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Original Article

Primary Central Nervous System Lymphoma: A Single-centre Experience of 55 Unselected Cases

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ABSTRACT:
Aims: Current treatment for primary central nervous system lymphoma (PCNSL) involves high-dose methotrexate (HDMTX) with or without radiotherapy. Many published studies describing this approach include a highly selected group of patients. We report a single-centre experience of unselected cases of PCNSL.
Materials and methods: We retrospectively reviewed the case notes of 55 consecutive patients diagnosed with biopsy-proven PCNSL between 1995 and 2003 at Addenbrooke's Hospital Cambridge, UK. We describe the treatment and outcome, including survival, treatment-related toxicity and long-term functional disability.
Results: At diagnosis, 45% of patients were considered unfit to receive treatment with HDMTX, owing to poor performance status or comorbidity. These patients had a median survival of 46 days and may not have been included in other published studies. The remaining patients were treated with a chemotherapy regimen, which included HDMTX. Patients who received at least one cycle of a chemotherapy containing HDMTX had a median survival of 31 months. Forty per cent did not complete planned chemotherapy owing to toxicity, disease progression or death. The median survival of patients treated with HDMTX aged 60 years compared with patients aged under 60 years was 26 months vs 41 months ($P = 0.07$), respectively. Younger patients treated with HDMTX, who achieved complete remission with chemotherapy, had a median survival of 56 months. We identified a high incidence of functional disability among survivors, resulting from a combination of the tumour itself, the neurosurgical procedure required for diagnosis and the late neurotoxicity of combined chemoradiotherapy.
Conclusion: The treatment of PCNSL is associated with significant early and late toxicity. Further attempts to improve treatment should address mechanisms to reduce this toxicity. In particular, the benefit of radiotherapy in patients who achieve complete remission with HDMTX will remain uncertain until it is addressed in a multicentre, randomised trial. Hodson, D. J. *et al*. (2005). *Clinical Oncology* **17,** 185–191

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Introduction

The incidence of primary central nervous system lymphoma (PCNSL) has trebled over the last 30 years and, in the USA, now stands at 4.8 new cases per million population [1]. A recent European study suggests an incidence of 2.7 per million population [2]. This increase cannot be explained solely by improved diagnostic technology, as the incidence of other cerebral tumours has not shown a similar increase. Neither can it be explained by the HIV epidemic, as the trend is observed in populations with a low prevalence of HIV, and it far outpaces the increase seen in other HIV-related malignancy, such as Kaposi's sarcoma [1].

Over the same period, the treatment of PCNSL has evolved considerably. The optimum treatment strategy still remains unclear, and long-term, disability-free survival remains poor. This is especially true for people over 60 years who comprise the majority of affected cases. Until 10 years ago, external beam radiation formed the mainstay of treatment for patients with primary PCNSL. Whole-brain radiotherapy was used because of the high frequency of microscopic infiltration of brain tissue distant to the tumour

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site. However, despite doses of radiation between 40 and 60 Gy, most studies report a high rate of local recurrence and median survival of around 12 months [3,4].

Initial attempts to improve these results combined radiation with chemotherapy, a strategy that had proved effective in systemic non-Hodgkin's lymphoma. However, several studies, including a randomised trial, have examined the use of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone) before radiotherapy, and have failed to show any survival benefit in PCNSL [5–7]. Although the presence of lymphoma may cause local disruption of the blood–brain barrier, allowing penetration of chemotherapy, this effect is only temporary because tumour response leads to a restoration of the blood–brain barrier, and further courses of chemotherapy fail to penetrate the tumour [6,7]. Furthermore, autopsy studies reveal widespread microscopic dissemination of lymphoma cells throughout areas of the brain apparently normal on magnetic resonance imaging (MRI) [8]. Effective chemotherapy must be able to penetrate the entire brain and, therefore, must be capable of crossing an intact blood–brain barrier.

Methotrexate crosses the blood–brain barrier when used in doses above 1.5 g/m^2. In doses above 3.5 g/m^2, it also reaches tumouricidal levels in the cerebrospinal fluid (CSF) [9]. Such CSF penetration is important, as 15–25% of lymphoma cells can be detected in the CSF. The true incidence of meningeal involvement is probably greater, and meningeal deposits can be found in most patients at autopsy [10]. A number of studies have confirmed an improved survival using combination chemotherapeutic regimens containing high-dose methotrexate (HDMTX) in addition to whole-brain irradiation [4,11–15]. The complete response rates in published series range from 64 to 100%, with median survival between 30 and 60 months. Indeed, it is now clear that HDMTX is the single most important chemotherapeutic agent in the treatment of PCNSL. Two recent studies examining the use of single-agent methotrexate show a high rate of early relapse, with median times to relapse of 12.8 months [16] and 13.7 months [17], suggesting that methotrexate may be most effective when used within a combination regimen. What remains unclear is the optimum combination of chemotherapeutic agents to be included. Evidence from non-randomised, retrospective studies has shown that the addition of cytarabine may improve survival [12,14,18]. A number of other agents have been examined in combination with methotrexate. However, these trials are small and non non-randomised, and recruit people with non-equivalent baseline characteristics. It is, therefore, difficult to compare results between studies.

The superiority of combined chemoradiotherapy over radiotherapy alone is now well established. However, whether chemoradiotherapy is superior to chemotherapy alone is now the most important unanswered question in the treatment of PCNSL. Late-onset neurotoxicity related to the combination of methotrexate and radiotherapy is common, especially among older people, in whom rates reach up to 90% [11,15,19,20]. The neurotoxicity can be severely disabling, and is the cause of death in up to 50% of affected people. Withholding radiotherapy for elderly people who achieve complete remission after chemotherapy has been shown to reduce the rate of neurotoxicity [11,16,18,21,22]. However, one study [23] has shown a higher relapse rate in younger people randomised to receive a reduced dose of radiation. Two recent studies have shown promising results using high-dose chemotherapy followed by autologous stem-cell rescue as consolidation therapy in place of radiotherapy [24,25].

In the present study, we review 55 unselected, consecutive cases of PCNSL diagnosed between 1995 and 2003 at Addenbrooke's Hospital, Cambridge, UK. We report patient characteristics, histological and radiological findings, treatment strategies, tolerance of therapy and outcome. We also assess functional ability in those patients surviving beyond 1 year. Our observations identify prognostic groups that can be assigned early in treatment: namely, fitness for chemotherapy and patient age. These groups have significant differences in outcome, in particular median survival, which ranges from 6 weeks to 5 years.

Methods

We examined the records of all patients diagnosed with PCNSL at Addenbrooke's Hospital between 1995 and 2003. Only patients with a histological diagnosis of PCNSL were included in the study. Known HIV-positive patients were excluded.

Details of tumour site, histological type, staging computed tomography (CT), bone marrow and lumbar puncture were recorded. Slit lamp examination was not carried out routinely. The date of diagnosis was taken as the date of biopsy. Throughout the study period, the intention was that all patients should receive treatment with a chemotherapy regimen involving HDMTX with or without radiotherapy. A number of patients were considered unfit to tolerate HDMTX on the basis of poor performance status, severe cardiorespiratory compromise, advanced renal failure or concurrent uncontrolled sepsis. These patients received either steroid or alternative chemotherapy with or without radiotherapy. Patients treated with HDMTX received one of three regimens (Table 1). Early in the study period, patients received MBVP (teniposide, carmustine, methylprednisolone) [26] or CHOD/BVAM (cyclophosphamide, doxorubicin, vincristine, dexamethasone/carmustine, vincristine, methotrexate, cytarabine) [27]. However, owing to excessive toxicity, later patients received a less myelotoxic regimen containing HDMTX, procarbazine and cytarabine. This was based on a regimen proposed by Abrey *et al.* [11]. Before 2002, the intention was to follow HDMTX with whole-brain radiotherapy. From 2002, radiotherapy was withheld from patients who had achieved complete remission because of concerns over delayed neurotoxicity.

Response to treatment was recorded as complete remission, defined radiologically by CT or MRI, partial remission defined radiologically by CT or MRI, or progressive disease defined radiologically or clinically. The date of any relapse was recorded along with details of