiretroviral therapy with or without cidofovir. Exposure to other antiviral drugs (as alpha-interferon or topotecan) or initiation of cidofovir more than 3 months from baseline were exclusion criteria.

A confirmed diagnosis of AIDS-associated PML required the confluence of 5 criteria: a documentation of HIV infection, a progressive focal cerebral deficit (documented by a neurologist) associated with findings of focal white matter lesions on brain MRI consistent with PML and the detection of JCV-DNA in CSF by PCR. Other etiologies such as viral infections (cytomegalovirus, varicella-zoster virus, herpes simplex virus, Epstein–Barr virus) were excluded by PCR assays in CSF.

Study variables

For the survival analysis, the HAART initiation date (de novo for na¨ve patients or intensification for HAART-experienced patients) was considered as the baseline. Living patients were right-censored to the end-date of the study (31 December 2000). For patients who died before, the survival time was defined as the period from the baseline until death.

CD4+ T lymphocyte count and plasma HIV-RNA load were collected prospectively: at baseline and monthly up to month 6 (M6) and then quarterly. CSF samples were collected at baseline and, mostly, once between M1 and M3 and once after M3. The JCV-DNA load was measured in CSF using a quantitative PCR assay, as previously described (Taoufik *et al*, 1998). The JCV clearance was defined as a JCV load in CSF below the detection level (500 copies/mL).

Kurtzke's Expanded Disability Status Scale (EDSS) is a standardized composite neurological examination, developed for multiple sclerosis clinical research (Kurtzke, 1983). EDSS produces a 20-step ordinal score graded from 0 (normal) to 10 (death). Slight modifications are necessary to use this score in PML assessment. In the current study, EDSS was generally performed at the initial clinical presentation, and monthly from baseline through M6, then quarterly to M12.

Cidofovir regimen

We used a classical schedule for the administration of cidofovir: 1 intravenous infusion of 5 mg/kg over 1 h, weekly for the first 2 weeks and then every 2 weeks in association with oral probenecid and intravenous normal saline hyperhydratation. Simultaneous use of potential nephrotoxic agents was excluded. The treatment regimen was not randomly assigned except for 6 patients included concomitantly in the European trial and considered for the present study with permission of Pharmacia and Upjohn. The initiation of cidofovir was made in most cases on compassionate grounds, generally when clinical worsening occurred prior to M3. All patients received appropriate neurological rehabilitation during follow-up.

Statistical analysis

A $\log_{10}$ transformation was applied to plasma and CSF viral loads before statistical analysis. The differences between both groups for categorical variables were tested with the chi-square test or Fisher's exact test. The Mann–Whitney *U*-test or Student's *t*-test was used to compare continuous variables between both groups. Survival analysis was done using the Kaplan–Meier product limit method. The difference between survival curves was tested with the log-rank test. Crude relative hazards (RH) of death and their 95% confidence intervals (Cl) were calculated using

the Cox proportional hazards model for all the following baseline variables after transformation in binary categories when necessary (HIV-exposure group, AIDS status, and HAART regimen before PML onset, cidofovir assignment, age, EDSS, CD4+ cell count, plasma HIV load, and CSF JCV load). All baseline variables with crude RH with a statistical significance of less than 0.05 were included in a multivariate model as well as the treatment group. The EDSS score at baseline, M2, M4, M6, and M12 were considered for statistical analysis. The neurological outcome during follow-up was assessed by changes in the EDSS score related to the baseline value until M2 and then to the M2 value. Progression was defined as an increment exceeding 1.0 in EDSS score, improvement as a decrement exceeding 1.0 in EDSS score, and stability as a lack of improvement or progression. The differences between both groups were tested with the Mann–Whitney *U*-test because the EDSS scores were not normally distributed.

All statistical analyses were performed using the SPSS software system (version 10.05, SPSS Inc, Chicago, IL, USA).

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