Journal of NeuroVirology, 7: 358–363, 2001
 ISSN 1355–0284/01 $12.00+.00

Clinical Trial Report

The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy

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The use of highly active anti-retroviral therapy in patients with HIV-related progressive multifocal leukoencephalopathy is associated with increased survival and disease stabilization. However, approximately half of the patients receive no benefit from these treatments. In a group of HIV-infected patients with histologically or virologically confirmed PML, we recognized two distinct patterns of response, i.e., long survivors versus nonresponders, but could not identify any factors at baseline predictive of PML outcome. In addition, the use of cidofovir did not substantially affect survival. However, the survival rate was higher during the first years of HAART, i.e., 1996–1997, with better outcomes observed in patients receiving a protease inhibitor-containing regimen either irregularly or after a switch from a 2-nucleoside reverse transcriptase inhibitor combination. In contrast, PML outcome was frequently poor in both HAART-naive and -experienced patients who responded promptly to anti-HIV therapy in terms of CD4 increase and viral load decrease. In addition, in a number of patients, PML onset was temporally associated with immune reconstitution. It may be that, in some patients, rapid immune reconstitution due to HAART paradoxically worsens the course of PML. Gradual reversal of immune deficiency might be associated with better outcome. *Journal of NeuroVirology* (2001) **7,** 358–363.

Keywords: JCV; HAART; HIV; PML

Before protease inhibitors became available, the prognosis of progressive multifocal leukoencephalopathy (PML) was extremely poor, with death ensuing within a few months from onset of symptoms. No treatment was demonstrated to benefit PML (Hall *et al*, 1998).

Following widespread introduction of highly active anti-retroviral therapy (HAART), a large number of PML patients were reported in whom survival was exceptionally long (Albrecht *et al*, 1998; Cinque *et al*, 1998; Miralles *et al*, 1998). First observations were confirmed by cohort studies demonstrating that HAART was the main factor responsible for such long survivals (Clifford *et al*, 1999; Dworkin *et al*, 1999; Gasnault *et al*, 1999; De Luca *et al*, 2000a). Thus, for the first time, a pharmacological approach seemed to have impacted markedly on the natural history of HIV-associated PML. The effect of HAART on PML was interpreted as a result of improved immune status, restoring natural defenses against this disease.

However, not all PML patients benefit from HAART. In fact, PML survival is not substantially different from that observed before the HAART era in approximately half of the cases (De Luca *et al*, 2000a; Clifford *et al*, 1999; Gasnault *et al*, 1999). To characterize the outcome of HIV-associated PML since the introduction of HAART, we reviewed all PML cases referred to three northern Italy infectious diseases clinics between 1996 and 2000.

Methods

Data from 27 PML patients were examined for demographic characteristics, risk factors, baseline and follow-up neuroradiologic and laboratory findings, survival, treatment with cidofovir, and anti-retroviral

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Received 7 March 2001; revised 17 April 2001; accepted 23 April 2001.

experience. Responders were defined as those with a survival ≥8 months after onset of PML. HAART was defined as a combination of at least three drugs belonging to one or more of the PI, NRTI, or NNRTI classes. PML was diagnosed when the presence of a suggestive clinical-neuroradiological pattern confirmed by either a positive CSF PCR for JCV DNA was seen (22 patients) or by histopathology (brain biopsy, 2 patients, or postmortem examination, 3 patients). CSF PCR was performed according to a previously described nested procedure (Cinque *et al*, 1996). Follow-up CSF samples drawn 1–12 months after onset of PML were available from 15 patients, including 9 responders and 6 nonresponders. CD4 positive cell counts and plasma viral loads were assessed periodically as required for patient monitoring; in a subgroup of more recently observed patients, these markers were measured every 1–2 months during the first months of PML.

Survival of cidofovir-treated and untreated patients was compared by Kaplan–Meyer analysis. The possible influence of the different variables at baseline or during follow-up on the response to HAART was calculated by means of the Mann–Whitney *U*-test and Fisher's exact tests.

Results

PML outcome

Of the 27 patients, 13 are still alive, with a median survival of 45 months (range 17–54) after onset of symptoms (responders); the 14 remaining patients died after a median of 4.25 months (range 2.5–7.75), (nonresponders). PML was the cause of death in 13 of the latter patients. Most of the responders (10 of 13), but only a minority of the nonresponders (3 of 14), developed PML in the earlier years of HAART, i.e., between 1996 and 1997.

A number of variables at baseline that might have influenced the response to HAART were examined, but none of these was significantly associated with a longer survival (Table 1). Among the responders, both the neurological picture and magnetic resonance images (MRI) stabilized or even improved over the first months after symptom onset. However, MR improvement was usually delayed and, in most of the patients, it was preceded by an initial deterioration (Giudici *et al,* 2000). At the onset of symptoms, JC virus (JCV) DNA was found in the cerebrospinal fluid (CSF) of 11 of 13 patients, whereas it was undetectable in all of 9 patients examined 2 to 12 months later (Table 1). A few years after PML presentation, these patients are left with mild to severe neurological sequelae, their immune status has significantly improved (median CD4+ cell count: 287/μl, range 61–566 at last observation), and their HIV-1 RNA levels are low or undetectable (median <80 copies/ml, range <80–2200). All of these patients have continued to receive HAART, with the exception of one patient, who stopped HAART and was temporarily lost at follow-up 5 months after onset of PML. This patient subsequently developed neurotoxoplasmosis 7 months after HAART withdrawal. At

Table 1 Association between variables at baseline or follow-up and survival in PML patients receiving HAART

Variables	*Responders* n = *13*	*Nonresponders* n = *14*	P
Survival	≥8 months	<8 months	
At baseline			
Age (year)	37 (32–41)	37 (25–55)	n.s.
Sex (M:F)	11:3	10:4	n.s.
Risk factor (IVDA:others)	9:4	11:3	n.s.
PML as first HIV disease	8 (62%)	10 (71%)	n.s.
Concomitant CN.S. OI	1 (8%)	4 (29%)	n.s.
Median CD4+/μl (range)	45 (8–397)	60 (6–418)	n.s.
Median CD8+/μl (range)	378 (305–656)	412 (180–1103)	n.s.
Median plasma $\log_{10}$ c/ml VL (range)	4.86 (3.34–6.00)	4.75 (<2.60–6.00)	n.s.
Median CSF $\log_{10}$ c/ml VL (range)	3.35 (<2.60–5.74)	2.88 (<2.60–6.00)	n.s.
CSF JCV DNA positive	11 (85%)	9 (64%)	n.s.
Infratentorial lesions at MRI	9 (69%)	9 (64%)	n.s.
Enhancement at MRI	0	0	n.s.
At follow-up			
CSF JCV DNA positive	0/9	4/6 (67%)	0.011
Cidofovir treatment ≥2 weeks	5 (38%)	11 (79%)	n.s.
Cidofovir treatment ≥4 weeks	5 (38%)	4 (29%)	n.s.
Median time between PML onset and start of cidofovir (weeks, range)	23 (9–44)	7 (1–19)	0.017
PI-based HAART	13 (100%)	7 (50%)	0.011
Median time between PML onset and start of HAART (weeks, range)*	7 (0–22)	4 (0–8)	n.s.

IVDA: intravenous drug addict; CNS OI: central nervous system opportunistic infections; VL: viral load; MRI: magnetic resonance imaging; n.s.: non-significant; *HAART-experienced patients not included.

that time, PML lesions were stabilized, and JCV was undetectable in the CSF.

The role of cidofovir
Sixteen of 27 patients received cidofovir, 9 of whom were treated for 4 weeks or longer. Overall, survival was not significantly different between cidofovir-untreated versus -treated patients. However, among those -treated ≥4 weeks, a better survival trend was observed. Eleven nonresponders, but only 5 responders (38%), started cidofovir (Table 1). During follow-up, JCV DNA was cleared from the CSF of 3 of 6 (50%) patients receiving HAART and cidofovir and of 9 of 12 (67%) receiving HAART alone. Four of 5 cidofovir-treated survivors discontinued this drug after 12–30 months because of serum creatinine elevation or uveitis, 2 patients each). Neither clinical nor radiological worsening of PML was observed after withdrawal.

The impact of HAART
Previous anti-retroviral treatment history at onset of PML varied largely in our population: 10 patients were anti-retroviral naive, whereas 17 had previously received anti-HIV medications (Table 2). In 5 patients (18%), PML symptoms presented within 9 weeks after beginning anti-retroviral therapy and experiencing CD4 cell count increase and viral load decline. Of these, 4 patients were taking HAART and 1 patient was taking a 2-nucleoside reverse transcriptase (NRTI) combination. HAART regimens following PML diagnosis included protease inhibitors (PI) in 20 patients (all the 13 responders and 7 of 14 nonresponders), nonnucleoside reverse transcriptase inhibitors (NNRTI) in 6 patients (all 6 nonresponders) and 3 NRTIs in 1 (nonresponder) patient. No difference was observed between responders and nonresponders in the time between onset of PML symptoms and start of HAART (Table 1).

Anti-retroviral-naive patients Five out of 10 antiretroviral therapy naive patients showed a good PML outcome following HAART. None of the variables examined in Table 1 for the 27 patients appeared to have influenced PML survival in this subgroup. However, differences were seen in the drug regimens during the first months of therapy. Two of 5 responding patients temporarily discontinued treatment or switched to a 2-NRTI regimen, due to side effects or problems with compliance. Two other patients received a 2-NRTI combination as initial treatment after PML, with a PI added only 4 and 5.5 months later, respectively. In contrast, all of the 5 nonresponders received full HAART as first line therapy and did not discontinue treatment until advanced disease progression. A sharp reduction of viral load was observed in these patients, with a marked increase of CD4 counts in 3 of them. Of note, in 2 of these patients with elevated CD4 positive cell counts (160 and 285/μl at baseline, and 342 and 346/μl, respectively, after 1 month of HAART), PML progressed paradoxically rapidly, with death ensuing 12 and 17 weeks, respectively, after onset of first symptoms.

Anti-retroviral-experienced patients At onset of PML, 5 patients were receiving a 2-NRTI-based regimen. Following initiation of a new PI-based HAART all of these patients responded with stabilization of disease and are still alive up to 54 months from PML onset. Four HAART-experienced patients had HIV-1 RNA levels >50,000 copies/ml at onset of PML. In all of them, PML, progressed despite switching to a salvage HAART regimen. Six HAART experienced patients had HIV-1 RNA levels either undetectable or below 3000 copies/ml at PML presentation. This group includes 4 of the previously mentioned patients with a probable immune reconstitution disease and 2 additional patients who had started HAART several months before PML onset. Neurological disease progressed in 4 of these patients, despite persistence of low plasma VL. Overall, the nonresponders showed no substantial changes in the CD4 and VL values after the first weeks of HAART. In

Table 2 PML outcome according to antiretroviral treatment (ART) history

	Number of patients		
ART history	*Total*	*Responders*	*Nonresponders*
Naive	10	5 (50%)	5 (50%)
Experienced	17	8 (43%)	9 (57%)
Dual NRTI-experienced	5	5	0
HAART-experienced, VL >50,000	4	0	4
HAART-experienced, VL <3000	6	2	4
Others*	2	1	1

*Including two patients who had previously received NRTIs, but were untreated at the time of PML onset.
Mean CD4+ and viral load (VL) changes from baseline (BL):
ART-naive patients:
Nonresponders (4 patients, 3–5 weeks from BL), CD4: +61 cells/μl, VL:−2.11 logs.
No sufficient data were available from the responders.
ART-experienced patients:
Responders (6 patients, 6–11 weeks from BL), CD4: +78 cells/μl, VL:−1.32 logs.
Nonresponders (5 patients, 6–10 weeks from BL), CD4: +7 cells/μl, VL: −0.40 logs.

contrast, both a CD4 and a VL response were observed in the responders, primarily in the NRTI-treated patients who switched to HAART. However, the virological response was apparently slower in these patients than in the anti-retroviral-naïve, nonresponder patients (Table 2).

Discussion

In agreement with previous studies (Clifford *et al*, 1999; Dworkin *et al*, 1999; Gasnault *et al*, 1999; De Luca *et al*, 2000a), approximately half of our patients responded to HAART in terms of survival and disease stabilization. In addition, two distinct patterns of response could be recognized according to individual survival. Baseline variables associated with a lower risk of progression had been identified by previous studies involving both HAART-treated and -untreated PML patients, including younger age, higher CD4 positive cell counts, better neurological status, and low level JCV replication in CSF (Clifford *et al*, 1999; Dworkin *et al*, 1999; Gasnault *et al*, 1999; De Luca *et al*, 2000a). However, none of the factors examined was associated with better prognosis in the present study. Treatment with cidofovir has also recently been reported to be a further predictor of longer survival among PML HAART-treated patients (De Luca *et al*, 2000b), but its efficacy remains controversial (Marra *et al*, 2001). In our group of patients, the better trend in survival observed in patients who received cidofovir for $\geq$4 weeks was likely to reflect a selection of patients who survived enough to receive the drug for a longer time. Overall, our observations clearly show that the majority of the responding patients survived despite having ever received cidofovir, thus indicating that this drug is probably not the main cause of increased survival in PML. Furthermore, the long-term rate of side effects of cidofovir was significant, as also observed in the earlier cytomegalovirus retinitis studies (SOCA, 2000).

In approximately one fifth of the patients, PML occurred a few weeks following the start of HAART. In line with previous reports, such cases were most likely associated with HAART-induced immune reconstitution (De Simone *et al*, 2000). The actual frequency of possible immune-reconstitution PML cases has not yet been estimated on large series. However, these events might account for the less dramatic reduction of PML incidence following HAART as compared to other HIV-related CNS complications (Ammassari *et al*, 2000).

To assess whether PML course could also have been influenced by differences in drug regimens, details on anti-retroviral treatments were carefully analyzed. HAART is a definition including a number of different anti-HIV drug combinations, the effects of which vary related to patient history and drug adherence. The availability of an increasing number of anti-HIV agents results in a continuous evolution of treatment recommendations and anti-HIV drug usage in clinical practice (Panel on Clinical Practices, 2001).

PML progressed in half of the HAART-naïve patients (Table 2), despite prompt virological and immunological response. Furthermore, the course of the disease was rapid in 2 of these patients with relatively high CD4 cell counts, in contrast to what had been observed in untreated patients with high CD4 numbers, in whom PML progression was frequently slow (Berger *et al*, 1998). It is intriguing to hypothesize that a rapid and efficient boosting of immunity may have exerted a deleterious effect on the PML course in some patients. On the other hand, it is possible that some of the naïve responding patients actually benefited from interrupted treatment that led to more gradual immune restoration. Patients who were on a 2-NRTI regimen before switching to HAART showed a very good response. Out of 12 long-term PML survivors described in an earlier report, half of these were also switched from a 2-NRTI to a PI-including regimen (Miralles *et al*, 1998). Although such patients are now rarely encountered, these observations support the hypothesis that gradual institution of an efficient anti-HIV treatment might be associated with PML stabilization. Furthermore, this may partly account for the better outcomes observed in the earliest PML cases, i.e., those observed between 1996 and 1997. The differences in response might also reflect the increasing usage of NNRTIs in drug combinations. In this regard, it is hard to hypothesize a direct effect of individual anti-HIV agents on JCV. However, it is possible that simpler and more easily tolerated regimens, such as those containing NNRTIs, are associated with better patient adherence compared to PI-containing regimens (DHHS, 2001) and may paradoxically yield poor outcome for PML.

Failure to respond to HAART, revealed by high plasma viral loads, has been associated with poor PML prognosis (Clifford *et al*, 1999). The progression of PML in our HAART patients who showed a virological failure was similar to that expected in the absence of antiretroviral therapy. Poor PML outcome, however, was also observed despite stabilization of HIV infection markers, as also previously noted (Tantisiriwat *et al*, 1999). In this group of patients, poor PML outcome could have resulted from inadequate immune response against JCV, either due to insufficient response to HAART or to permanent loss of JCV specific immunity. In this regard, patients whose outcome was poor have been demonstrated to show no response using cytotoxic T-lymphocyte assays (Koralnik *et al*, 2001).

Hypothetically, both loss of immune competence and HAART-induced boosting of immune response could lead to brain damage, through opposite pathogenic pathways. Whereas demyelination would result from JCV infection of oligodendrocytes in the former case, an adjunctive immune-mediated damage, as observed in other demyelinating CNS

diseases, can be suggested in the latter. The relative importance of either mechanism in determining brain damage might vary in the individual patients, according to patient genetic background and her or his HIV infection and treatment history. Whether infection with different JCV strains can also influence disease outcome remains another issue deserving evaluation (Sala *et al*, 2001).

Conclusion

In summary, these data suggest that both patient anti-retroviral history previous to PML and the potency of anti-retroviral therapy administered during the first weeks of PML are crucial for the course of this disease. At least in a fraction of patients, HAART-induced boosting of immunity might be related to PML onset and worsening outcome. This hypothesis is supported by the not infrequent onset of PML in the context of HAART-induced immune reconstitution and the rapid disease progression observed in patients showing excellent CD4 and VL responses to HAART. Further evidence for this view is also the recent demonstration of perivascular infiltrates at brain biopsy of patients in whom PML progressed rapidly (Miralles *et al*, 2001). On the other hand, the favorable course of PML in patients who switched to HAART from a 2-NRTI combination regimen, received interrupted therapy, or whose initial regimen was 2 NRTIs only, suggests that a gradual reversal of immunity might be associated with better PML outcomes.

Larger retrospective analyses of PML cases are necessary to extend these preliminary observations and build up a solid working hypothesis. Prospective studies involving frequent sampling during the first—crucial—weeks of PML will also be required, to both assess the systemic response to HAART and to explore the role of JCV-specific cellular and humoral immunity. Ideally, a better understanding of the immunological mechanisms involved in the PML response to HAART could lead to the identification of patients at risk of progression and to targeted therapeutic interventions. Should HAART-induced immune reconstitution be confirmed to be harmful on PML outcome, then some patients might benefit from a modulation of their initial anti-retroviral regimen.

Acknowledgements

We wish to acknowledge our colleagues who have contributed to this work with patient follow-up and fruitful discussion: Anna Maria Brambilla, Barbara Giudici, Simona Bossolasco, Roberta Marenzi, Antonella Castagna, Fulvio Crippa, Brunella Capiluppi, Salvatore Casari, Carla Fornara, Stefania Medaglini, and Maria Rosa Terreni.

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