Clinical Oncology 25 (2013) 400–405

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Is There a Role for Radiotherapy in the Primary Management of Primary Central Nervous System Lymphoma? A Single-centre Case Series

R. Muirhead *‡, E.C. Murray *, S.L. Bell †, W. Stewart †, A. James *

* The Beatson, West of Scotland Cancer Centre, Glasgow, UK
† Neuropathology Department, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK
‡ The Gray Institute for Radiation Oncology and Biology, Oxford, UK

Received 20 December 2012; received in revised form 4 March 2013; accepted 27 March 2013

Abstract

Aims: In recent years, the optimum primary management of primary central nervous system lymphoma (PCNSL) has evolved from combined modality chemoradiotherapy to chemotherapy alone. We describe a single-centre case series of PCNSL with a view to assessing the role of radiotherapy in primary disease management.

Materials and methods: West of Scotland PCNSL cases between 2001 and 2010 were identified by neuropathology. Observational data were collected retrospectively from case notes and electronic systems.

Results: Forty-nine patients fulfilled the eligibility criteria. The median age was 61 years. Chemotherapy with a view to consolidation radiotherapy on completion was delivered to 61% ($n = 30$). Regimens varied, but were generally methotrexate-based. Chemotherapy was discontinued prematurely in 80% ($n = 24$) due to progressive disease ($n = 12$), intolerable toxicity ($n = 7$) or death ($n = 4$). In all patients who progressed or did not tolerate chemotherapy, treatment was changed to immediate salvage radiotherapy; modal irradiation was 40 Gy. Radiotherapy alone was delivered to those not suitable for chemotherapy (18%, $n = 9$) and best supportive care to those with poor performance status (18%, $n = 9$). The overall median survival was 8 months. In those receiving single modality radiotherapy or chemotherapy, the median survival was 5 and 8 months, respectively. For those completing chemoradiotherapy in its entirety, 3 year survival was 100%; in groups receiving salvage radiotherapy despite progressive disease or chemotherapy toxicity, moderate survival was maintained with immediate radiotherapy with 3 year survival rates of 33 and 60%, respectively.

Conclusions: Although chemotherapy alone remains the optimal treatment of PCNSL, out with clinical trials only a minority of patients complete chemotherapy due to toxicity and disease progression; in such patients, immediate salvage radiotherapy provides an effective and safe alternative with maintenance of good outcomes.

Key words: Case series; chemotherapy intolerance; chemotherapy toxicity; lymphoma; PCNSL; radiotherapy

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin's lymphoma isolated to the nervous system (brain, leptomeninges, spinal cord or eyes) and representing about 3% of primary central nervous system malignancies, with a reported incidence of 2–3 per million population [1–3].

Over the last decade, treatment has been comprised of methotrexate-based combination chemotherapy followed by radiotherapy [4–7]. Radiotherapy is delivered as whole-brain irradiation and alone, results in a median survival of 11–18 months [8,9]; the addition of chemotherapy, with methotrexate being the chemotherapeutic agent of choice, yields survivals of over 30 months, although high doses are required to achieve adequate blood–brain barrier penetration [10,11]. In 2009, Ferreri *et al.* [12] carried out a randomised phase II trial and reported that the combination of high-dose cytarabine and high-dose methotrexate was superior to methotrexate alone. Whole-brain radiation was optional after initial chemotherapy. This phase II study set the gold standard for future trials [12]. Despite this, detailed management of PCNSL varies considerably, with clinical trials hindered by the rarity of the disease and cross-trial

Author for correspondence: R. Muirhead, Flat 2/2, 275 West Princes Street, Glasgow G4 9EE, UK. Tel: +44-7989-445591; Fax: +44-141-3017083.
E-mail address: rebeccamuirhead@hotmail.com (R. Muirhead).

0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.04.007

comparisons limited by heterogeneity. In order to standardise treatment, guidelines on assessment, management and outcome measures of PCNSL have been released by both the British Neuro-Oncology Society and the International PCNSL Collaborative Group [13,14].

Both methotrexate and radiotherapy, individually and in combination, have long been associated with neurotoxicity and cognitive dysfunction [15–17]. As a result of the potential morbidity of a combined approach, in the last few years there has been a shift in management away from immediate consolidation radiotherapy. Thiel *et al.* [5] undertook a prospective randomised trial to assess whether the addition of radiotherapy in patients who had responded to induction chemotherapy offered any overall survival benefit. The results showed no statistical difference in median overall survival between the two groups [10]. One of the randomisations within the current UK study IELSG-32 is between whole-brain radiotherapy and autologous stem cell transplant in those who have shown a complete response [18]. As a result, there has been a shift towards observing patients with a complete response after chemotherapy, reserving radiotherapy for younger patients who fail to respond to chemotherapy and for palliative and relapse settings [12,14].

In view of the recent suggested changes in management, our aim was to collate a single-centre case series of consecutive PCNSL patients in order to assess local demographics, treatment and survival outcomes; and to evaluate the role of radiotherapy in a routine clinical setting, out with the stringent selection criteria of clinical trials.

Materials and Methods

All patients who had undergone surgical intervention for a central nervous system lymphoma for the 10 year period between January 2001 and December 2010 were identified using the reporting database of the Department of Neuropathology. Cases were excluded if they were transferred to another centre for treatment postoperatively, if they had systemic lymphoma at staging or if they developed systemic lymphoma within 6 months of diagnosis. In all cases included in this review, the original pathology sections were retrieved and assessed by two independent pathologists to confirm the diagnosis. Microsoft Office Excel 2007 and the statistical program **R** 2.15.2, run on Windows, were used for data analysis; survival curves were generated by the Kaplan–Meier method.

Case notes and electronic systems were reviewed retrospectively to ascertain details of each case. Information gathered included performance status at presentation, presenting symptoms and any associated risk factors. In addition, detail on routine staging investigations was recorded, namely magnetic resonance imaging brain and spine, fundoscopy, cerebrospinal fluid analysis, computed tomography to rule out systemic lymphoma and bone marrow examination. Although some centres also recommend testicular ultrasound, this was not our standard practise.

Therapeutic data collected included the surgical procedure carried out, the subsequent intended treatment and any deviation from this. Overall survival was calculated from the date of initial surgical intervention to the date of death, or censored at the time of data collection (5 October 2011). Any neurological deficit attested to in clinic letters during the follow-up period was recorded.

Results

Patient Demographics

Sixty patients were initially identified with a lymphoma diagnosis, of which 11 were excluded for the following reasons: postoperative care being delivered out with the region ($n = 3$); having systemic disease at presentation ($n = 4$); developing systemic disease within 6 months of diagnosis ($n = 4$). Thus, eight (13.3%) patients initially presumed to have PCNSL had occult systemic lymphoma identified either through staging investigations at presentation or within 6 months of diagnosis. The sites of occult systemic disease were paravertebral mass ($n = 2$); abdominal nodes ($n = 2$); sphenoid sinus ($n = 1$), testicle ($n = 1$) and breast ($n = 2$).

Of the eligible 49 patients, the median age at presentation was 61 years (range 42–81 years), with 58% of good performance status (World Health Organization 0 or 1). Eighteen per cent of patients had recognised risk factors, namely: immunosuppressant treatment for autoimmune liver disease, myasthenia gravis and rheumatoid arthritis; two patients had pre-existing low-grade lymphoma, one previously treated with chlorambucil and fludarabine, the other with chlorambucil only; previous adjuvant chemotherapy for breast carcinoma; and HIV ($n = 2$). In both patients with chronic lymphocytic lymphoma (CLL), PCNLS was considered a new primary tumour with no documentation regarding possible transformed disease. Patient demographics are shown in Table 1.

Staging Investigations

Documentation or electronic confirmation of staging investigations was inconsistent. Only positive results have been reported, as negative results were not thoroughly documented. From all 49 patients, three patients (6%) were found to have ocular involvement; one patient (2%) had positive cerebrospinal fluid; two patients (4%) had disease identified in their spine on imaging (Table 1). There were no positive bone marrow aspirates.

Pathology

One patient had a low-grade T-cell lymphoma, the remainder were diffuse large B-cell lymphoma.

Treatment

Thirty-five patients (71%) underwent a biopsy as the surgical procedure, eight (16%) a formal debulking procedure,