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Original Paper

Treatment Outcome in Presumed and Confirmed AIDS-related Primary Cerebral Lymphoma

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A retrospective analysis identified 38 HIV seropositive patients with a diagnosis of presumed ($n = 26$) or confirmed ($n = 12$) primary cerebral lymphoma (PCNSL). All patients had failed to respond to empirical antitoxoplasma therapy and the clinical diagnosis of PCNSL was confirmed by brain biopsy ($n = 4$), cerebrospinal fluid (CSF) examination for Epstein–Barr virus (EBV) by PCR ($n = 7$) or post-mortem examination ($n = 1$). There was no difference in the age, performance status, CD4 counts, antiretroviral usage or interval since first HIV serodiagnosis between patients with presumed or confirmed PCNSL. 16 patients received either radiotherapy ($n = 14$) or chemotherapy ($n = 2$). Patients with confirmed or presumptive PCNSL were equally likely to receive treatment. The median overall survival, which was measured from the end of unsuccessful antitoxoplasma therapy, was 1.2 months for the whole cohort. There was no difference in overall survival between patients with presumptive (median 0.8 months) and confirmed (median 1.3 months) PCNSL (logrank $P = 0.69$). This suggests that there may be little value in positively diagnosing PCNSL in the current diagnostic algorithm. Recent improvements in outcome have been reported with systemic chemotherapy in HIV-PCNSL and may influence the need for earlier definitive diagnosis in the future. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

NEUROLOGICAL DISEASE causes much morbidity and mortality in patients with AIDS and the majority have central nervous system (CNS) pathology at autopsy [1, 2]. Cerebral *Toxoplasma gondii*, primary CNS lymphoma (PCNSL) and progressive multifocal leukoencephalopathy (PML) account for the vast majority of focal neurological lesions in this patient population [3, 4], although the differential diagnosis is not straightforward. Neither clinical features nor radiological investigations can be relied upon to establish the cause of focal neurological lesions [5]. Since toxoplasmosis is a frequent cause of these lesions and responds promptly to treatment, empirical antitoxoplasma therapy has become an established step in the diagnostic algorithm for the management of HIV-infected patients with focal neurological lesions [6]. A presumptive diagnosis of toxoplasmosis is based upon the combination of positive *Toxoplasma* serology (serum IgG antibodies), radiological features including multiple or occasionally solitary parenchymal nodular or ring-enhancing lesions, and response to empiric antitoxoplasma therapy [7]. Brain biopsy and molecular analysis of cerebrospinal fluid are usually reserved for patients who fail to respond to antitoxoplasma therapy.

Although this diagnostic algorithm has the advantages of pragmatism and allows rapid initiation of therapy, it delays the diagnosis of other causes of focal lesions including PCNSL, requires patients to remain off steroids where possible to avoid spurious positive radiological responses [8] and 20% of patients treated with antitoxoplasma therapy will develop toxicity [9–11]. This retrospective study examines the diagnosis of PCNSL and outcome of AIDS patients.

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Table 1. *Comparison of clinicopathological features of patients with confirmed and presumptive primary cerebral lymphoma (PCNSL)*

	Prior AIDS diagnosis	ECOG 2	ECOG 3	ECOG 4	Prior ART usage	Median CD4	Mean Age	Mean interval from HIV to PCNSL
Presumptive PCNSL ($n=26$)	24 (92%)	3 (12%)	15 (58%)	8 (31%)	10 (38%)	15/μl	37 years	55 months
Confirmed PCNSL ($n=12$)	9 (75%)	2 (17%)	5 (42%)	5 (42%)	8 (67%)	7/μl	35 years	58 months
	χ^2 $P=0.14$		χ^2 $P=0.65$		χ^2 $P=0.15$	MW U $P=0.33$	*t*-test $P=0.47$	*t*-test $P=0.82$

ECOG, Eastern Cooperative Oncology Group performance status; MW U = Mann Whitney U test; ART, antiretroviral therapy.

PATIENTS AND METHODS

Since 1986, the diagnostic algorithm for the management of cerebral mass lesions in HIV seropositive patients has included a 2-week trial of antitoxoplasma therapy. Patients who fail to respond to this therapy are offered further diagnostic procedures either a brain biopsy or since 1994 a diagnostic lumbar puncture if there are no contra-indications. The cerebrospinal fluid is examined for Epstein–Barr viral DNA by polymerase chain reaction amplification, a validated methodology for the detection of PCNSL [12, 13]. A positive brain biopsy or lumbar puncture confirms the diagnosis of primary cerebral lymphoma whilst failure of antitoxoplasma treatment without further diagnostic intervention is classified as presumptive diagnosis of primary cerebral lymphoma. In many cases a positive diagnosis of PCNSL is not pursued because raised intracranial pressure may preclude a lumbar puncture and both patient and physician may feel that a brain biopsy is too invasive in patients with a very poor performance status.

Statistical methods

Survival was calculated from the day of diagnosis, either confirmed by biopsy or lumbar puncture or after failure of 2 weeks antitoxoplasma therapy. Overall survival duration curves were plotted according to the method of Kaplan and Meier [14]. The log rank method was used to test for the significance of differences in survival distributions [15]. Comparison of variables between groups was by χ^2 test for nominal variables, Mann–Whitney U-test for non-parametric variables and *t*-test for parametric variables.

RESULTS

Retrospective analysis of the database of 2500 HIV seropositive patients identified 38 patients with a diagnosis of presumptive or confirmed PCNSL diagnosed between 1986 and 1998. All 38 were men and the mean age was 36 years (range 26–54 years). 33 (87%) had a prior AIDS defining diagnosis and the median CD4 count at presentation of PCNSL was 13 cells/μl (range 0–293/μl). The median interval from first HIV seropositive diagnosis to PCNSL diagnosis was 3.9 years (range 0–11.3 years). 16 (42%) had received treatment with antiretroviral therapy prior to PCNSL diagnosis. The prospectively recorded Eastern Cooperative Oncology Group (ECOG) performance status at presentation was 2 for 5 patients (13%), 3 for 20 patients (53%) and 4 for 13 patients (34%).

26 patients with presumed PCNSL had no further diagnostic procedures following failure of antitoxoplasma therapy for cerebral mass lesions whilst 12 patients had the diagnosis confirmed by brain biopsy ($n=4$), cerebrospinal fluid (CSF) examination for EBV (Epstein–Barr virus) DNA ($n=7$) or by post mortem examination ($n=1$). There was no difference in the age, performance status, CD4 counts, antiretroviral usage or the interval from first HIV serodiagnosis to development of PCNSL, between patients with presumed or confirmed PCNSL (Table 1).

16 patients received therapy for PCNSL, either whole brain irradiation using 20 Gy in five daily fractions (14 patients) or high-dose (3 g/m^2) systemic methotrexate (2 patients). Patients with a better ECOG performance status were more likely to receive chemotherapy or radiotherapy (χ^2 $P=0.005$). However, there was no difference in the use of active treatment for PCNSL between those patients with a presumptive diagnosis (10/26) and those with a confirmed diagnosis (6/12 including both patients treated with chemotherapy) (χ^2 $P=0.50$).

Overall survival was measured from the time of presumptive diagnosis after failure of antitoxoplasma therapy or from diagnostic CSF or brain biopsy examination. The median overall survival for the cohort of 38 patients was 1.2 months. There was no difference in overall survival between patients with presumptive (median 0.8 months) or confirmed diagnosis (median 1.3 months logrank $P=0.69$) (Figure 1). A prior AIDS defining diagnosis (log rank $P=0.57$) did not influence survival duration. Furthermore, the CD4 count at PCNSL diagnosis (proportional hazard $P=0.71$), ECOG performance status (proportional hazard $P=0.18$), and the age at PCNSL diagnosis (proportional hazard $P=0.12$) did not influence overall survival. The overall survival was longer in patients who received chemotherapy or radiotherapy (median survival 2.0 months) than those who did not (median survival 0.7 months, logrank $P=0.0008$) (Figure 2).

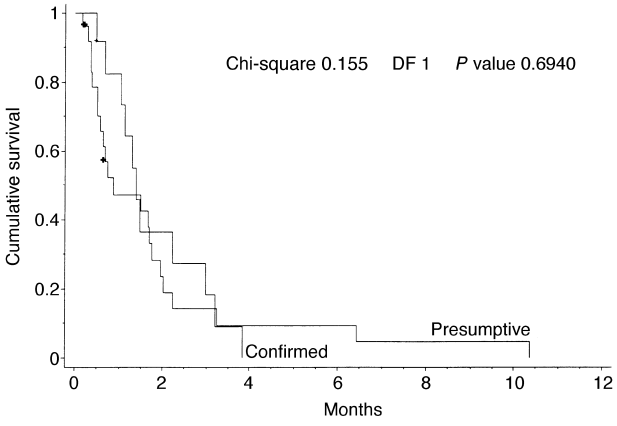

Figure 1. Kaplan–Meier overall survival duration curve following diagnosis of PCNSL according to whether the diagnosis was confirmed or presumptive.

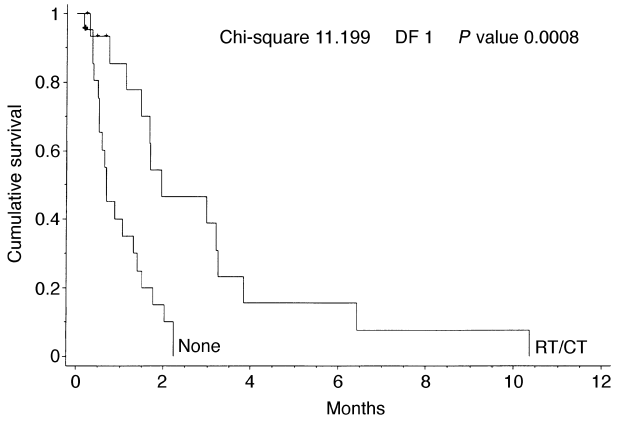

Figure 2. Kaplan–Meier overall survival duration curve following diagnosis of PCNSL according to whether the patient received radiotherapy/chemotherapy for PCNSL or not.

DISCUSSION

The prognosis of AIDS-associated PCNSL is dismal, survival is generally quoted as 2–3 months [16, 17], although the point from which it is measured varies and not all patients are included in some series. The very poor overall survival in this cohort may in part be accounted for measuring survival from confirmed diagnosis or completion of unsuccessful antitoxoplasma therapy. In other studies the onset of symptoms [18] has been used in survival analysis which obviously favourably influences survival duration figures. A second factor that may relate to the very poor survival documented here is the inclusion of all patients with confirmed or presumptive PCNSL in the HIV seropositive database without any patient selection. In other series only treated patients [19, 20], or those with confirmed diagnoses [21] have been included. The high number of patients who did not have a confirmed diagnosis of PCNSL did not influence outcome in our cohort, but the fact that the majority of patients did not receive chemotherapy or radiotherapy is related to their poor performance status, and non-treatment was shown to be an adverse prognostic factor.

Although caution must be used when interpreting non-randomised retrospective data such as the results presented here, the lack of difference in survival between patients who did or did not undergo a diagnostic procedure following failure of antitoxoplasma therapy suggests that there may be little value in positively diagnosing PCNSL in the current diagnostic algorithm that includes an initial 2-week period of empirical antitoxoplasma treatment. A smaller study of the outcome of radiotherapy in the management of presumed and confirmed AIDS-related PCNSL similarly demonstrated no difference in overall survival between the two groups [22]. However, recent reports have documented dramatic improvements in median survival in non-HIV associated PCNSL with systemic chemotherapy [23] and this has led to increased interest in managing HIV-associated PCNSL with this approach. A phase II study of high-dose systemic methotrexate in HIV-associated PCNSL has yielded a median survival of 18 months [24]. This result suggests that earlier confirmatory investigations for PCNSL may be warranted.

Advances in diagnostic investigations for focal neurological lesions may result in attempts to diagnose positively these lesions before awaiting the outcome of empirical therapy. These improvements are based upon molecular diagnostics and functional imaging techniques that have made the transition from laboratory bench to bedside.

Lumbar puncture is a safe investigation in the absence of midline shift, ventricular effacement or noncommunicating hydrocephalus on conventional imaging. Molecular analysis of CSF using DNA and RNA amplification protocols have been developed for the diagnosis of EBV, *Toxoplasma gondii* [25], JC virus [26], *Mycobacterium tuberculosis* [27] and other pathogens. EBV DNA has been detected in tumour samples from nearly all HIV-associated PCNSL although not in most immunocompetent patients developing PCNSL [12, 28]. The detection of EBV DNA in the CSF by PCR in patients with PCNSL has been established as a diagnostic test with high sensitivity (83–100%) and specificity (> 90%) [13, 29, 30].

Functional neuroimaging techniques that measure metabolic activity in focal lesions have been evaluated for their ability to discriminate between *Toxoplasma* infection and PCNSL. The most widely studied technique is thallium-201 (^{201}Tl) single photon emission CT (SPECT). ^{201}Tl accumulates in metabolically active tissues, so uptake is high in PCNSL but low in normal brain tissue and *Toxoplasma* lesions. ^{201}Tl-SPECT has been successfully employed to differentiate Toxoplasmosis and PCNSL in a number of studies [31, 32], although both false-negative and false-positive scans have been documented.

Positron emission tomography (PET) scanning following administration of ^{18}fluorodeoxyglucose (^{18}FDG) also detects areas of high metabolic activity such as PCNSL. This method of functional imaging has been successfully employed to differentiate PCNSL and toxoplasmosis [33–35], but PML may mimic PCNSL and PET scanning facilities are not widely available. Finally, ^{1}Hydrogen magnetic resonance spectroscopy (^{1}H-MRS) allows non-invasive biochemical analysis of focal brain lesions and has been evaluated as a diagnostic tool in AIDS patients with focal brain lesions with variable success [36, 37].

Although these functional neuroimaging techniques have a high specificity for PCNSL, they lack sensitivity and are probably best used in combination with CSF molecular analysis by PCR [38, 39]. The two tests used together in the diagnosis of 27 patients with contrast enhancing focal brain lesions demonstrated positive and negative predictive values of 100% and 80%, respectively [40].

It remains to be seen whether earlier definitive diagnosis based upon these novel techniques combined with increased use of systemic chemotherapy will influence survival outcomes in HIV-associated PCNSL which would encourage clinicians to pursue a definitive diagnosis more keenly.

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