

Phase II intergroup trial of sequential chemotherapy and radiotherapy for AIDS-related primary central nervous system lymphoma

Research Article

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Abbreviations: primary central nervous system lymphoma (PCNSL), Epstein-Barr virus (EBV), cerebrospinal fluid (CSF), computerized tomography (CT), human immunodeficiency virus (HIV), antiretroviral therapy (HAART), CHOD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone)

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Summary

The purpose of this study is to determine the value of a systemic evaluation in patients with primary central nervous system lymphoma (PCNSL) associated with human immunodeficiency virus (HIV) infection, to investigate the diagnostic utility of detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF), and to determine the overall survival in patients treated with one cycle of chemotherapy followed by radiation therapy. Patients underwent computerized tomography (CT) and bilateral bone marrow biopsy. CSF was analyzed for EBV DNA. A single cycle of an anthracycline containing combination chemotherapy regimen was followed by radiation therapy. Thirty-five patients were enrolled. Bone marrow biopsy did not reveal lymphoma in any case. Chest X ray identified one patient with a coexistent thoracic lymphoma. EBV DNA was detected in CSF in 8 of 10 patients. The median survival was 2.4 months (C.I. 1.1 to 3.2 months). Four patients survived more than a year. **CONCLUSIONS:** In HIV-infected patients with intracranial mass lesions, systemic evaluation with CT scan and bone marrow biopsy has a low yield. EBV DNA is usually detected in CSF. A single cycle of an anthracycline-containing regimen followed by radiation was associated with a poor survival.

I. Introduction

The incidence of primary central nervous system lymphoma (PCNSL) in individuals infected with the human immunodeficiency virus (HIV) was 3,600-fold greater than in the general population in the era before highly active antiretroviral therapy (Cote et al, 1996). Since the introduction of highly active antiretroviral therapy (HAART), there has been a decline in the incidence of HIV-associated PCNSL (Sparano et al, 1999; Besson et al, 2001; Kirk et al, 2001; Hoffmann et al, 2003). The diagnostic yield of a systemic work up, including computerized tomography (CT) of the body and bilateral bone marrow biopsy has not been previously

evaluated. In addition, at the time that this study was performed, brain biopsy was considered necessary for establishing a definitive diagnosis, but was known to be associated with considerable morbidity and occasional mortality (Corn et al, 1995; Skolasky et al, 1999). Results of standard therapy with radiation were poor engendering therapeutic nihilism (Baumgartner et al, 1990). Finally, the relationship between PCNSL and systemic lymphoma, particularly in the setting of acquired immunodeficiency syndrome (AIDS) was not clear. Extranodal-presentations of systemic AIDS-related lymphoma are common. The central nervous system is one of the most frequent extranodal sites, raising the concern that central nervous system involvement at presentation may be a

manifestation of systemic disease. We sought to determine whether a systemic work up (particularly bone marrow biopsy) was necessary to exclude occult systemic disease. We also sought to determine whether in light of the nearly uniform EBV-PCNSL association (MacMahon et al, 1991) a likely diagnosis could be established without brain biopsy by sampling the cerebrospinal fluid for EBV DNA by polymerase chain reaction (PCR) (Arribas et al, 1995; Antinori et al, 1997, 1999; Cinque et al, 1993). Finally, we sought to determine whether chemotherapy administered before radiation might improve the outcome (DeAngelis et al, 1992; Forsyth et al, 1994).

In 1995, the Eastern Cooperative Oncology Group (ECOG) initiated a multi-institutional study to address each of these issues. Other participating groups included the Radiation Therapy Oncology Group (RTOG), the Cancer and Acute Leukemia Group B (CALGB), and the AIDS Clinical Trials Group (ACTG). This study forms the basis for this report.

II. Patients and methods

A. Methods

This study plan included a diagnostic step (step 1), a treatment step (step 2), and a correlative laboratory component. To be eligible for step 1, patients were required to be HIV seropositive and to have biopsy proven PCNSL of intermediate or high-grade histology involving the parenchyma of the brain with an intracranial space-occupying lesion documented on an imaging study. Other requirements included no prior chemotherapy (unless given for Kaposi's sarcoma), no prior cranial irradiation, to be within 3 weeks of diagnostic brain biopsy, age 16 or older, no prior history of lymphoma or clinical evidence of systemic lymphoma, no prior or concomitant malignancy other than Kaposi's sarcoma or curatively treated carcinoma of the cervix, or squamous cell or basal carcinoma of the skin. To be eligible for step 2, patients were required to have no evidence of systemic disease as documented by computerized tomography (CT) of the chest, abdomen, and pelvis, and bilateral bone marrow biopsies. Other requirements included an ECOG performance status of 0-3, adequate hematologic function (absolute neutrophil count of $1,000/\text{mm}^3$ and platelets $50,000/\text{mm}^3$) and adequate renal and hepatic function (serum creatinine 3.0 mg/dl and bilirubin $\leq 3 \times$ the upper limit of normal), and no active acute infection. Lumbar puncture was required for the evaluation of cerebrospinal fluid (CSF) for malignant cells and EBV DNA unless clinically contraindicated. Patients were excluded if they were receiving concurrent treatment with investigational agents other than investigational antiretroviral agents, if they had an active duodenal ulcer, uncontrolled diabetes mellitus, active heart disease, or were pregnant or lactating. Patients were required to provide written informed consent. The protocol was approved by the institutional review board at each participating institution.

B. Chemotherapy

Patients without systemic lymphoma were registered on step 2 and received intravenous cyclophosphamide 750 mg/m^2 , doxorubicin 50 mg/m^2 , vincristine 1.4 mg/m^2 (2 mg maximum) and dexamethasone 16 mg/m^2 , followed by the same dexamethasone dose orally or intravenously on a daily basis; daily dexamethasone treatment was permitted to maintain the patient's best neurologic function. Patients with positive CSF cytology were treated with intrathecal cytarabine, 50 mg twice

weekly until cytology was negative, then once weekly for six weeks, and once monthly for ten months.

C. Radiotherapy

Patients started radiotherapy 7-10 days after chemotherapy. Daily treatments of 2.5 Gy were given 5 days per week for 12 days to the entire cranial contents using opposed shaped lateral whole brain treatment portals. Four daily 2.5 Gy fractions were then delivered via shaped reduced fields to the identifiable lesion(s) with a margin. The total tumor dose was 40.0 Gy in 16 fractions given in less than 4 weeks. Treatment plans, diagnostic imaging, and field localization were reviewed on all treated patients by the radiation.

D. Supportive care

Granulocyte colony stimulating factor (G-CSF) was given at 5 ug/kg subcutaneously beginning on day 2 for a minimum of 10 days until granulocyte counts exceeded $5000/\text{ul}$ for two days. Prophylaxis for *pneumocystis carinii* (trimethoprim/sulfamethoxazole, dapsone or aerosolized pentamidine) and fungal infection (fluconazole, ketoconazole, or clotrimazole oral troches) were standard. As this trial was initiated before the availability of highly active antiretroviral therapy, antiretroviral therapy consisted of standard doses of didanosine, zidovudine, or zalcitabine unless contraindicated.

E. Cerebrospinal fluid polymerase chain reaction to detect EBV DNA

CSF samples from patients enrolled in this study and specimens that had been archived in the Johns Hopkins AIDS Neurological Tissue Bank were studied for EBV DNA by polymerase chain reaction (PCR). CSF from study participants was shipped overnight on dry ice and stored at -70°C until analysis. CSF archived in the AIDS Neurological Tissue Bank were collected from patients treated at Johns Hopkins with HIV infection who had neurological signs or symptoms or who were asymptomatic. These samples were amplified with PCR primers to two regions of the genome in two separate assays as described (Ambinder et al, 1990; Arribas et al, 1995). For these assays, a $20\mu\text{L}$ aliquot of CSF was heated at 95°C for 10 minutes. PCR products were analyzed by agarose gel electrophoresis with Southern blot transfer and hybridization with ^{32}P -labeled oligonucleotide probes. Autoradiography was carried out overnight with Kodak X-Omat film. To prevent contamination PCR set up and amplification were performed in separate rooms.

F. Statistical considerations

The primary objectives of the trial were descriptive. The methods of Kaplan and Meier were used to estimate survival curves. With the intent of estimating one-year survival with a maximum 90% confidence interval width of $\pm 16\%$, the goal was to enroll at least 30 patients. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CSF EBV DNA in patients not yet treated for PCNSL were calculated using standard definitions (Dunn, 1995).

III. Results

A. Patient Characteristics

This study accrued 35 patients between April 1994 and April 1997 to step 1, including patients accrued from ECOG (N=24), CALGB (N=6), RTOG (N=3), and ACTG (N=2). The characteristics of the study population are

summarized in **Table 1**. The median age was 36 years and 33 (94%) were male. The median CD4 count was 10.5/ μ L (range 1-91/ μ L). The ECOG performance status was 0 or 1 in 11 (34%), 2 in 10 (31%) and 3 in 10 (31%). Prior opportunistic infection included *pneumocystis carinii* in 10 (33%), cytomegalovirus infection in 9 (30%), candida esophagitis in 7 (24%), mycobacterium *avium intracellulare* in 6 (19%), and other infections in 11 (42%). CSF cytology was performed in 16 patients, of whom three were positive for malignant cells consistent with meningeal lymphoma. In many instances lumbar puncture was felt to be contraindicated and CSF cytology not available.

B. Systemic diagnostic workup

Bone marrow biopsy revealed no evidence of lymphoma in any patient. In one patient the CXR revealed coexistent lymphoma in the lung, which was confirmed on computerized tomography (CT) of the chest.

C. Clinical and radiographic presentation of CNS disease

Clinical and radiographic features are shown in **Table 2**. All patients had neurologic symptoms at diagnosis. The most common presenting signs and/or symptoms included motor deficits in 13 (37%), altered mental status in 11 (31%), headache in 10 (29%), visual disturbance in 9 (26%), cranial nerve deficits in 8 (23%), speech impairment in 8 (23%), cerebellar deficits in 7 (20%), sensory deficits in 6 (17%), and papilledema in 1 (4%). Imaging studies of the brain revealed the tumors to be unilateral in 23 patients (66%), and the median tumor size was 5.2 cm² (1.5-27.5). Supratentorial structures were involved in 20 patients (57%) and infratentorial structures were involved in 4 patients (11%).

D. Response and survival

Thirty-four patients proceeded to step 2 and received protocol treatment. Complete response occurred in 3 patients (9%), and partial response in 1 patient (3%).

Fifteen patients (43%) did not complete radiation therapy, including seven patients who died before completion, five patients who declined to complete therapy, and three patients who had showed tumor progression during radiation therapy. The median survival was 2.4 months (95% confidence intervals 1.1, 3.2 months) (**Figure 1**). Four patients survived at least one year. The characteristics of the responders and/or long-term survivors are summarized in **Table 3**.

E. Toxicity

There were 8 patients (23%) who died within 30 days of initiating treatment, including four patients who died of infectious complications, two patients who had pulmonary failure, one patient who had a brain herniation, and one

Table 1. Patient Characteristics

Age		
Median		36 years
Range		22 - 54 years
ECOG Performance Status (N=32)		
0, 1		11 (34.4%)
2		10 (31.3%)
3		10 (31.3%)
4		1 (3.1%)
CD 4 Count (N=26)		
Median		10.5/uL
Range		1-91/uL
Neutrophil Count (N=31)		
Median		2800/ul
Range		1000-15,100/ul
Hemoglobin (N=31)		
Median		12.0 g/dl
Range		9.2-15.7
Platelet Count (N=31)		
Median		210,000/ul
Range		64,000-452,000

Table 2. Clinical and Radiographic Findings

Clinical Findings	Number	Percent
Motor deficits	13	37%
Altered mental status	11	31%
Headache	10	29%
Visual disturbance	9	26%
Cranial nerve deficits	8	23%
Speech impairment	8	23%
Cerebellar deficits	7	20%
Sensory deficits	6	17%
Papilledema	1	4%
Radiographic Findings		
Unilateral lesions	23	66%
Supratentorial lesions	20	57%
Infratentorial lesions	4	11%

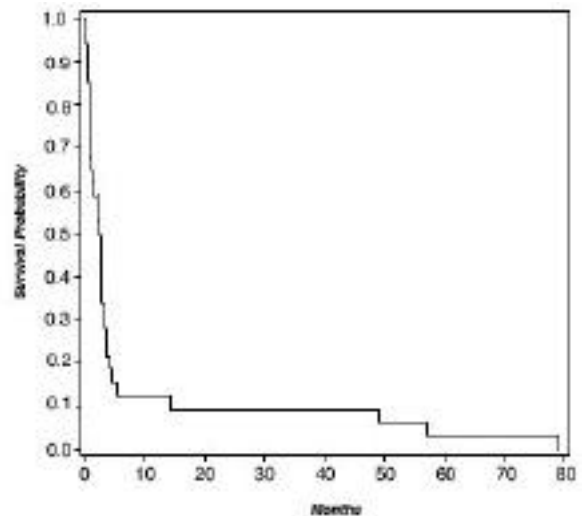


Figure.1. Overall survival of treated patients (N=34).

patient who died during a grandmal seizure. Grade 4 toxicity included leukopenia in 63%, thrombocytopenia in 20%, and liver, pulmonary, neurosensory, neuromotor, and metabolic toxicities one patient each (3%).

F. Evaluation of cerebrospinal fluid for EBV DNA

The results of the studies of CSF for EBV DNA are shown in **Table 4**. CSF specimens from 15 patients with PCNSL enrolled on this study and 73 patients with HIV infection and other conditions obtained from the Johns Hopkins AIDS Specimen Bank were available for analysis by EBV PCR. Of the 15 patients with PCNSL who had specimens evaluated, in 10 patients the CSF was obtained before therapy. EBV DNA was detected in 8 of 10 patients with pre-treatment CSF specimens available. In 5 patients with CSF obtained after either complete tumor excision by surgery (1 patient) or the initiation of chemotherapy (4 patients), EBV DNA was not detected. In addition, EBV DNA was detected in 1 of 16 patients (6%) with toxoplasmosis, 1 of 27 patients (4%) with progressive multifocal leukoencephalopathy, 2 of 8 patients (25%) with cytomegalovirus encephalitis, and none of 15 patients without neurologic diagnoses. In 7 patients with systemic lymphoma without central nervous system involvement, EBV was detected in none. In patients with PCNSL, detection of EBV DNA in the CSF had a sensitivity of 80%, specificity of 94 %, positive predictive value of 67%, and a negative predictive value of 97%.

IV. Discussion

We report the results of a multi-institutional trial evaluating a diagnostic algorithm and treatment program for patients with HIV infection and biopsy-confirmed PCNSL. The objectives of this study were to evaluate the role of routine screening for systemic disease, the accuracy of detecting EBV DNA in the cerebrospinal fluid for diagnosing PCNSL, and whether the administration of a single cycle of chemotherapy prior to brain irradiation improved the outcome for patients with this condition.

At the time the study was initiated, bone marrow biopsy and computerized tomography of the chest, abdomen and pelvis were routinely recommended in order to rule out the possibility of occult systemic disease. Patterns of involvement by B-cell and B-cell derived malignancies are notably distinct in HIV-infected patients and cannot be predicted by extrapolation from uninfected hosts. Thus non-Hodgkin's lymphoma much more commonly involves extra lymphatic sites in HIV patients than in others (Levine et al, 2001; Sparano, 2001). Similarly, Hodgkin's disease not uncommonly presents with bone marrow involvement in HIV patients (Levine, 1998). Finally, visceral plasmacytomas occur in HIV-infected patients (Carraway and Ambinder, 2002). There has been no previous systematic study of bone marrow involvement in AIDS PCNSL. The results of step 1 of this study showed that the most invasive staging test, bone marrow biopsy, never showed lymphomatous involvement. CT scanning identified systemic lymphoma in only one patient who had intrathoracic disease demonstrable on chest x-ray. Our findings suggest that routine bone marrow biopsy and CT scans of the body have a low diagnostic yield in this setting and are generally not indicated.

A related diagnostic issue is the utility of detecting EBV DNA in the CSF by PCR in patients with HIV infection and intracranial mass lesions. Previous reports have documented the presence of EBV DNA in the CSF in the majority of patients with HIV infection and PCNSL (MacMahon et al, 1991; Cinque et al, 1993; Arribas et al, 1995; Antinori et al, 1997, 1999). For example, Cingolani et al (1998) evaluated CSF EBV DNA by PCR in 122 patients with HIV infection, including 42 patients with PCNSL and 80 with a variety of non-malignant conditions. CSF EBV DNA had a sensitivity of 80% (95% confidence intervals 61%, 92%) and a specificity of 100% (95% confidence intervals 93%, 100%). The authors concluded that sampling of the lumbar CSF would have led to a correct diagnosis in 63% of patients with HIV-associated PCNSL, and would have excluded this diagnosis in 76%.

Table 3. Summary of Patient Data for Responders and/or Long Term Survivors

Case	Response	Age	Performance Status	CD4	Survival (Months)	Survival Status
14001	CR	32	1	-	14.3	Dead
14004	CR	46	1	11	37.9	Alive
14011	PR	38	0	50	3.2	Dead
14020	CR	32	1	59	23.4	Alive
14601	SD	22	0	91	16.3	Alive

Table 4. Analysis of CSF for EBV DNA

Diagnosis	No. Positive/Samples	Percent Positive
PCNSL	8/10	80%
Systemic lymphoma	0/7	0%
Cerebral toxoplasmosis	1/16	6%
Progressive multifocal leukoencephalopathy	1/27	4%
Cytomegalovirus encephalitis	2/8	25%
Other neurological diagnosis	1/15	7%

In addition, the same group reported that EBV DNA in the CSF usually disappears with treatment of the lymphoma (Antinori et al, 1999). Our findings are consistent with these previous reports. In combination with imaging techniques, a positive EBV PCR result may obviate the need for brain biopsy in some patients with intracranial mass lesions and HIV infection. The identification of EBV in the CSF of some patients with HIV is consistent with the occasional identification of EBV in patients with infectious mononucleosis and associated neurological symptoms. It is curious that in this series (**Table 4**), EBV in the CSF in patients without lymphoma was most commonly found in HIV patients with cytomegalovirus encephalitis. Whether the detection of EBV in this setting points to some specific interaction between the two viruses or simply reflects profound cellular immunodeficiency is not clear. Future studies using quantitative methods for EBV load in CSF may facilitate differentiation between benign and malignant central nervous system disease.

Chemotherapy used alone or in combination with brain irradiation has been used for the treatment of non-HIV-associated PCNSL (Dahlborg et al, 1996; Freilich et al, 1996; Mead et al, 2000). The Radiation Therapy Oncology Group (RTOG) reported that CHOD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone) chemotherapy preceding brain irradiation was not associated with improved survival when compared with historical data employing radiation alone in non-immunocompromised patients (Schultz et al, 1996). A study from the United Kingdom also showed no advantage to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy following radiation therapy (Mead et al, 2000). Recent evidence suggests that high-dose methotrexate based regimens may be effective for immunocompetent patients with PCNSL. (DeAngelis et al, 1992; Glass et al, 1994; Guha-Thakurta et al, 1999; O'Brien et al, 2000; Batchelor et al, 2003). For example, DeAngelis and colleagues (1992) reported a five-year survival of 22% for patients treated with methotrexate, high dose cytarabine, and irradiation, compared with 4% for historical controls treated with radiation alone. A subsequent multicenter study confirmed improved survival compared with historical data using irradiation alone, although delayed neurotoxicity was a major complication of therapy, especially in patients older than 60 years of age (DeAngelis et al, 2002). Likewise, Sandor and colleagues (1998) treated 14 patients with PCNSL or intraocular lymphoma with high dose methotrexate with leucovorin rescue, thiopeta, vincristine, and dexamethasone. The complete response rate was 79%, and 69% of the patients survived nearly five years, of whom about one-half were progression-free. Others have also evaluated high-dose methotrexate alone, with deferral of irradiation until relapse or progression, with encouraging results (Batchelor et al, 2003). An expert panel has recommended high-dose methotrexate-based regimen with deferred irradiation for older (more than 60 years) in order to reduce the risk of delayed neurotoxicity in this group, and high-dose methotrexate and cytarabine based-combinations in conjunction with irradiation in younger patients; the panel

did not address treatment of primary CNS lymphoma in patients with HIV infection (Ferreri et al, 2003).

The treatment of PCNSL in AIDS patients presents two obstacles: the blood brain barrier and the patients profound immunocompromised status. With regard to the blood brain barrier, imaging studies make clear that the integrity of this barrier evolves with therapy. Contrast enhancement of tumors prior to treatment suggests that the tumor itself leads to profound disruption of the barrier. As treatment proceeds, the barrier is often reestablished. Poor tolerance of chemotherapy in AIDS patients has established a role for reduced-dose or reduced-length treatment in some settings (Kaplan et al, 1997). Thus for our study we reasoned that a single cycle of chemotherapy administered prior to the initiation of radiation therapy might increase tumor kill with only minimal increase in toxicity. We gave one cycle of CHOD chemotherapy followed by irradiation in a manner similar to that employed by the RTOG for PCNSL in immunocompetent patients. Our results are similar to other reports that included radiation therapy alone (Donahue et al, 1995; Bower et al, 1999). Although those who survived more than 1 year had CD4 counts that exceeded the median in every case in which they were available, and the patient with the highest CD4 count was among the longer survivors. CD4 count was not a very good prognosticator. Thus, the longest survivor (37.9 months) had a CD4 count of only 11_barely above the median. Our findings suggest that administration of a single cycle of an anthracycline containing combination chemotherapy regimen before radiation in patients with PCNSL and HIV infection fails to improve patient outcome.

Our study was conducted prior to the use of HAART in clinical practice. Several reports have indicated that patients with HIV-associated PCNSL treated in the post-HAART era had a much improved prognosis, especially those who had a substantial reduction in viral load due to HAART therapy (Skiest and Crosby, 2003). This finding parallels improvements in survival also noted for patients with systemic HIV-associated lymphoma treated with standard cytotoxic therapy (Vaccher et al, 2001). Spontaneous remission of PCNSL has been reported in immunocompetent patients after treatment with dexamethasone (Al-Yamany et al, 1999), and in patients with HIV infection after treatment with HAART and corticosteroids (Terriff et al, 1992; McGowan and Shah, 1998). In addition, Raez reported the use of parenteral zidovudine (1.6 g twice daily), gancyclovir (5 mg/kg twice daily), and interleukin-2 (2 million units twice daily) in five patients with HIV-associated PCNSL, some of whom had progressive disease after prior brain irradiation (Raez et al, 1999). The treatment regimen was based upon the premise that the treatment was effective against Epstein-Barr virus-positive B-cell lymphoma cell lines in vitro. Four of five had an objective response, of whom two were alive and disease-free at 22 and 13 months. These findings suggest that the prognosis may be improved for patients with PCNSL diagnosed in the post-HAART era. Treatment with high-dose methotrexate-based regimens plus optimization of HAART therapy may therefore

represent a prudent strategy for patients with HIV-associated PCNSL that merits evaluation in clinical trials.

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