Cytarabine Therapy for Progressive Multifocal Leukoencephalopathy in Patients with AIDS

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To evaluate the efficacy and safety of intravenous cytarabine in the treatment of AIDS-associated progressive multifocal leukoencephalopathy (PML), we reviewed the charts of all human immunodeficiency virus–infected patients with PML who were seen during a 28-month period at our institution. Patients with biopsy-proven PML were offered therapy with intravenous cytarabine (2 mg/[kg • d] for 5 days every 4 weeks). The diagnosis of PML was histologically confirmed for 13 patients. The median CD4 cell count was 91 x 10^9/L. A median of three courses of cytarabine was administered to eight patients. Two patients developed mild drug-related toxicities. Clinical and/or radiological signs of improvement were observed for three patients treated with cytarabine; no signs of improvement were noted for the untreated patients. Median survival time after the diagnosis of PML was 102 days (range, 46–220 days) for patients who received cytarabine and 60 days (range, 28–72 days) for untreated patients matched for Karnofsky scores (P = .06, logrank test). Although cytarabine is well tolerated by patients with AIDS and PML, only modest short-term clinical improvement in the conditions of patients treated with the drug has been observed, with no significant impact on survival.

Materials and Methods

We reviewed the charts of all HIV-infected patients at our institution who developed PML during the period January 1993 through April 1995. Uniform data were collected for all patients and included demographics, clinical and radiological manifestations of PML, antiretroviral agents administered, prophylaxis for opportunistic infections, clinical course, and survival time. During the study period, patients with suspected PML received information about the nature and clinical course of the disease, including the lack of effective therapy and the poor outcome observed for most patients. Stereotactic brain biopsy was performed for most patients. Therapy with cytarabine was recommended to patients whose general conditions were relatively good and whose quality of life was good (in general, patients with a Karnofsky score of >40). Only patients with biopsy-confirmed PML are described in this report.

Patients who were treated for PML received intravenous cytarabine at a dosage of 2 mg/(kg • d) for 5 days every 4 weeks. Posttreatment evaluation included assessment for symptoms and signs of PML, CT scans of the brain (some patients), and assessment for potential adverse events. Blood counts and renal and liver function tests were performed every 2 weeks to monitor for signs of drug-related toxicity. We assessed the effects of cytarabine by comparing the progression of disease and the survival times among treated and untreated patients. We used the Kaplan-Meier product limit method to compare survival times for treated and untreated patients; P values refer to logrank test results.

Results

During the study period 22 HIV-infected patients were found to have PML; the disease was histologically confirmed for 13...
patients (59%). Most of these 13 patients were male (77%), and most were intravenous drug users (62%). PML was the AIDS-defining condition in eight (62%) of the 13 patients; the median CD4 cell count among these patients was $91 \times 10^3/\text{L}$. Seven (54%) of the 13 patients were receiving zidovudine at the time that PML was diagnosed.

The demographic and clinical characteristics of the 13 patients with PML are shown in Table 1. The clinical presentation of PML was characterized by focal neurological deficits and a lack of fever, headaches, and other organic or systemic manifestations. Hemiparesis was the most frequent neurological deficit (85% of patients). No patient presented with seizures; however, seizures developed during the course of the disease in three (23%) of the 13 patients. Analysis of the CSF, performed for seven patients, showed no abnormalities in any case. Brain CT scans showed abnormalities in all the patients; six patients (46%) had multiple lesions, and seven (54%) had single lesions. MRI demonstrated an increase in the number of lesions in three of the four patients who underwent the procedure. The baseline characteristics of the patients treated with cytarabine and of untreated patients were similar.

Cytarabine was administered to eight (62%) of the 13 patients. Three patients received concomitant antiretroviral therapy (zidovudine, two patients; didanosine, one patient). Patients received a median of three courses of cytarabine (two patients received one course, two received two courses, and each of the remaining four received three, four, five, and six courses, respectively). Reasons for stopping therapy included death (two patients) and severe progression of PML (five). At the time of this writing, one patient is still alive and receiving cytarabine.

Therapy with cytarabine was well tolerated. Only two patients developed minor drug-related toxicities (rash, one, and vomiting, one). No significant hematologic, renal, or liver toxicities were detected while the patients were receiving cytarabine; thus, therapy did not have to be discontinued for any patient because of toxicity.

Clinical follow-up was adequate in all eight patients who received cytarabine. The neurological conditions of two patients markedly improved, and the condition of one patient stabilized clinically for a prolonged period; the other five patients had no improvement in their conditions. Follow-up CT scans were performed for six patients (five who were treated and one who was not treated). Only the follow-up CT scans of the three patients whose conditions improved or stabilized showed a decrease in the number and/or size of preexisting lesions. Although the number of patients in this study was too small to draw any significant conclusion, no association was found between the clinical and radiological signs of disease progression and the effects of antiretroviral therapy or the CD4 cell count.

Death occurred a mean of 79 days after PML was diagnosed (range, 28–220 days). The causes of death were progression of PML in 10 patients and upper gastrointestinal bleeding in one; the cause of death was undetermined for one patient. The median survival time after the diagnosis of PML was 102 days (range, 46–220 days) for patients who received cytarabine and 60 days (range, 28–72 days) for patients who were not treated. The survival time was significantly longer for patients who received cytarabine than for untreated patients ($P = .03$, log-rank test). As previously stated, some of the patients were not offered therapy with cytarabine because their general conditions were poor and were rapidly deteriorating. When these patients are excluded, the median survival time for patients in the untreated group was 80 days ($P = .06$ when these patients are compared with the treated patients). There was no association between survival and the CD4 cell count or the use of antiretroviral drugs after the diagnosis of PML.

Discussion

Our study shows an uniformly poor prognosis for HIV-infected patients with PML; the maximal survival time for untreated patients was <3 months, a finding in agreement with the findings of earlier published reports [13, 14]. Systemic therapy with cytarabine was associated with the improvement or stabilization of the conditions of three of the eight treated patients. Although a trend toward a longer survival time was associated with the administration of cytarabine, the difference between the groups could be explained by baseline differences between treated and untreated patients.

There are few reports on therapy for AIDS-associated PML. The scarce available data derive from case reports or short series of patients treated with a variety of drugs including adenine arabinoside [15]; acyclovir, foscarnet, and zidovudine [16]; other antiretrovirals; and cytarabine [5–12]. None of these drugs has been shown to be uniformly effective. Inter-

Table 1. Characteristics of 13 patients with AIDS and progressive multifocal leukoencephalopathy who were treated with cytarabine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated (n = 8)</th>
<th>Untreated (n = 5)</th>
<th>Total (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of males</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Median age in y (range)</td>
<td>33 (27–40)</td>
<td>34 (29–49)</td>
<td>34 (27–49)</td>
</tr>
<tr>
<td>Risk factor for HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Homosexuality</td>
<td>1</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Previous diagnosis of AIDS</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Median Karnofsky score (range)</td>
<td>70 (50–90)</td>
<td>60 (30–90)</td>
<td>60 (30–90)</td>
</tr>
<tr>
<td>Median no. of CD4 cells × 10^3/L (range)</td>
<td>115 (59–272)</td>
<td>91 (5–272)</td>
<td>91 (5–272)</td>
</tr>
<tr>
<td>Multiple lesions on CT scan</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Concomitant antiretroviral therapy</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE: PML = progressive multifocal leukoencephalopathy.
pretation of the data from these reports is compounded by the fact that prolonged survival time and spontaneous partial recovery among patients with AIDS-associated PML have been well described, and no comparative studies have been performed [17].

Until recently, most reports on cytarabine therapy for PML have shown a beneficial clinical effect of the drug and regression of the radiological findings associated with the disease; the overall efficacy of cytarabine approaches 60% among treated patients [9]. However, these results may be biased because of the tendency to describe patients in whom therapy has been successful. A favorable response in consecutively treated patients has been reported only by Portegies et al. (three patients) [7] and Nicoli et al. (two patients) [8]. Nevertheless, two recent reports have failed to show any consistently beneficial effect of cytarabine therapy for PML [11, 12].

As was noted in these reports, we also noted a beneficial clinical effect of cytarabine therapy in a modest number of patients with PML. The variability in response may be secondary to factors such as the extension of PML, the baseline clinical and immunologic conditions of the patients, and the concomitant administration of antiretroviral therapy. We have not observed a relation between the clinical effect of cytarabine and any of these variables. Other authors have emphasized the importance of the number of courses of cytarabine administered and attribute failure to early discontinuation of therapy. Among our patients, interruption of therapy was secondary in most cases to rapid deterioration in their clinical conditions; thus this interruption may have been the consequence and not the cause of a lack of response.

Despite the lack of conclusive data regarding the efficacy of cytarabine for the treatment of PML, some recommendations can be made based on the available information. Since no significant toxicity of the drug has so far been found in patients with AIDS, and clinical and radiological signs of improvement have been observed in a percentage of patients, cytarabine could be considered for patients with PML whose clinical status is otherwise good. Future clinical trials are needed to define the role of this drug as well as that of concomitant antiretroviral therapy in the treatment of patients with PML and in the prolongation of survival time.

References