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Original Article

Analysis of Radiotherapy in 1054 Patients with Primary Central Nervous System Lymphoma Treated from 1985 to 2009

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Abstract

Aims: Data on primary central nervous system lymphoma that had been collected through surveys for four consecutive periods between 1985 and 2009 were analysed to evaluate outcomes according to treatment.
Materials and methods: All had histologically proven disease and had received radiotherapy. No patients had AIDS. Among 1054 patients, 696 died and 358 were alive or lost to follow-up. The median follow-up period for surviving patients was 37 months.
Results: For all patients, the median survival time was 24 months; the 5 year survival rate was 25.8%. Patients treated with methotrexate-based chemotherapy and radiation had a higher 5 year survival rate (43%) than those treated with radiation alone (14%) and those treated with non-methotrexate chemotherapy plus radiation (20%), but differences in relapse-free survival were smaller among the three groups. The 5 year survival rate was 25% for patients treated with whole-brain irradiation and 29% for patients treated with partial-brain irradiation ($P = 0.80$). Patients receiving a total dose of 40–49.9 Gy had a higher 5 year survival rate (32%) than those receiving other doses (21–25%, $P = 0.0004$) and patients receiving a whole-brain dose of 30–39.9 Gy had a higher 5 year survival rate (32%) than those receiving ≥40 Gy (13–22%, $P < 0.0005$). Patients receiving methotrexate-based chemotherapy and partial-brain radiotherapy (≥30 Gy) had a 5 year survival rate of 49%.
Conclusions: The optimal total and whole-brain doses may be in the range of 40–49.9 and <40 Gy, respectively, especially in combination with chemotherapy. Patients receiving partial-brain irradiation had a prognosis similar to that of those receiving whole-brain irradiation. With methotrexate-based chemotherapy, partial-brain radiotherapy may be worth considering for non-elderly patients with a single tumour.

Key words: Brain neoplasm; central nervous system; chemotherapy; lymphoma; neurocognitive function; radiotherapy

Introduction

Treatment strategies for primary central nervous system lymphoma (PCNSL) are gradually changing. Previously, radiotherapy played the most important role. PCNSL responds relatively quickly to radiotherapy, and the complete disappearance of enhancing tumour masses is frequently observed after radiotherapy. However, local recurrence in the irradiated volume as well as remote central nervous system (CNS) recurrence outside the treatment volume are frequently observed, and so the reported outcome of patients treated by radiation alone was relatively poor [1–3]. In addition, a proportion of PCNSL patients treated with radiotherapy develop neurocognitive dysfunction and/or show a reduced performance status [3–6]. These observations led neuro-oncologists to use systemic chemotherapy after the late 1970s.

The combination of radiation and standard chemotherapy regimens used for systemic lymphoma was attempted, but it did not yield markedly favourable results [7–11]. Subsequently, high-dose methotrexate (MTX)-containing regimens proved to be effective [12–16]. As long-term remission is often achieved with such chemotherapy, a recent trend has been to treat PCNSL with MTX-based chemotherapy first, and reserve radiotherapy for recurrence, especially in elderly patients [17,18]. However, higher

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rates of progression-free survival were noted with the use of radiation in the first-line treatment in a randomised European trial comparing chemotherapy with chemo-radiotherapy [19]. Therefore, the optimal treatment for PCNSL still remains to be determined; the role of radiotherapy should be clarified, especially in non-elderly patients, and optimal forms of radiotherapy, with regard to the treatment volume and radiation dose, should be investigated.

Until very recently, radiotherapy was used in the first-line treatment of PCNSL in Japan, either alone or in combination with chemotherapy, regardless of the patient's age. To evaluate the changes in patient, tumour and treatment characteristics in PCNSL, our group has conducted surveys of Japanese PCNSL patients treated in radiotherapy departments. Data have been collected on patients treated during the four periods of 1985–1994, 1995–1999, 2000–2004 and 2005–2009. Results of respective surveys have been published [20–24]. Through the surveys, data on a total of 1054 patients with histologically proven PCNSL have been accumulated. The purpose of this study was to evaluate the treatment outcome of these patients according to the treatment modality and radiation methods.

Materials and Methods

This study was approved by the institutional review board of Nagoya City University (approval number 506). Submission of the data was approved by institutional review boards at each institution. Informed consent for the use of data for research purposes was obtained from patients. Methods for the collection of data used for this analysis have been described in detail previously [20–24]. The surveys were carried out by the Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group (JLSG), the Chubu Radiation Oncology Group (CROG) and the Japan Radiation Oncology Study Group. Subjects of all surveys were patients with histologically proven PCNSL who received radiotherapy. Patients who were suspected of having secondary CNS lymphoma were excluded. Those who did not complete the planned radiotherapy were included.

Data on 466 patients who started radiotherapy between 1985 and 1994 were collected from 62 institutions. For the period of 1995–1999, 142 patients were accumulated from 25 institutions with the two surveys conducted by the JLSG and CROG. For the period of 2000–2004, 131 patients were accumulated from 17 institutions by JLSG and CROG. Data on 315 patients treated between 2005 and 2009 were collected from 20 institutions. Combining the data, 1054 patients were therefore the subjects of this study. Table 1 summarises the patient and tumour characteristics and treatment details. Among the 1054 patients, 449 (42.6%) and 267 (25.3%) were ≥65 and 70 years old, respectively. Among the patients, 696 died and 358 were alive or lost to follow-up. The median follow-up period for surviving patients was 37 months.

The HIV titre was negative in all patients tested, and no other patients were considered to have AIDS-related PCNSL. The extent of surgical resection had not been ascertained in the survey for 1985–1994, but it was included in the subsequent surveys. Other items were common to all surveys. The performance status before radiotherapy scored with the World Health Organization criteria was used in this analysis. The neurocognitive status of the patients during follow-up periods was asked; all investigators judged neurocognitive function from clinical and neurological symptoms, and a standard battery of neurocognitive tests was not routinely used. Responses to induction chemotherapy and salvage treatment at recurrence were not requested. As expected in such a survey, a number of items were not answered by the investigators.

Although techniques of radiotherapy were not asked, it was confirmed in the group meetings that whole-brain irradiation was delivered using parallel opposing fields,

Table 1
Patient and tumour characteristics and treatment details

	Characteristics	Number (%)
Gender	Male/female	630(60)/424(40)
Age (years)	Median, range	62, 5–93
Performance status	0/1/2/3/4/unknown	76(8.5)/313(35)/248(28)/215(24)/38(4.3)/164
Lactate dehydrogenase	Normal/high/unknown	530(66)/276(34)/248
Phenotype	B/T/unknown	735 (95)/36(4.7)/283
Tumour number	1/≥2/unknown	580(55)/466(45)/8
Tumour size (cm) at diagnosis	Mean ± SD	3.7 ± 1.4
Surgery	Biopsy/resection/unknown	395(67)/193(33)/466
Brain irradiation field	Whole brain/partial brain	969(92)/85(8.1)
Spinal irradiation	+/−/unknown	54(5.3)/967(95)/33
Total dose (Gy)	Mean ± SD	47.8 ± 10.2
Whole-brain dose (Gy)	Mean ± SD	34.5 ± 12.1
Systemic chemotherapy	+/−/unknown	643(64)/365(36)/46
Methotrexate-based regimen	+/−	351(55)/292(45)
Intrathecal chemotherapy	+/−/unknown	98(9.9)/896(90)/60

Figures in parentheses indicate percentage of patients, excluding those with unknown data.