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Clinical Report

Topotecan in the treatment of acquired immunodeficiency syndrome–related progressive multifocal leukoencephalopathy

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Progressive multifocal leukoencephalopathy (PML) affects about 1 in 20 individuals with the acquired immunodeficiency syndrome (AIDS) and has been associated with poor survival. This report describes the results of a phase II clinical trial using the drug topotecan, a semisynthetic analogue of camptothecan, administered to a cohort of subjects with AIDS-related PML. Data were evaluated on 11 of 12 subjects enrolled in the study. Three responded to therapy. Additionally, one patient was treated off-protocol and showed a response to treatment. Progression occurred after the first course; however, a partial response was noted after five courses. One study patient died from accidental overdose of topotecan. Overall, responders had higher pretreatment Karnofsky and lower Kurtzke expanded disability status scale scores than nonresponders. The most frequent toxicities were hematologic (anemia, neutropenia, and thrombocytopenia). Five patients had dose delays; all delays were due to hematologic adverse events. This study demonstrates that topotecan treatment may be associated with decreased lesion size and prolonged survival from the infection. Because of the small number of subjects in the study, further studies are required to evaluate the efficacy of topotecan in treating this disease. *Journal of NeuroVirology* (2003) **9,** 411–419.

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Introduction

Progressive multifocal leukoencephalopathy (PML) occurs as a complication of human immunodeficiency virus type 1 (HIV-1) infection in about 5% of individuals with acquired immunodeficiency syndrome (AIDS) (Berger and Major, 1999). In the large majority of cases, the causative agent is JC virus, a ubiquitous polyomavirus that, in immunocompetent individuals, is associated with subclinical infection (Brown *et al*, 1975; Major *et al*, 1992). Among untreated patients with AIDS-related progressive PML, the median survival is about 4 months (Berger *et al*, 1987; Fong and Toma, 1995). In recent years, the introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV-1 infection has resulted in a decrease in the frequency of a number of nervous system complications, including HIV-1–associated dementia, cytomegalovirus encephalitis, toxoplasmic encephalitis, and primary central nervous system lymphoma (Dore *et al*, 1999; Moore and Chaisson, 1999; Sacktor *et al*, 2001). The median survival from PML in the post-HAART era has increased from 4 months to 10.5 months (Clifford *et al*, 1999). However, it is unlikely that currently available anti–HIV-1 therapies alone will be adequate for providing long-term control of the infection.

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Topotecan is a semisynthetic derivative of the drug camptothecin, which is approved by the United States Food and Drug Administration for the treatment of ovarian cancer in humans (Barnett, 1996). The mechanism of action of topotecan involves the inhibition of topoisomerase I, an enzyme that creates nicks in DNA during replication. The nicks promote unwinding of supercoiled DNA as the replication complex advances and are subsequently repaired by topoisomerase I. Topotecan prevents the normal repair of these nicks by the enzyme, resulting in the death of the cell. The potential utility of this class of agents in the treatment of viral infections was initially demonstrated by studies in which camptothecin suppressed the *in vitro* replication of simian virus (SV)-40 in cultured simian cells (Sausville and Horwitz 1978; Yang *et al*, 1987). In subsequent studies, topotecan suppressed replication of JC virus DNA in human glioblastoma cells at drug levels that were not toxic to the host cells (Kerr *et al*, 1993). These investigations, therefore, provided the rationale for this phase II study, in which the safety, tolerability, and efficacy of topotecan administered as a 21-day infusion administered every 28 days to patients with AIDS-related PML was evaluated.

Results

Patient characteristics

A total of 12 subjects were enrolled in the study; evaluable data were obtained from 11. The patient group included 10 males and 1 female; 8 were Caucasian, 1 Black, and 2 Hispanic; 1 subject had a Karnofsky score worse than 50. All of the study subjects were on a HAART combination at the time of enrollment into the study (Table 1). One subject who was diagnosed with PML by brain biopsy withdrew before completion of the first course of topotecan. A second patient with a progressive clinical course and radiographic features on magnetic resonance imaging (MRI) consistent with PML was treated off-protocol after his biopsy was misplaced in the hospital pathology department before it was examined.

Table 1 Characteristics of 11 patients with AIDS-related PML treated with a continuous intravenous infusion of topotecan

Characteristic	*Number of patients*
Age (years)	
18–40	6
41–64	5
Range: 25–47 years	
Gender	
Male	10
Female	1
Race	
Caucasian	8
Hispanic	2
Black	1

Treatment responses

Of the 11 patients, 9 were randomized to receive immediate therapy. Two patients were randomized to the delayed treatment group; one was determined to have progressive PML and, therefore, received immediate treatment. The second patient in the delayed-treatment group initiated treatment with topotecan 57 days after randomization. Three patients were treatment responders (patients 2, 3, and 9) per protocol definition, with two alive at last contact (patients 2 and 9). Of the responders, two were randomized to immediate (patients 2 and 9) and one to delayed therapy (patient 3). The time to radiographic response was about 2 months for all three responders; the time to clinical response was less than 1 month for patient 9 and more prolonged for the other two patients. One subject showed progression on MRI after the first course of topotecan; however, with continued treatment, subsequent partial radiographic improvement was observed. Seven patients did not respond to treatment with topotecan and died of progressive PML within 30 days of treatment initiation. One patient died as a result of an accidental topotecan overdose caused by incorrect mixing of the drug by a contracting pharmacy that had specific experience in the administration of chemotherapy.

Baseline Karnofsky scores were slightly higher and Kurtzke expanded disability status scale (EDSS) scores lower for topotecan treatment responders than for nonresponders (Table 2). Viral load measures at baseline and at the end of the study were undetectable for one individual who showed a treatment response and for three nonresponders (Table 2). CD4 counts were <200 per mm^3 for patients with baseline values. MRI studies were obtained at baseline on 10 of the 11 patients; the patient with no baseline MRI was withdrawn from the study after 2 weeks of treatment due to progressive disease. Two responders and no nonresponders had temporal involvement; otherwise, there was no obvious pattern of involvement that distinguished responders from nonresponders.

Toxicity associated with topotecan treatment

A total of 38 treatment courses were administered to the 11 patients, the majority at a dose of 0.3 gm/m^2/day or higher. The maximum dose administered was 0.6 mg/m^2/day. Moderately severe to severe neutropenia, anemia, and thrombocytopenia developed in, respectively, 10, 6, and 5 subjects. The most frequently reported nonhematologic adverse events possibly related or related to therapy were nausea (4), vomiting (3), fever (3); diarrhea, fatigue, rash, and alopecia each developed in 2 subjects. Grade 4 fever developed in one individual who was infused with the overdose of topotecan (2.42 mg/m^2/day) and died of hematologic toxicity.

Individual case studies

The clinical course for patient 01 is demonstrated in Figure 1. The patient, a 39-year-old Caucasian male,

Table 2 Plasma viral load measurements among the topotecan study patients

	EDSS (Karnofsky score)			*CD4 count (cells/ml)*			*HIV RNA (copies/ml)*			
Patient	*Baseline*	*Best score*	*End of study*	*Baseline*	*Peak*	*End of study*	*Baseline*	*Peak*	*End of study*	*Nadir*
Responders										
02	2.0 (70)	1.5 (90)	1.5 (80)	126	299	141	1937	5640	1488	156
03	3.5 (70)	2.0 (80)	2.5 (70)	54	54	7	368,744	1,521,739	323,697	22,664
09	7.5 (50)	2.0 (60)	3.0 (60)	165	165	90	<400	<400	<400	<400
Nonresponders					54	ND				
01	8.5 (50)	9.0 (40)	9.5 (20)	47	257	173	3,640	150,581	150,581	3,640
04	6.5 (50)	8.5 (30)	9.5 (10)	122	88	42	<400	<400	<200	<200
05	6.0 (50)	* (*)	* (*)	88	12	ND	517	517	<400	<400
06	7.5 (30)	9.5 (20)	10.0 (20)	12	229	170	ND	ND	ND	ND
07	2.5 (60)	2.5 (**)	3.5 (**)	160**	86	50***	<200	488	<400	<200
08	8.0 (50)	8.0 (40)	8.5 (40)	86	49	49	86,814	998,711	443,741	13,000
10	6.0 (50)	6.0 (40)	9.0 (40)	49	106	54	<400	<400	<400	<400
11	6.5 (50)	6.5 (40)	8.5 (40)	106	5084	1573	5084	7906	1573	1573

ND = test not performed.
*No scores were obtained after baseline.
**Obtained 23 days prior to study start.
***Patient 8 had five courses. Last CD4 count was performed at end of course 4.

presented to study investigators in December 1996 with a history of HIV infection and a right frontal-parietal and a left parietotemporal lesion (Figure 1). Brain biopsy performed in December was positive for JC virus infection. At the time of study entry, his EDSS was 8.5 and his Karnofsky score was 50. CD4 count was 47 cells per mm^3 at the time of treatment initiation, and his plasma viral load was 3640 copies per ml. The patient's antiretroviral regimen included stavudine, lamivudine, and indinavir at the time of study entry. He was randomized to the immediate treatment group and was started on topotecan at an infusion rate of 0.3 mg/m^2/day. One month later, he demonstrated evidence of clinical and radiographic progression, with an increase in his cerebrospinal fluid (CSF) and plasma viral load to 5994 copies/ml and >150,000 copies/ml, respectively. This occurred despite advancing his topotecan dose to 0.4 mg/m^2/day and adding didanosine to his antiretroviral drug regimen. The patient expired 16.6 weeks after study entry.

Patient 02, a 47-year-old Caucasian male, also presented with PML in December 1996. His brain MRI showed a large left parietal-occipital lesion (Figure 2), and biopsy of the lesion was consistent with the diagnosis of PML. EDSS at the time of entering the study was 2.0; Karnofsky score was 70. Brain MRI showed a left parietal-temporal-occipital lesion. Baseline CD4 count was 126 cells/μl, and plasma viral load was 1937 copies/ml. The patient's antiretroviral medications at the time of study entry were zidovudine, lamivudine, and indinavir. He was randomized to immediate therapy and was treated with a total of nine courses of topotecan at doses of 0.3 mg/m^2/day and 0.4 mg/m^2/day. Six days before starting the topotecan infusion, he was begun on acyclovir for herpes simplex virus (HSV)-2 prophylaxis. After being clinically stable during the first 8 weeks of therapy, he subsequently showed evidence of a radiographic response, with a decrease in MRI lesion size, and a clinical response was documented at 11 weeks. Between the first two topotecan courses, he was treated for neutropenia with granulocyte-macrophage colony-stimulating factor (GM-CSF). His peak CD4 count during the period of treatment and follow-up was 299 cells/μl and his nadir was 156 cells/μl. The patient's plasma viral load showed a rise during courses 7 to 9; peak and nadir viral loads were about 5600 copies/ml and about 156 copies/ml, respectively. At the time of last follow-up, 174 weeks after study entry, the patient showed no evidence of clinical or radiographic progression.

Discussion

There is currently no proven effective therapy for treating PML in patients with AIDS. Therefore, drugs such as topotecan, which have specific mechanisms of action, hold promise for treating this condition. In oncology trials in which topotecan was administered as a 21-day continuous infusion to patients with ovarian cancer, the maximum tolerated dose of the drug was demonstrated to be 0.53 mg/m^2/day (Hochster *et al*, 1994). In these individuals, the most prominent manifestation of toxicity was also bone marrow suppression, which was dose-limiting, followed by less severe impairment of renal and hepatic function. For our studies, we initiated treatment with a lower dose of topotecan than that which had been selected for the cancer trial, i.e., 0.3 mg/m^2/day. This dose and, in most cases, infusion rates delivering doses as high as 0.6 mg/m^2/day, were generally well tolerated. Nevertheless, as observed with the oncology trial, marrow toxicity was frequent. A number of antiretroviral agents and other drugs that are important in the

management of HIV infection, as well as HIV-1 infection itself, can adversely affect hematologic precursor cells in the bone marrow compartment and may have contributed to the observed toxicity (Evans and Scadden, 2000). However, among all of our study subjects who were treated according to protocol, these effects reversed with decreasing the topotecan dose, delaying the initiation of subsequent infusions and with other interventions such as treatment with G-CSF and packed red blood cell (RBC) transfusions.

During the $2^1/_2$ years of the study, 12 patients were enrolled, 11 who were actually treated with the study drug. This number is too small to provide conclusive information about the drug's efficacy. In addition, the majority of the patients who entered the study were late in their PML course. Of note, two of the three treatment responders had high Karnofsky scores and low EDSS scores. This is consistent with the observation that treatment early in the clinical course of the disease is more likely to be associated with a more favorable outcome (Gasnault *et al*, 1999), and suggests that subjects with early disease should be targeted for future clinical trials with topotecan. In addition, longer follow-up of patients begun on

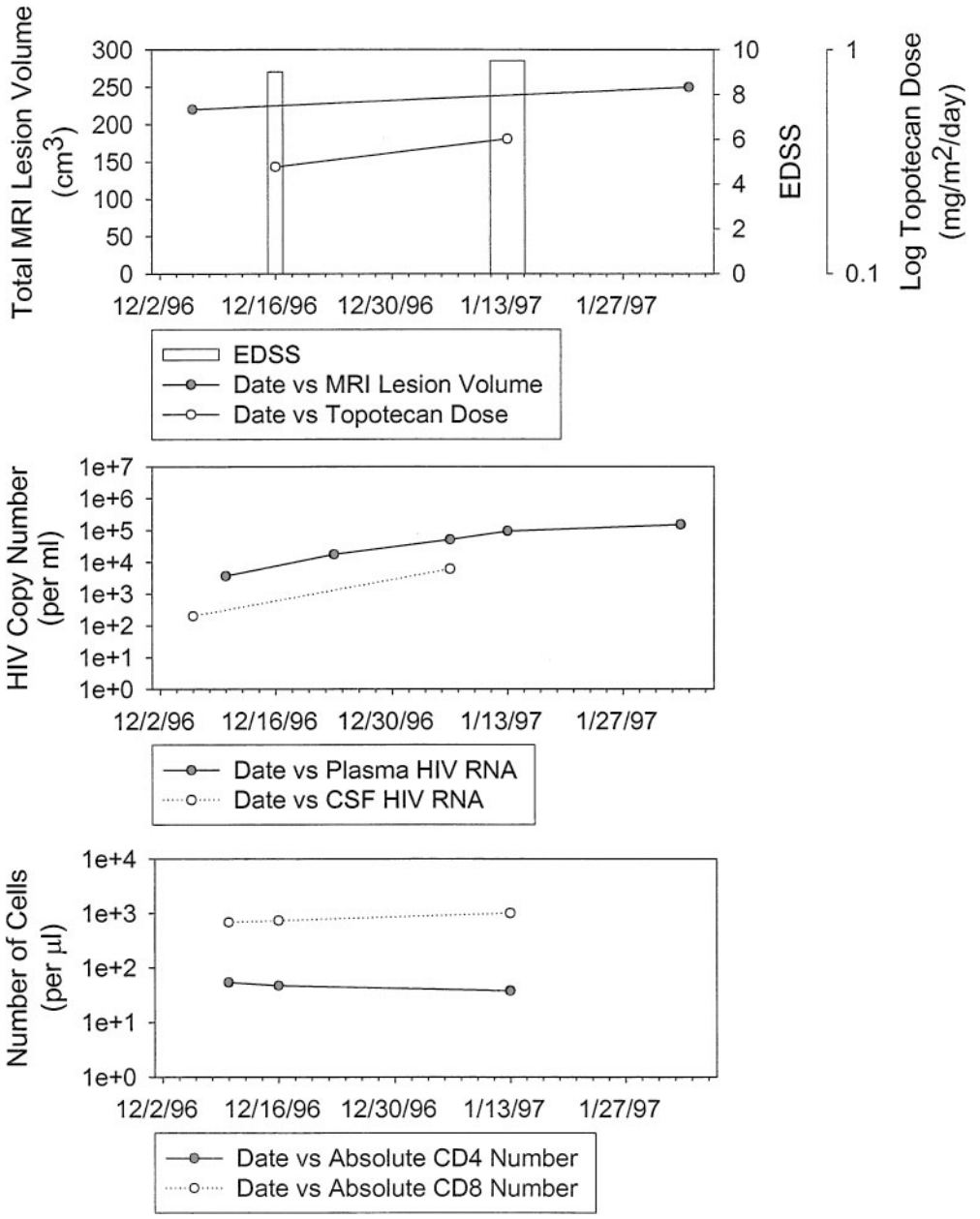

Figure 1 Clinical course of patient 1 (treatment nonresponder): composite plots of log topotecan dose, MRI volumetric measurements, EDSS, plasma and CSF HIV RNA concentration, and peripheral blood absolute CD4 and CD8 cell counts (see text). *(Continued)*

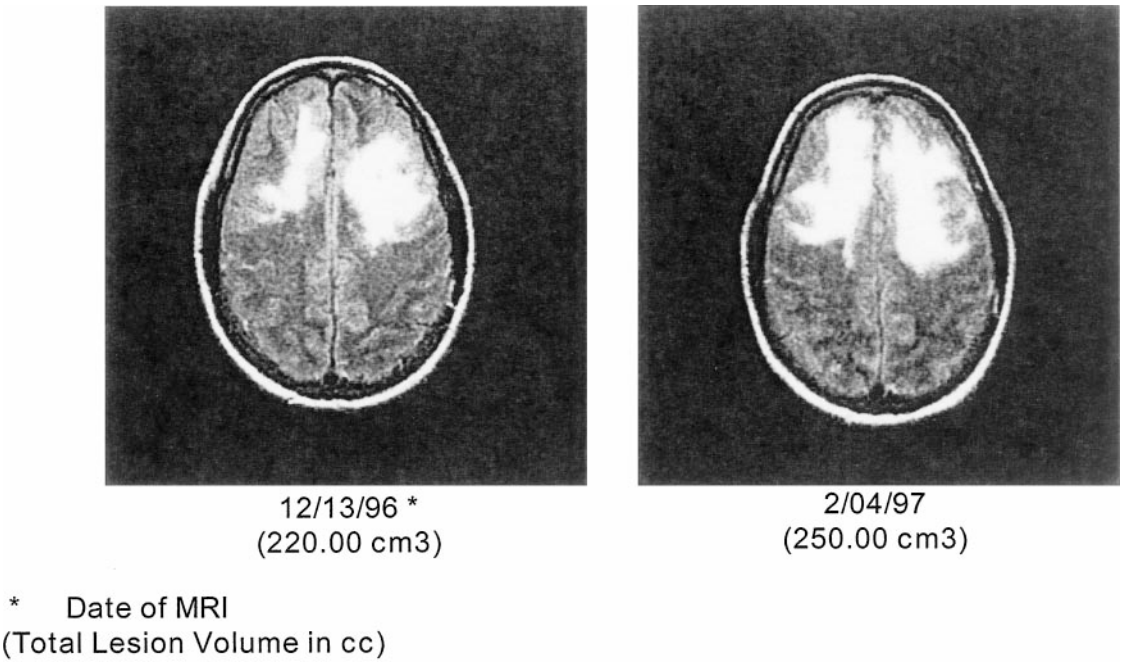

Figure 1 (Continued)

treatment early during their PML course would make it possible to better distinguish a possible treatment response from either improved immunity induced by antiretroviral treatment or spontaneous remission (Berger and Major, 1999).

It has been suggested in other studies that treatment with HAART significantly improves survival in patients with PML (Clifford *et al*, 1999; Dworkin *et al*, 1999; Gasnault *et al*, 1999). However, this may not be observed in some cases (Tantisiriwat *et al*, 1999; Taoufik *et al*, 2000; Weiner *et al*, 2000). We observed no association between topotecan treatment response and prior or concurrent HAART administration. Treatment outcome was also not associated with baseline or follow-up CD4 cell count or with HIV-1 load measures, an unexpected finding because topotecan can inhibit activation of the HIV-1 replication in infected cells *in vitro* (Li *et al*, 1993; Zhang *et al*, 1997). This suggests that beneficial clinical effects from topotecan treatment can occur apart from any potential effect of the drug on HIV replication. However, it is also possible that treatment resulted in the production of replication-defective variant virus and that continued suppression of CD4 cell counts occurred due to the formation of immune complexes or other toxic effects that can be induced by HIV proteins. Quantitative JC virus load measures in CSF were not performed as a part of this study and may have been useful for assessing treatment efficacy.

The measurement of lesion volume using MRI appeared to provide sensitive measures of changes in lesion size in response to treatment. However, as noted with one of the study subjects, treatment can be associated with transient worsening on MRI prior to the appearance of evidence of decreased lesion size (Enting and Portegies, 2000; Huang *et al*, 1998; Nicoli *et al*, 1992; Portegies *et al*, 1991). This effect may be potentially caused by improved immune responses generated against PML virus with acute mobilization of tissue edema fluid. In future studies, it may be useful to also perform assessments using magnetic resonance spectroscopy, which, by demonstrating changes in lesion metabolic activity, can detect infection-related abnormalities in brain with greater sensitivity than conventional MRI and may be used to follow patients longitudinally (Chang *et al*, 1997). Similarly, magnetization transfer MR imaging can detect early evidence of PML-related myelin damage (Ernst *et al*, 1999) and, potentially, responses to therapy.

There is much that remains to be understood regarding the efficacy of topotecan in the treatment of patients with PML. Outcomes resulting from other treatment approaches, i.e., interferon μ (Berger, 2000; Geschwind *et al*, 2001; Huang *et al*, 1998) and cidofovir (Brambilla *et al*, 1999; De Luca *et al*, 2000; Gasnault *et al*, 2001), have been encouraging, but similarly inconclusive, and have not shown clear benefit over HAART alone. Of note is the fact that one of the treatment responders (patient 09) had been treated with cidofovir prior to initiating treatment with topotecan. Although the patient did not appear to respond to cidofovir therapy, it is possible that treatment with the drug was a contributing factor in his subsequent response to topotecan. This study was closed due to poor recruitment and that fact that the early data did not suggest a beneficial treatment effect. The ability to perform future studies of

intravenous topotecan in AIDS-related PML may be inhibited by the demonstrated toxicity of the drug and the lack of convenience associated with its administration. However, an oral formulation of topotecan is currently in development, which might facilitate evaluation of the drug in clinical trials. The use of the oral drug, combined with modifications in clinical trial design that might increase patient accrual, such as less stringent entry criteria compensated by stratification of the treatment and control groups and the use of a toxicity grading system that incorporates effects from multiple etiologic factors (Yiannoutsos and De Luca, 2001), should, with appropriately planned interim analyses of the data (Yiannoutsos and De luca, 2001), improve our ability to assess the efficacy of topotecan in the treatment of AIDS-related PML.

Materials and methods

Patients

A total of 12 patients with AIDS-related PML were recruited for the study between September 1997 and January 1999. The diagnosis of PML was initially based on the presence of characteristic pathologic

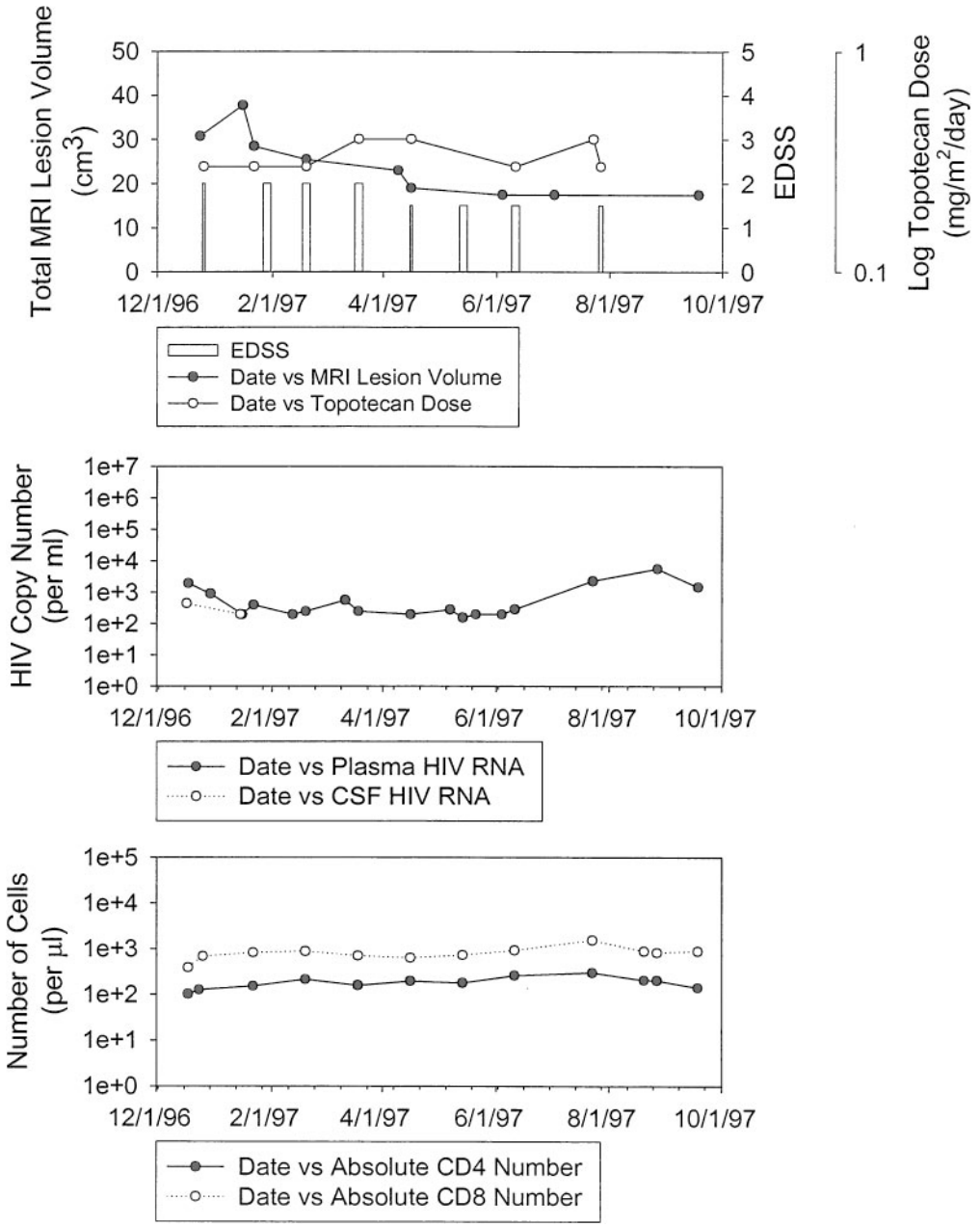

Figure 2 Patient 2 (responder) clinical course (see text). *(Continued)*

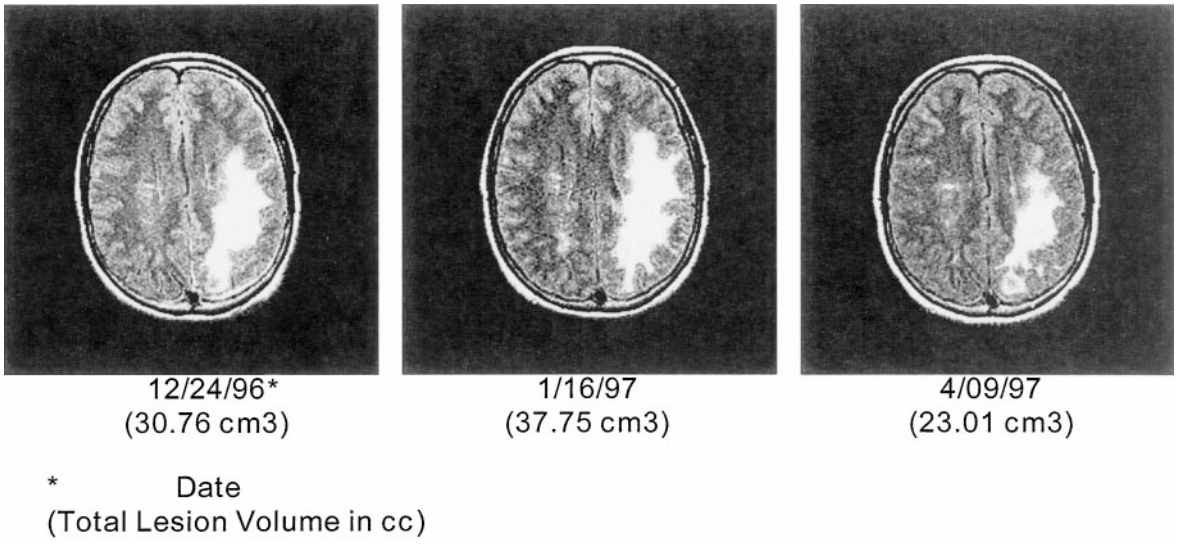

Figure 2 (Continued)

abnormalities observed in tissue obtained by biopsy of a typical lesion noted on brain MRI. In September 1998, the diagnostic criteria were changed so that the diagnosis could be made based on a positive CSF polymerase chain reaction (PCR) test for JC virus, with biopsy remaining a requirement for those with a negative PCR test. Patients eligible for the study were at least 18 years old, had a history of HIV-1 infection, at least one 1-cm white matter lesion on MRI that was associated with symptoms that were consistent with the diagnosis of PML (subacute onset of progressive symptoms and focal signs referable to central nervous system [CNS] demyelination such as hemiparesis, hemisensory loss, visual field deficits, aphasia, apraxia, etc). The protocol stipulated that patients should have a Karnofsky performance status scale score $\geq$50%; however, an exception was made for this requirement in one patient. The following was also required: at least a 3-week history of being clinically stable on treatment with an antiretroviral therapy regimen; prophylactic treatment for *Pneumocystis* pneumonia if there was a prior history of this infection or if the patient had a CD4 count $<200/mm^3$; no treatment with other investigational drugs within 30 days of study entry unless an exception was granted; no prior chemotherapy for PML within 14 days of study entry; and blood studies within 1 week of study enrollment that showed a hemoglobin $\geq$9.0 g/dl, an absolute neutrophil count $\geq1500/mm^3$, a platelet count $\geq100{,}000/mm^3$, and normal renal and hepatic function. Patients were not eligible who did not meet these criteria or who had evidence of other active or prior HIV-1–related CNS disease other than HIV encephalitis, active cytomegalovirus (CMV) infection requiring systemic therapy, active or prior axis I or axis II psychiatric disorder that might confound the diagnosis or interfere with therapy, or pregnancy or nonuse of an effective contraceptive. In all cases, it was necessary that patients be mentally competent or have durable power of attorney or a legal guardian in order to enter the study.

Study protocol

Patients were randomized to receive either immediate or delayed treatment with topotecan. Neurologically stable patients who were randomized to the delayed-treatment group were to be followed with monthly neurological assessments for up to two treatment courses (8 weeks). Individuals in this group who developed evidence of progressive PML were immediately begun on therapy. Topotecan was administered as a continuous 7-day infusion, pumped by a battery-operated cassette through a chronic indwelling catheter. The infusions were administered in 4-week cycles: 3 weeks with active drug being pumped and the 4th week with no drug. At weekly intervals, the cassette reservoir was changed and the infusion then restarted. The topotecan infusion was initiated at a rate of 0.3 mg/m^2/day. At the time of the weekly cassette changes, patients underwent the following blood studies: serum chemistries (sodium, potassium, chloride, glucose, carbon dioxide, calcium, phosphorus, magnesium, blood urea nitrogen, creatinine, uric acid, alkaline phosphatase, lactate dehydrogenase, aspartate and alanine aminotransferases [AST, ALT], total bilirubin, total protein, albumin), white blood cell count with a differential and platelet count. Monthly blood studies were absolute CD4 and CD8 cell counts, and quantitative plasma HIV-1 RNA levels. For patients who developed bone marrow toxicity (platelet count <100,000 or neutrophil count <1500), the subsequent infusions were delayed while these blood tests were checked at weekly intervals, then, with normalization of the blood count abnormalities, restarted at a

lower dose. For subjects who developed a platelet count $<50{,}000/mm^3$ or neutropenia $<500/mm^3$, the topotecan infusion was discontinued immediately for the remainder of the cycle. The patient was then either observed for spontaneous improvement in the abnormality or treated with G-CSF. With the start of the subsequent treatment cycle, the infusion rate was reduced. Erythropoietin was administered to individuals who developed anemia. For those who tolerated the infusion with no significant toxicity, subsequent infusions were increased by increments of 0.1 mg/m^2/day up to a dose not to exceed 0.8 mg/m^2/day. The minimum infusion rate allowed for the study was 0.1 mg/m^2/day. Patients were to be withdrawn after two dose reductions if no response was observed or if the topotecan infusion was delayed for 4 weeks or if it was necessary to maintain the infusion at a rate of 0.1 mg/m^2/day despite the prior administration of G-CSF.

Standardized monthly neurological examinations were performed on all patients; those with evidence of clinical progression were examined more frequently. MRI studies were also performed monthly using 1.5-tesla scanners that were located at the individual study sites and were analyzed in a blinded fashion at Harbor-UCLA using a validated automatic segmentation method (Itti *et al*, 2001). Scanning was initiated with a sagittal T1-weighted localizer (echo time/relaxation time [TE/TR] 11/500, 4-mm slice thickness, no gap, 24-cm field of view), followed by a coronal fast double spin echo (TE1/TE2/TR 17/102/4000, 5-mm slice thickness, no gap, 24-cm field of view). For quantitative analysis of the white matter lesions, an axial FLAIR (fluid-attenuated inversion recovery) sequence was acquired (TE/TR/TI 142/11,000/2,600, 4-mm slice thickness, no gap, 24-cm field of view).

Clinical response was defined as an improvement in the Kurtzke score of 0.5 or more and a radiological response as a 10% or greater decrease in measurable PML marker lesion volume on MRI. Stable disease was that which was clinically associated with no new neurological deterioration lasting for at least 8 weeks and, radiographically, with no new MRI lesions or an increase in MR lesion volume of no more than 25%. Patients were determined to have progressive disease if they were found to have an increase in Kurtzke score of 0.5 or more or if there was an increase in MRI lesion volume of greater than 25%.

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