Journal of NeuroVirology, 9(suppl. 1): 47–53, 2003
 ISSN 1355-0284/03 $12.00+.00
DOI: 10.1080/13550280390195388

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Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: Data from the Italian Registry Investigative Neuro AIDS (IRINA)

Andrea Antinori,[1] Antonella Cingolani,[2] Patrizia Lorenzini,[1] Maria Letizia Giancola,[1] Ilaria Uccella,[1] Simona Bossolasco,[3] Susanna Grisetti,[1] Francesca Moretti,[4] Beniamino Vigo,[5] Marco Bongiovanni,[6] Bruno Del Grosso,[1] Maria Irene Arcidiacono,[7] Giovanni Carlo Fibbia,[8] Maurizio Mena,[9] Maria Grazia Finazzi,[10] Giovanni Guaraldi,[11] Adriana Ammassari,[2] Antonella d'Arminio Monforte,[5] Paola Cinque,[3] and Andrea De Luca,[2] for the Italian Registry Investigative Neuro AIDS (IRINA) Study Group

[1]Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani," IRCCS, Roma, Italy; [2]Clinica Malattie Infettive, Università Cattolica S. Cuore, Roma, Italy; [3]Divisione Malattie Infettive, Ospedale San Raffaele, IRCCS, Milano, Italy; [4]Clinica Malattie Infettive, Spedali Riuniti, Brescia, Italy; [5]Ospedale Niguarda, Milano, Italy; [6]Clinica Malattie Infettive e Tropicali, Ospedale Luigi Sacco, Milano, Italy; [7]ASL U.O. Ospedale Maggiore, Sant'Angelo Lodigiano, Lodi, Italy; [8]Divisione Malattie Infettive Ospedale "Carlo Poma," Italy; [9]Ospedale Civile Milano, Cuggiono, Legnano, Italy; [10]Ospedali Riuniti, Bergamo, Italy; and [11]Università di Modena, Modena, Italy

Human immunodeficiency virus (HIV)-associated progressive multifocal leukoencephalopathy (PML) remains a relevant clinical problem even in the era of highly active antiretroviral therapy (HAART). Aims of the study were to analyze clinical and treatment-related features and the survival probability of PML patients observed within the Italian Registry Investigative Neuro AIDS (IRINA) during a 29-month period of HAART. Intravenous drug use, the presence of focal signs, and the involvement of white matter at neuroradiology increased the risk of having PML. A reduced probability of PML was observed when meningeal signs were reported. Patients starting HAART at PML

Address correspondence to Dr. Andrea Antinori, Clinical Department, National Institute for Infectious Diseases, "Lazzaro Spallanzani," IRCCS, via Portuense 292, 00149 Roma, Italy. E-mail: antinori@inmi.it

This work was supported by Programma Nazionale di Ricerca sull'AIDS, Istituto Superiore di Sanità, and by Ricerca Corrente e Finalizzata degli IRCCS, Ministero della Salute, Italy. IRINA, *Scientific Committee*: A Antinori (Study Coordinator), CF Perno, G Ippolito (National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Roma, Italy), P Cinque (Department of Infectious Diseases, San Raffaele Hospital, IRCCS, Milano, Italy), A Cingolani, A De Luca, A Ammassari (Department of Infectious Diseases, Catholic University, Roma, Italy), A d'Arminio Monforte, C Balotta (Department of Infectious Diseases, L. Sacco Hospital, Milano, Italy), P Pezzotti, G Rezza (Centro Operativo AIDS, National Institute of Health, Roma, Italy). *Coordinating center, database management and statistics*: P Lorenzini, F Soldani, ML Giancola, I Uccella (Clinical Department, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy). *Centers participating in the IRINA study*: Az. Osp. Umberto I—Ancona (F Burzacchini); Osp. S. M. Ann.—Antella (FI) (L Mecocci); Osp. S. M. sopra i ponti—Arezzo (P Giorni); Pol. Univ. Bari (L Monno); Osp. Riun.—Bergamo (MG Finazzi); Sp. Civili—Univ. Brescia (F Moretti); Osp. Magg—Bologna (G Fasulo); Osp. Gen. Reg. Bolzano (O Moling); Osp. M. Bufalini—Cesena (S Brighi); Osp. Civ. Legnano—Pres. Osp. Cuggiono (MI) (M Mena); Az. Osp.—Univ. Ferrara (L Sighinolfi); Osp. Careggi—Firenze (P Corsi); Osp. S. Giov. Dio—Fondi (LT) (MT Di Toro); Osp. G. B. Morgagni—Forlì (A Mastroianni); Osp. S. C. Gesù—Gallipoli (LE) (M De Simone); Osp. S. Martino—Genova (G Mazzarello); Osp. Grosseto (T Carli); Osp. Felettino—La Spezia (S Artioli); Osp. S. M. Goretti—Latina (A Vetica); Osp. V. Fazi—Lecce (P Congedo); Osp. Maggiore—Lodi (MI Arcidiacono); Osp. C. Poma—Mantova (GC Fibbia); Osp. SS. Giacomo e Crist.—Massa Carrara (P Zannoni); Osp. L. Sacco—Univ. Milano (M Bongiovanni); IRCCS—Osp. S. Raffaele—Milano (S Bossolasco); Osp. Niguarda—Milano (B Vigo); Osp. Univ. Modena (G Guaraldi); Osp. S. Gerardo—Monza (S Foresti); Osp. Cotugno—Napoli (M Figoni); P. O. Casa del Sole—Palermo (ER Dallenogare); Osp. Guadagna—Palermo (G Rotondo); Osp. Civ.—Pescara (A Agostinone); Univ. Perugia (A Mariano); Osp. Civ. Piacenza (A Donisi); Osp. Pistoia (A Vivarelli); I, II, III, IV Div.–INMI–L Spallanzani IRCCS—Roma (L Loiacono, B Gigli, S Grisetti, B Del Grosso); Univ. Cattolica–Pol. A. Gemelli—Roma (D Larussa); Pol. Umberto I—Roma (M Ciardi); Osp. Rovigo (F Viviani); Osp. S. Paolo—Savona (M Palumbo); Osp. SS. Annunziata—Taranto (L Cristiano); Osp. E. S. Macchi—Varese (F Speranza).

Received 13 October 2002; accepted 13 October 2002.

diagnosis and previously naïve for antiretrovirals showed significantly higher 1-year probability of survival (.58), compared to those continuing HAART (.24), or never receiving HAART (.00). Higher CD4 cell count were associated with a higher survival probability (.45). At multivariate analysis, a younger age, higher CD4, starting HAART at PML diagnosis, the absence of previous acquired immunodeficiency syndrome (AIDS)-defining events, and the absence of a severe neurologic impairment were all associated with a reduced hazard of death. The use of cidofovir showed a trend towards a reduced risk of death.
Journal of NeuroVirology (2003) **9(suppl. 1),** 47–53.

Keywords: AIDS; antiretroviral therapy; central nervous system; HIV; JCV; PML; prevalence

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system caused by the JC polyomavirus (JCV). In people with acquired immunodeficiency syndrome (AIDS), it represents an important cause of morbidity and mortality. Studies performed before the introduction of highly active antiretroviral therapy (HAART) reported a prevalence of PML ranging from 1% to 5% of AIDS cases in clinical studies and up to 10% in autoptic series (Berger *et al*, 1998b), and was the recognized cause of death for 0.7% of people with AIDS (Holman *et al*, 1991). During the years before the introduction of HAART, the incidence rate among human immunodeficiency virus (HIV)-infected patients had significantly increased (Bacellar *et al*, 1994; Berger *et al*, 1998b). Even if preliminary observations showed a reduction trend of the disease in the years of antiretroviral combination therapy (Brodt *et al*, 1997), several subsequent studies reported a stable trend during the HAART era (Ledergerber *et al*, 1999; Sacktor *et al*, 2001). Among the AIDS-related focal brain disorders, PML prevalence remained stable over time following the introduction of HAART, different from what observed for other disorders such as primary brain lymphomas (Ammassari *et al*, 2000). The median survival time after the diagnosis of PML was approximately 4 months before the introduction of HAART because no specific efficacious therapy was available (Berger *et al*, 1987; Hall *et al*, 1998). In recent years, several observational studies reported an improved survival in patients with AIDS-related PML treated with HAART compared to patients not treated or treated with nucleosides analogues alone (Tassie *et al*, 1999; Miralles *et al*, 1998; De Luca *et al*, 2000; Clifford *et al*, 1999; Dworkin *et al*, 1999; Cinque *et al*, 1998). Nevertheless, not all PML cases have an improved prognosis with potent antiretroviral therapies (De Luca *et al*, 1998), and it has been observed that PML may progress despite virologic and immunologic response to HAART, and that HAART-induced immunoreconstitution could paradoxically worsen the course of neurologic disease (Cinque *et al*, 2001). Several prospective observational studies (De Luca *et al*, 2000, 2001; Gasnault *et al*, 2001; Berenguer *et al*, 2001) reported improving survival in patients treated with HAART plus cidofovir compared with those treated with HAART alone. However, even in case of a survival benefit, an improving neurologic picture was not always associated with cidofovir therapy (Gasnault *et al*, 2001) and an uncontrolled clinical trial failed to demonstrate the improvement of neurologic scores when cidofovir was added to HAART (Marra *et al*, 2002). In the present study, the epidemiological, clinical, and treatment-related features of PML patients observed within the Italian Registry Investigative Neuro AIDS (IRINA) between January 2000 and June 2002 were reported. Specific aim of the study was to analyze prevalence of PML among neurologic disorders in the HAART era, characteristics and predictive factors of PML, and survival probability on the basis of main baseline covariates.

Results

Prevalence and clinical characteristics of PML cases
During the period of the study, among 714 neurologic patients registered, 101 cases were notified as PML (14.1%). Prevalence of PML according to drug exposure at diagnosis, HIV-1 RNA, and CD4 levels are illustrated in Figure 1.

Analyzing general characteristics, 80% of PML patients were male and 57.4% were intravenous drug users (IDUs). The median CD4 cell count was 88 cells/mm^3 (interquartile range [IQR] 27–176), with 16.8% of patients having CD4 cell count more than 200/mm^3. Median plasma HIV RNA was 4.79 copies/ml (IQR 3.73–5.33). At physical examination, focal signs were reported in 79.2% of patients, cognitive symptoms in 67.3%, and an abnormal mental status in 24.8%. Neuroimaging (computed tomography [CT] scan in 39% and magnetic resonance imaging [MRI] in 62%) revealed white matter lesions in 94.1% of cases, with a multifocal pattern in 77.2%. T1-hypointensity and T2-hyperintensity were reported in 60.2% and 80.7% of all MRI-investigated patients, respectively. A contrast enhancement was observed in 21.8% of cases, with a mass effect in 5.9%, whereas signs of atrophy were reported for 36.6% of cases.

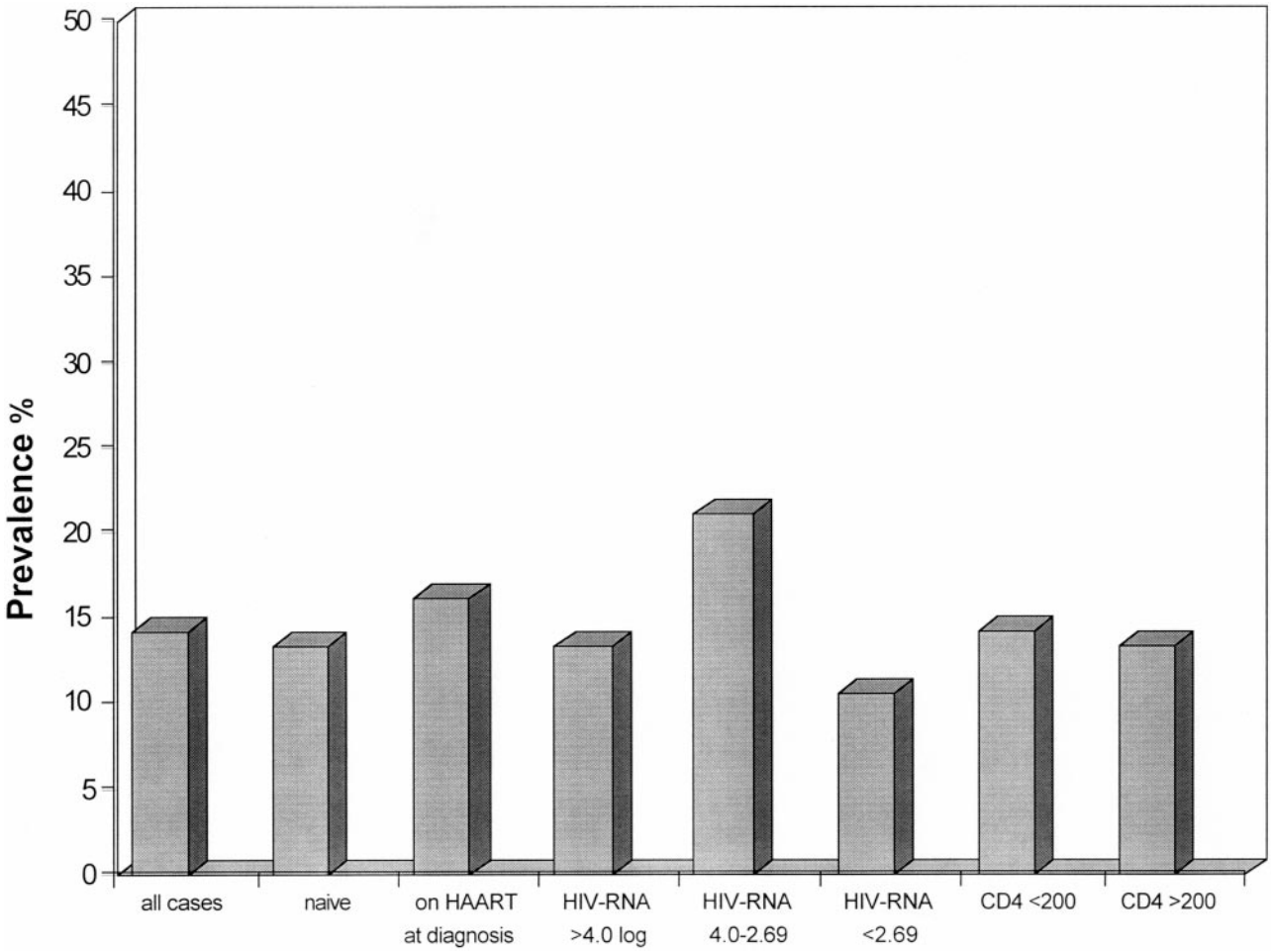

Figure 1 Prevalence of PML cases according to exposure to HAART and CD4 and HIV-1 RNA subgroups.

Fifty-two (51.5%) of all patients with PML had a previous antiretroviral exposure, 43 (82.7%) to HAART, while only 9 (17.3%) were exposed to nucleoside analogues alone. Among the HAART-exposed patients, 36 had been on potent triple combination at the time of neurologic diagnosis for a median of 15 months (IQR 6–39). In 32 patients, cidofovir was added to HAART, but the collection of additional information on the number of administrations, baseline performance status, HAART treatment, and HIV-1 RNA level at cidofovir start were not planned in the study design.

At logistic regression analysis, PML diagnosis despite a previous exposure to HAART was significantly associated to a previous AIDS-defining event (odds ratio [OR] 10.2; 95% confidence interval [CI] 3.2–39.5) to harbor a lower amount of HIV-1 RNA copies per milliliter in plasma at neurologic diagnosis (OR 0.58; 95% CI 0.39–0.87 for each $\log_{10}$ increase) to have a focal lesion at CT/MRI (OR 2.69; 95% CI 1.18–6.12), and to a reduced probability of an abnormal mental status at diagnosis (OR 0.33; 95% CI 0.13–0.86).

Diagnostic features of PML cases

Diagnosis of PML was performed according to histology in 4 cases (3.9%), to JCV DNA detection with suggestive clinical and neuroimaging features in 48 cases (47.5%), to a compatible clinical and neuroimaging picture despite a JCV DNA–negative detection in 32 cases (31.6%), or without performing a lumbar puncture in 17 (16.8%) patients. JCV DNA was detected in the cerebrospinal fluid (CSF) of PML patients by polymerase chain reaction (PCR) in 49 (in 1 with a contemporary histology available) out of 84 patients in whom a lumbar puncture was performed (58.3%). Analyzing the main baseline variables, no significant association was found between the detection of JCV DNA in CSF and gender, age, HIV transmission route, viroimmunological status, exposure to HAART, and clinical and radiological features.

Factors predictive of PML

Among the demographic and epidemiologic features, intravenous drug use as HIV-1 transmission significantly increased the risk of developing PML at

multivariable logistic regression analysis (OR 2.56; 95% CI 1.05–6.28). The presence of meningeal signs at diagnosis strongly reduced the probability of having a diagnosis of PML (0.31; 95% CI 0.10–0.97), as well as the presence of atrophy (OR 0.42; 95% CI 0.23–0.78) or mass effect (OR 0.07; 95% CI 0.02–0.22) at CT/MRI examination. Conversely, the risk of a PML diagnosis was significantly higher when focal signs were detected at physical examination (OR 7.90; 95% CI 4.00–15.59) and whether a white matter involvement was found at neuroimaging (OR 23.83; 95% CI 8.63–65.79). Age, gender, risk factors other than intravenous drug use, CD4 level, plasma HIV-1 RNA, antiretroviral exposure before diagnosis, taking antiretroviral drugs penetrating brain-blood barrier, cognitive symptoms, abnormal mental status, and contrast enhancement at neuroimaging where not associated with a diagnosis of PML.

Survival analysis

After a median follow-up of 93 days (IQR 14–200), a total of 44 PML patients died. All deaths were reported related to PML. Kaplan-Meier analysis revealed that patients naïve for antiretrovirals who started HAART at time of PML diagnosis showed a longer survival than patients with a previous exposure to HAART who continued treatment and patients who did not perform any antiretroviral treatment after PML diagnosis. The 1-year cumulative proportion of survivors was 0.58 in naïve patients starting HAART, 0.24 in experienced patients continuing treatment, and 0.00 in patients not treated overall (P at log rank test <.0001). Moreover, patients with CD4 cell count higher than 150/mm^3 had a higher estimated proportion of survivors (0.45) than patients with CD4 between 50 and 150/mm^3 (0.38) and patients with CD4 less than 50/mm^3 (0.22) ($P = .017$). A poorer 1-year probability of survival was observed in persons with a previous AIDS-defining event (0.48) compared to patients without a previous AIDS diagnosis (0.07) ($P = .007$).

At univariate Cox regression, a CD4 cell count <50 cell/mm^3 at the time of neurological diagnosis compared to >150 cell/mm^3 as reference was associated with an increased risk of death (hazard ratio [HR] 2.30; 95% CI 1.10–4.81). Moreover, patients who started HAART at the time of PML diagnosis (HR 0.10; 95% CI 0.04–0.26), but also patients previously exposed to HAART who continued therapy after diagnosis (HR 0.20; 95% CI 0.09–0.44) had a significantly reduced risk of death compared to patients who did not receive any antiretroviral treatment after PML. At multivariable analysis, a younger age, higher CD4 counts, starting HAART at PML diagnosis or continuing a previous antiretroviral therapy, the absence of previous AIDS-defining events, and the presence of a less severe neurological impairment were all independently associated with a reduced risk of death. Treatment with cidofovir did not influence survival in a univariate approach (HR 0.81; 95% CI 0.45–1.48), whereas in multivariable Cox regression, receiving cidofovir showed a trend towards a reduced hazard of death (Table 1).

Table 1 Multivariate Cox regression analysis on 101 cases of PML

	HR	*95% CI*	P
Age (×10 years)	2.08	1.24–3.51	.006
HIV transmission route			
IVDU	1.00	—	
MSM	1.09	0.31–3.84	.89
Heterosexual	1.19	0.47–3.05	.71
Others	1.64	0.62–4.35	.31
CD4 cell count/mm^3			
>150	1.00	—	
50–150	0.77	0.29–2.02	.59
0–50	3.36	1.34–8.45	.01
Previous AIDS			
No	1.00	—	
Yes	2.31	1.09–4.86	.03
Contrast enhancement			
No	1.00		
Yes	1.89	0.81–4.38	.14
Cidofovir			
No	1.00		
Yes	0.40	0.15–1.06	.06
PCR for JCV DNA			
LP not performed	1.00		
JCV DNA+	1.58	0.62–4.00	.33
JCV DNA−	1.14	0.43–3.05	.79
HAART			
No HAART after PML diagnosis	1.00		
HAART at PML diagnosis	0.10	0.03–0.32	<.0001
HAART-naïve starting therapy	0.07	0.02–0.22	<.0001
Signs/symptoms			
Only cognitive symptoms	1.00		
Focal signs and/or cognitive symptoms	3.24	1.01–10.40	.04
Abnormal mental status	4.76	1.39–16.32	.01

Discussion

The results of the present study confirm that, even in the era of potent antiretroviral therapy, PML still appears as a relevant disorder in terms of morbidity and mortality in HIV-infected patients. In fact, within the IRINA cohort, PML shows a 14% prevalence, representing overall the third cause of neurologic disorders after toxoplasmic encephalitis (TE) and HIV encephalopathy (HIVE). Indeed, PML frequency was very close to that of HIVE, generally reported as the main HIV-associated neurological disorder in the pre-HAART period (Clifford, 2000). These data are in agreement with the previously reported, less marked incidence decrease of PML as result of the impact of the HAART introduction when compared to that of other neurologic disorders such as HIV dementia, TE, and primary brain lymphoma (Sacktor *et al*, 2001; Ammassari *et al*, 2000).

Accordingly, PML prevalence was not substantially influenced by exposure to antiretrovirals and it remained relatively stable in different subgroups independently from CD4 and HIV-1 plasma viremia

levels. In patients taking HAART at diagnosis and in those with low-level plasma viremia, PML was even more prevalent than HIVE. This finding is consistent with the observation that PML may occurr few months after starting HAART (Ledergerber *et al*, 1999) and with data on the development of disease in patients with relatively high CD4 count (Berger *et al*, 1998a; Gasnault *et al*, 1999). Indeed, PML may be a HAART-induced immune reconstitution disease (Shelburne *et al*, 2002). In addition, the lack of control of HIV-1 replication in the central nervous system (CNS) compartment during HAART in patients with neurologic disorders (Antinori *et al*, 2002) may represent a further explanation for the PML occurrence in HAART-treated patients even after a control of plasma viral replication was achieved. Intravenous drug use was associated with PML occurrence in the multivariable model. This association was not previously reported in the literature. It is conceivable that, even adjusting with antiretroviral therapy exposure as a covariate, intravenous drug use remains a negative factor due to a lower antiretroviral medication adherence and a less regular access to therapeutic programs by this patients category. The other PML-associated predictive factors were in accordance with previously reported historical clinical and neuroimaging features (Berger *et al*, 1987, 1998).

The present study confirms published observations concerning the evidence of improved survival in patients with PML treated with HAART (Dworkin *et al*, 1999; Albrecht *et al*, 1998; De Luca *et al*, 2000; Clifford *et al*, 1999; Tassie *et al*, 1999). As additional information about the role of timing of antiretroviral exposure, in our study the higher benefit on survival was observed in patients previously naïve to antiretrovirals who started HAART at the time of PML diagnosis. It could be hypothesized that, in antiretroviral-naïve patients starting HAART after neurological diagnosis, a more rapid control of viral replication or the absence of HIV-1–resistant mutants harbored in plasma or the CSF, may induce a more effective control of HIV-1 replication, resulting in a more complete JCV-specific immune recovery (Weber *et al*, 2001). This observation is in accordance with the association of reduced CSF JCV burden with prolonged survival (De Luca *et al*, 2000; Koralnik, 1999; Yiannoutsos *et al*, 1999). Moreover, our finding that higher levels of CD4 cell counts were independently associated with an improved survival is consistent with other clinical observations (Berger *et al*, 1998; Clifford *et al*, 1999; Berenguer *et al*, 2001) and with the notion that JCV-specific immune response plays a role in the prevention of disease progression and death (Koralnik *et al*, 2001, 2002). In the present study, we failed to prove a clear benefit of cidofovir administration on PML survival. In previous observational studies, it has been reported that the addition of cidofovir to HAART was independently associated with improved survival (De Luca *et al*, 2000, 2001; Gasnault *et al*, 2001). The apparent discrepancy between previous findings and the present results may be due to design differences such as a more heterogeneous case recruitment and time period only partially overlapping with previous reports. In the ACTG 363 study, even though cidofovir failed to improve neurologic examination of PML cases, clinical scores were significantly better in patients who started cidofovir after suppression of HIV-1 plasma viremia by HAART (Marra *et al*, 2002). In the present study, no information about time of starting cidofovir after HAART was available, and we cannot exclude that in several centers, cidofovir was added preferably later to patients with a more severe neurologic picture, a worsening evolution, or no effective response to HAART. However, after adjusting for baseline prognostic factors, cidofovir treatment showed a trend towards increased survival, with a 60% mean reduction of the risk of death, but this result was not significant due to large confidence limits and possibly low detection power of the study. Nevertheless, we cannot adjust for several other prognostic factors, such as CSF JCV burden, virologic efficacy of HAART at the time of cidofovir introduction, duration of cidofovir treatment, patients' performance status, and neurologic severity. For all these considerations, we think that benefit of cidofovir in HIV-associated PML will require further definitive evidences in larger prospective studies.

Methods

IRINA is an ongoing prospective multicenter study designed to survey epidemiologic changes and natural history of HIV-related neurological disorders in the era of HAART. The secondary aim of the study is to assess diagnostic criteria used in clinical centers based on available resources and to work out standardized guidelines. The study started in January 2000 and included all the HIV-related neurologic disorders observed among 45 infectious diseases centers in Italy involved in the medical care of HIV-infected patients. For each new neurologic case observed, each center had to fill a notification sheet including demographic and epidemiologic variables, natural history of HIV infection and antiretroviral therapy, clinical and radiological characteristics, and diagnostic criteria. Moreover, a questionnaire of diagnostic procedures employed was administered at each center: it investigated the availability of diagnostic tools (neurologic scores, neuroimaging, PCR tests on cerebrospinal fluid, serology, histologic features) and the minimal diagnostic criteria employed for each neurologic disorder. Every 6 months, a follow-up sheet was filled with information regarding treatment outcome and survival.

The current study includes all cases of PML reported to IRINA between January 2000 and June 2002. Diagnostic criteria for PML included, besides the Centers for Disease Control and Prevention (CDC)

1993 revised case definition, presumptive diagnostic criteria based on (i) the detection of JCV DNA in the CSF by PCR in the presence of suggestive clinical and neuroimaging features, (ii) the presence of a compatible clinical and neuroimaging picture even in the absence of JCV DNA detection in CSF, or when the lumbar puncture was not performed or the test was not available, after excluding other neurological diseases. All the notified PML diagnoses were revised by a panel of experts within the Scientific Committee of IRINA in order to verify the likelihood of employed criteria. For statistics, univariate and multivariable logistic regression models were employed to assess crude and adjusted OR of PML occurring for all main baseline factors. Survival analysis was performed by Kaplan-Meier estimates for each group and adjusting for baseline covariates in a Cox proportional hazards model. All reported *P* values are two-sided.

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