Primary central nervous system lymphoma in Japan: Changes in clinical features, treatment, and prognosis during 1985–2004

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We have conducted nationwide surveys of primary central nervous system lymphoma (PCNSL) treated since 1985. In the present study, we newly collected data between 2000 and 2004 and investigated changes in clinical features and outcome over time. A total of 739 patients with histologically proven PCNSL undergoing radiotherapy were analyzed. Seventeen institutions were surveyed, and data on 131 patients were collected. These data were compared with updated data that were previously obtained for 466 patients treated during 1985–1994 and 142 patients treated during 1995–1999. Recent trends toward decrease in male/female ratio, increase in aged patients, and increase in patients with multiple lesions were seen. Regarding treatment, decrease in attempts at surgical tumor removal and increases in use of systemic chemotherapy and methotrexate (MTX)–containing regimens were observed. The median survival time was 18, 29, and 24 months for patients seen during 1985–1994, 1995–1999, and 2000–2004, respectively, and the respective 5-year survival rates were 15%, 30%, and 30%. In groups seen during 1995–1999 and during 2000–2004, patients who received systemic or MTX-containing chemotherapy had better prognosis than those who did not. Multivariate analysis of all patients seen during 1985–2004 suggested the usefulness of MTX-containing chemotherapy as well as the importance of age, lactate dehydrogenase level, and tumor multiplicity as prognostic factors. Thus, this study revealed several notable changes in clinical features of PCNSL patients. The prognosis improved during the last 10 years. Advantage of radiation plus chemotherapy, especially MTX-containing chemotherapy, over radiation alone was suggested. *Neuro-Oncology 10, 560–568, 2008 (Posted to Neuro-Oncology [serial online], Doc. D07-00151, June 17, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-028)*

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Primary central nervous system lymphoma (PCNSL) is becoming one of the most important tumors in neuro-oncology. It was rare previously but has increased during the last two decades.[1] With the increase in incidence, clinical features, diagnostic procedures, and physicians' recognition and treatment policy for the disease seemed to have changed considerably. With widespread recognition of the disease and improvement

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of diagnostic modalities, the disease may be diagnosed more readily than before. Treatment policy appears to have also changed considerably with respect to the role of surgical resection and the use of chemotherapy and radiotherapy.[2,3] Unfortunately, however, randomized studies on treatment have been scarce, and uncertainties still remain regarding the efficacy of chemotherapy, appropriate chemotherapy regimens, and appropriate use of radiation therapy.[2–5] Many studies using high-dose methotrexate (MTX)–containing chemotherapy have reported favorable treatment outcome,[6–17] whereas other studies have not necessarily supported the results.[1,18–20] Also, high toxicity of an MTX-containing regimen has been reported.[21]

In view of the relative rarity but importance of the disease, we have conducted nationwide studies on it. The purposes of the studies were to analyze clinical features and treatment characteristics and evaluate patient outcomes. The first study was conducted for the patients seen between 1985 and 1994 by Hayabuchi et al.[22] The next studies were conducted for those seen between 1995 and 1999 by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) Lymphoma Study Group (JLSG) and the Chubu Radiation Oncology Group (CROG) separately.[23,24] Recently, we collected new data on 131 patients seen between 2000 and 2004. In this study, we analyzed all these patients from the previous and recent surveys. Follow-up data were updated as far as possible also for the patients reported in the previous studies.

Materials and Methods

Subjects of all of the surveys were patients with histologically proven PCNSL who received radiation therapy. Patients who were suspected of having secondary CNS lymphoma were excluded at each institution. Those who did not complete planned radiotherapy were included. Clinical characteristics, treatment, and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 466 patients had been collected from 62 institutions for patients seen between 1985 and 1994. For the period 1995–1999, a total of 142 patients were collected from 25 institutions with the two surveys conducted by JLSG and CROG; the results were published separately,[23,24] but in the present study, the data from the two surveys were combined. Recently, data on 131 patients seen between 2000 and 2004 were collected from 17 institutions belonging to JLSG or CROG. Submission of the data was approved at each institution. Thus, a total of 739 patients with histologically proven PCNSL were the subject of this study. Results for HIV titer were negative in all patients who had had the examination, and no other patients were considered to have AIDS-related PCNSL. For the most recent survey, 76% of the institutions had also been surveyed for the period 1995–1999, and 68% of the institutions surveyed for the period 1995–1999 had been included in the survey for the period 1985–1994.

Extent of surgical resection had not been asked in the survey for 1985–1994, but it was done in the subsequent surveys. Other items were common to all surveys, but because of the nature of the survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, but for convenience of analysis, they were categorized as high-dose (>1 g/m^2) MTX-containing regimens or other regimens. Details of other chemotherapy regimens used during 1985–1999 were described previously;[22–24] 58% of non-MTX-containing regimens were cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or similar regimens.[25] In the most recent period (2000–2004), 68% of non-MTX-containing regimens were CHOP or CHOP-based regimens and 18% were a dexamethasone-etoposide-ifosfamide-carboplatin (DeVIC) regimen. The remaining 14% were miscellaneous ones.

Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test or *t*-test. Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups, and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using computer programs, StatView Version 5 (SAS Institute Inc., Cary, NC, USA) and HALWIN (Gendaisuugakusha, Kyoto, Japan).

Results

Table 1 shows patient and tumor characteristics in the three groups treated during the three periods. Several remarkable changes were noted. There were more female patients in the period 2000–2004 than in the preceding period; the male/female ratio was near unity in the most recent series. Also, the median patient age was higher in the period 2000–2004 than in the preceding period. The proportion of patients with multiple tumors increased to 55% in the most recent series, whereas it was 38% and 40% in the previous series. Other patient and tumor characteristics did not differ significantly between the two pairs of groups.

Table 2 shows changes in treatment. Radiotherapy characteristics were similar in all three groups. Nearly 90% or more of the patients were treated with whole-brain irradiation with or without focal boost, and the mean total and whole-brain doses were 47–49 Gy and 36–38 Gy, respectively. Whole-spinal irradiation was employed in less than 10% of the patients throughout the three periods. However, there were steady increases in the proportion of patients undergoing systemic chemotherapy. Particularly, MTX-containing regimens have been increasingly used (in 72% of patients undergoing chemotherapy in the most recent period).

Figure 1 shows overall survival curves for the three groups. Patients treated between 1995 and 1999 and

Table 1. Patient and tumor characteristics

Characteristic		Period (Year) 1985–1994	1995–1999	2000–2004	*p**
Gender	Male (%)	276/466 (59)	96/142 (68)	67/131 (51)	0.077
					0.0066
Age (years)	Median (range)	60 (5–86)	59 (15–93)	65 (30–90)	0.49
					0.017
Performance status	3, 4 (%)	209/438 (48)	55/138 (40)	37/128 (29)	0.12
					0.071
Lactate dehydrogenase	High (%)	103/267 (39)	42/113 (37)	32/121 (26)	0.82
					0.092
B symptom	Yes (%)	33/418 (7.9)	13/127 (10)	6/122 (4.9)	0.47
					0.15
Phenotype	T cell (%)	20/234 (8.5)	6/115 (5.2)	2/120 (1.7)	0.29
					0.16
Tumor number	Multiple (%)	175/460 (38)	56/140 (40)	72/131 (55)	0.69
					0.015
Tumor size (cm) at diagnosis	Mean ± SD	3.8 ± 1.4	3.8 ± 1.6	3.8 ± 1.2	0.71
					0.96
CSF dissemination	Yes (%)	56/422 (13)	23/122 (19)	20/126 (16)	0.14
					0.62

Abbreviation: CSF, cerebrospinal fluid.

*First and second *p* values are for comparison between 1985–1994 and 1995–1999 data and between 1995–1999 and 2000–2004 data, respectively. B symptom: fever (>38°C for 3 consecutive days), weight loss (>10% in 6 months), and/or drenching night sweats.

Table 2. Treatment characteristics

Characteristic		Period (Year) 1985–1994	1995–1999	2000–2004	*p**
Surgery	Biopsy (%)	—	71/142 (50)	83/131 (63)	—
					0.028
Radiotherapy course	Not completed	25/466 (5.4)	6/142 (4.2)	5/131 (3.8)	0.67
					1.0
Brain radiation field	Partial brain (%)	37/466 (7.9)	12/142 (8.5)	15/131 (11)	0.86
					0.42
Spinal radiation	Yes (%)	37/445 (8.3)	8/142 (5.6)	4/131 (3.1)	0.37
					0.38
Total dose (Gy)	Mean ± SD	48.4 ± 11.2	48.7 ± 10.8	47.0 ± 9.0	0.78
					0.20
Whole-brain dose (Gy)	Mean ± SD	35.6 ± 13.7	37.5 ± 8.0	36.4 ± 6.0	0.082
					0.43
I.v. chemotherapy	Yes (%)	212/420 (50)	87/142 (61)	99/131 (76)	0.032
					0.013
MTX-containing regimen	Yes (%)	47/212 (22)	27/87 (31)	71/99 (72)	0.14
					<0.0001
I.t. chemotherapy	Yes (%)	42/415 (10)	16/142 (11)	8/131 (6.1)	0.75
					0.14

Abbreviations: i.v., intravenous; MTX, methotrexate; i.t., intrathecal.

*First and second *p* values are for comparison between 1985–1994 and 1995–1999 data and between 1995–1999 and 2000–2004 data, respectively.

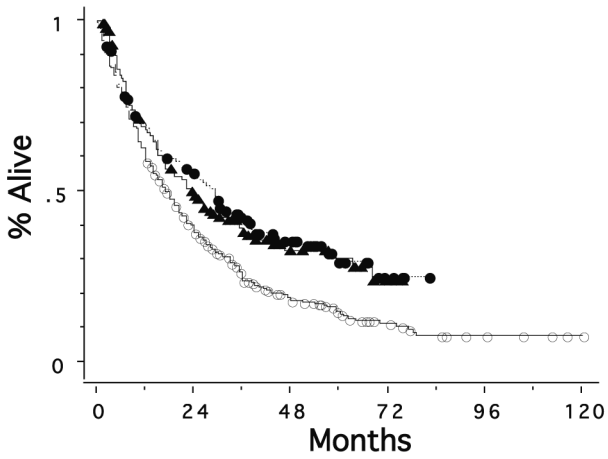

Fig. 1. Survival curves for patients with primary CNS lymphoma seen in 1985–1994 (○, *n* = 466), in 1995–1999 (●, *n* = 142), and in 2000–2004 (▲, *n* = 131). The second and third groups had significantly better survival rates than the first group ($p = 0.0004$ and 0.0033, respectively).

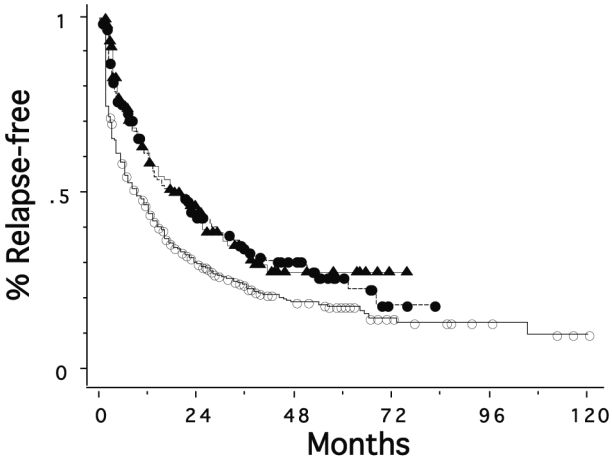

Fig. 2. Relapse-free survival curves for patients with primary CNS lymphoma seen in 1985–1994 (○, *n* = 408), in 1995–1999 (●, *n* = 137), and in 2000–2004 (▲, n = 127). The second and third groups had significantly better relapse-free survival rates than the first group ($p = 0.0020$ and 0.0010, respectively).

those treated between 2000 and 2004 had significantly better survival rates than those seen between 1985 and 1994 ($p = 0.0004$ and 0.0033, respectively); median survival time increased from 18 months to 29 and 24 months, respectively. The 5-year survival was 15%, 30%, and 30% for the periods 1985–1994, 1995–1999, and 2000–2004, respectively. Figure 2 shows relapse-free survival curves for the patients with known data on recurrence in the three periods. Relapse-free survival of the patients was also better in the more recent two periods than in the period 1985–1994 ($p = 0.0020$ and 0.0010, respectively). The median time to recurrence was 9, 18, and 20 months, and the 5-year relapse-free survival was 18%, 26%, and 28% for the periods 1985–1994, 1995–1999, and 2000–2004, respectively.

Table 3 summarizes survival data in the three groups according to patient- and tumor-related potential prognostic factors. In all the study periods, patients with age <60 years, WHO performance status (PS) of 0–2, or normal lactate dehydrogenase (LDH) level had significantly higher survival rates. Patients without B symptom or with a single tumor had better prognoses than those with B symptom or with multiple tumors, respectively, in the groups treated between 1985 and 1994 and between

Table 3. Survival data according to patient or tumor-related potential prognostic factors

		1985–1994				1995–1999				2000–2004			
Prognostic Factor		***n***	**MST (Months)**	**5-YSR (%)**	***p***	***n***	**MST (Months)**	**5-YSR (%)**	***p***	***n***	**MST (Months)**	**5-YSR (%)**	***p***
Gender	Male	276	17	17	0.92	96	30	31	0.23	67	17	29	0.40
	Female	190	20	13		46	23	27		64	26.5	32	
Age	<60	216	22	27	<0.0001	75	39	40	0.0011	44	68	53	0.0001
	≥60	250	14	5.2		67	16	17		87	17	18	
Performance status	0–2	229	24	20	<0.0001	83	37	32	0.0024	91	26.5	40	0.0010
	3, 4	209	12	10		55	12	27		37	13	5.8	
B symptom	Yes	33	10	0	0.030	13	13	15	0.0093	6	19	21	0.72
	No	385	18	17		116	35	34		116	25	36	
Lactate dehydrogenase	Normal	164	22	26	0.0007	71	38	36	0.016	89	35	37	0.0024
	High	103	14	5.7		42	16	25		32	13	15	
Tumor number	Single	285	22	18	0.0012	84	39	36	0.026	59	24	38	0.72
	Multiple	175	12	11		56	23	21		72	22	24	
Tumor size (cm)*	≤4 cm	204	19	14	0.84	69	29	29	0.38	61	26.5	31	0.21
	>4 cm	189	17	19		63	37	34		69	18.5	31	
CSF dissemination	Yes	56	10	14	0.039	23	50	33	0.50	20	32	37	0.74
	No	366	19	16		99	29	32		106	24.5	31	

Abbreviations: MST, median survival time; 5-YSR, 5-year survival rate; CSF, cerebrospinal fluid.

*Maximum tumor diameter at diagnosis.

Table 4. Survival data according to treatment-related factors

Prognostic Factor		1985–1994				1995–1999				2000–2004			
		n	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*
Surgical resection	Extensive	—	—	—	—	32	28	32	0.99	21	23	27	0.45
	Nonextensive	—	—	—		104	29	29		105	24	29	
Radiation field	Whole brain	405	19	15	0.72	126	29	29	0.72	111	22	26	0.17
	Partial brain	34	16	17		10	35	38		15	37	47	
Spinal radiation	Yes	36	24	19	0.16	8	—	50*	0.76	3	—	67	0.23
	No	384	18	15		128	29	29		123	23	27	
Total dose (Gy)	<50	134	18	17	0.97	35	30	34	0.79	45	26	35	0.71
	≥50	305	8	16		101	29	29		81	23	27	
Whole-brain dose (Gy)	<40	156	18	18	0.43	54	30	32	0.68	54	36	36	0.048
	≥40	283	18	14		82	29	27		72	18.5	22	
I.v. chemotherapy	Yes	202	20	16	0.30	85	39	39	<0.0001	95	26.5	39	0.0006
	No	192	16	17		51	14	14		31	14.5	7.5	
MTX-containing chemotherapy	Yes	46	20	19	0.49	25	NR	54	0.0039	67	29	47	0.0016
	No	348	18	16		111	25	24		59	16.5	12	
I.t. chemotherapy	Yes	39	16	20	0.78	15	—	58	0.13	7	24	43	0.52
	No	350	19	16		114	27	26		119	23	27	

Abbreviations: MST, median survival time; 5-YSR, 5-year survival rate; i.v., intravenous; MTX, methotrexate; NR, not reached; i.t., intrathecal.

*4-year survival rate.

1995 and 1999, but the trends were not seen in the most recent series.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (receiving less than 30 Gy) and died soon were excluded. Table 4 shows survival data according to the treatment-related factors; no factors were found to be associated with improved prognosis throughout all three periods. In groups treated during 1995–1999 and during 2000–2004, patients receiving systemic chemotherapy had better survival rates than those treated with radiation alone, and those who received MTX-containing chemotherapy had better prognosis than those who did not. However, these phenomena were not observed in patients treated during the preceding decade. In the most recent series, patients receiving whole-brain doses less than 40 Gy (including those treated with partial-brain fields alone) did better than those receiving higher doses. No other treatment-related factors were found to be associated with prognosis in univariate analysis. Figure 3 shows survival curves for patients receiving or not receiving chemotherapy during the three periods. In the two more recent periods, patients receiving chemotherapy had better survival rates than those receiving radiation alone ($p < 0.0001$ and $= 0.0006$, respectively). Figure 4 shows survival curves according to the chemotherapy regimen (with or without high-dose MTX). Although there were no differences by the use of MTX, there was a trend toward improved survival in patients undergoing high-dose MTX-containing chemotherapy during the period 1995–1999 ($p = 0.060$).

To further analyze the effect of chemotherapy, patients seen during 1995–1999 and 2000–2004 were combined and those with ages >70 years and PS 3 or 4 were excluded in addition to those receiving radiation doses of less than 30 Gy, because these patients are often not indicated for intensive systemic chemotherapy. Figure 5 shows survival curves for patients with or without chemotherapy and according to the chemotherapy regimens. In this selected group of patients, those receiving systemic chemotherapy had markedly better survival rates than those receiving radiation alone ($p = 0.0004$), and those receiving MTX-containing chemotherapy had better survival than those receiving other regimens of chemotherapy ($p = 0.049$). However, in patients seen during 1995–2004 with ages >70 years and/or PS 3 or 4 who received radiation doses of 30 Gy or higher, those receiving systemic chemotherapy had better survival rates than those receiving radiation alone (median survival: 19.5 vs. 8.5 months; 5-year survival: 24% vs. 4.9%; $p = 0.010$), whereas those receiving MTX-containing chemotherapy and those receiving other regimens had similar prognosis (median survival: 22 vs. 16.5 months; 5-year survival: 32% vs. 20%; $p = 0.57$).

Multivariate analyses were carried out for potential prognostic factors that were significant in univariate analyses (Table 5). Analyses were carried out for patients seen during 1995–1999 and 2000–2004 and for all the patients combined. Multivariate analysis for patients during 1985–1994 was carried out previously.[22] In the patient group seen between 1995 and 1999, lower age, better PS, absence of B symptom, and single tumor num-

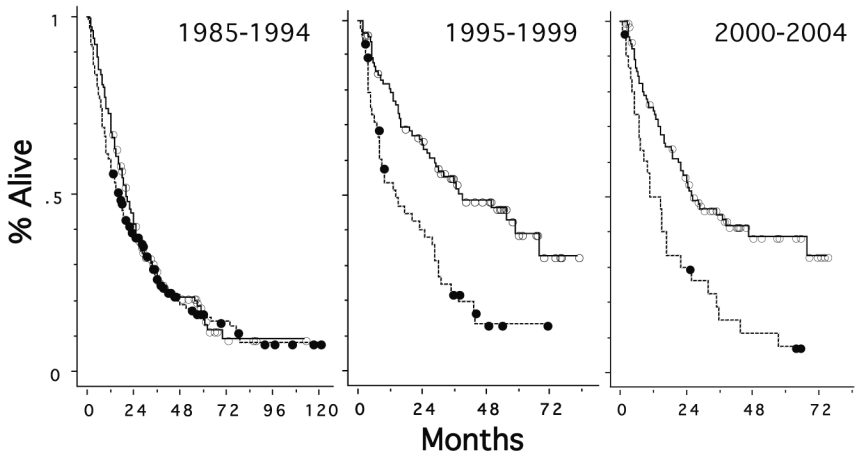

Fig. 3. Survival curves for patients with or without systemic chemotherapy. ○: chemotherapy (+) (n = 202, 85, and 95 for the three periods, respectively); ●: chemotherapy (–) (n = 192, 51, and 31 for the three periods, respectively). The difference was significant in the second and third groups (p = <0.0001 and 0.0006, respectively).

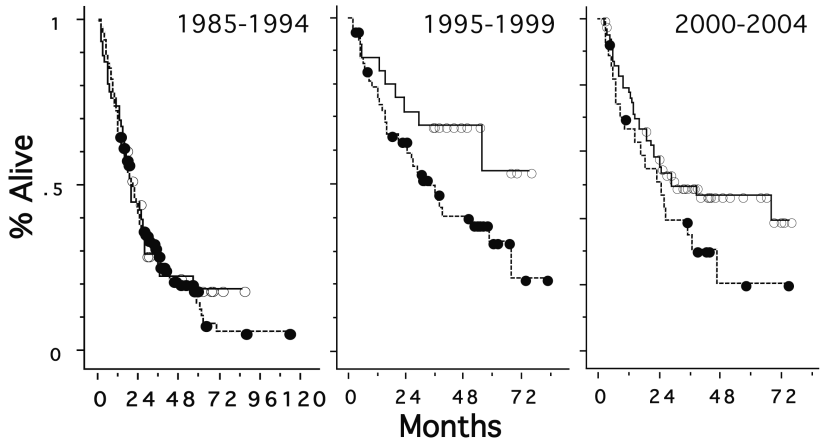

Fig. 4. Survival curves according to chemotherapy regimens. ○: high-dose methotrexate-containing regimens (n = 46, 25, and 67 for the three periods, respectively); ●: other regimens (n = 156, 60, and 28 for the three periods, respectively). The p values were 0.66, 0.060, and 0.13, respectively, for the three periods.

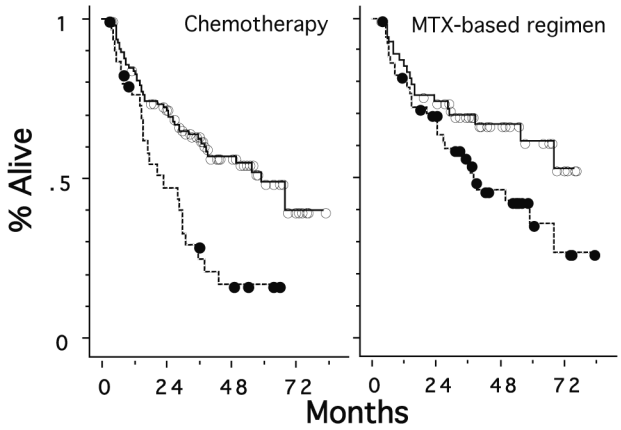

Fig. 5. Survival curves for patients with or without chemotherapy and according to chemotherapy regimens in patients seen between 1995 and 2004 with WHO performance status of 0–2 and ages <70 years receiving radiation doses of 30 Gy or higher. Left panel, ○: chemotherapy (+) (n = 108); ●: chemotherapy (–) (n = 31); p = 0.0004. Right panel, ○: high-dose methotrexate-containing regimens (n = 56); ●: other regimens (n = 52); p = 0.049.

Table 5. Multivariate analyses for potential prognostic factors that were significant in univariate analysis

	1995–1999 (*n* = 98)		2000–2004 (*n* = 114)		1985–2004 (*n* = 413)	
Factor	***p***	**Relative Risk**	***p***	**Relative Risk**	***p***	**Relative Risk**
Age (<60 vs. ≥60 years)	0.0028	0.40 (0.22–0.73)*	0.0010	0.36 (0.20–0.66)	<0.0001	0.53 (0.41–0.68)
Performance status (0–2 vs. 3, 4)	0.016	0.47 (0.26–0.87)	0.34	0.78 (0.46–1.31)	0.12	0.82 (0.64–1.06)
B symptom (– vs. +)	0.010	0.33 (0.14–0.77)	—	—	0.18	0.75 (0.49–1.15)
Lactate dehydrogenase (normal vs. high)	0.24	0.71 (0.40–1.26)	0.020	0.55 (0.33–0.91)	0.0001	0.61 (0.47–0.78)
Tumor number (single vs. multiple)	0.0025	0.41 (0.23–0.73)	—	—	0.017	0.74 (0.57–0.95)
CSF dissemination (– vs. +)	—	—	—	—	0.82	1.04 (0.72–1.51)
Whole-brain dose (<40 vs. ≥40 Gy)	—	—	0.0019	0.42 (0.24–0.72)	0.31	0.88 (0.68–1.13)
I.v. chemotherapy (– vs. +)	0.87	1.05 (0.56–1.99)	0.088	1.81 (0.92–3.56)	0.69	1.06 (0.81–1.38)
MTX-containing chemotherapy (– vs. +)	0.082	2.08 (0.91–4.74)	0.52	1.23 (0.66–2.30)	0.0014	1.82 (1.26–2.63)

Abbreviation: CSF, cerebrospinal fluid; i.v., intravenous; MTX, methotrexate.

*Figures in parentheses are 95% confidence intervals.

ber were associated with better survival. In the group treated during 2000–2004, lower age, normal LDH level, and lower whole-brain dose were associated with better survival. When all patients were combined, age, tumor number, LDH level, and use of MTX-containing chemotherapy were significant factors.

Discussion

PCNSL has been increasing and is becoming an important tumor in neuro-oncology. So, it was considered meaningful to survey data on PCNSL in our country every 5 years. Various changes have been noted with regard to patient and tumor characteristics. The reason for the decrease of the proportion of male patients to nearly 50% observed in this study is unknown, and the phenomenon is in contrast to that observed in other studies showing male preponderance.[1,26] Further studies will clarify whether this trend is a universal one. The increase of aged patients may be due to recent better recognition of the disease; previously, aged patients might have remained undiagnosed, but with the recent establishment of managing PCNSL, the proportion of aged patients undergoing biopsy appeared to have increased. The recent increase in the incidence of multiple tumors is striking; it was as high as 55% in the most recent period, whereas it was between 30% and 40% in the two previous periods as well as in most previous reports.[7,21,26,27] Probably, improvement in imaging modalities and techniques, including more frequent use of MRI, has contributed to the improved detection of small tumors.

Regarding treatment, attempts at resection of tumors have decreased, because it is now clear that surgical resection does not contribute to improved prognosis.[3] This was also suggested in the present study. No major changes appeared to have occurred regarding radiotherapy. Shibamoto et al.[28] suggested the possible use of partial-brain radiation for a solitary lesion, but the idea has not yet spread nationwide. To reduce radiation doses by using chemotherapy has not become popular in our country. Increased use of systemic chemotherapy, especially MTX-based regimens, appears to be a worldwide trend, and it was confirmed in the present study.

Prognosis of PCNSL patients has certainly improved during the last decade. The 5-year survival was 30% in two periods: 1995–1999 and 2000–2004. However, further improvement was not observed in the latter period as compared with the former period, despite the fact that more patients underwent MTX-containing chemotherapy. One reason for this observation may be the higher patient age in the newest period (median: 65 vs. 59 years). In addition, prognosis of patients undergoing MTX-containing chemotherapy appears to be poorer in the newest period than in the preceding period, suggesting that some patients who were not necessarily expected to benefit from MTX-containing chemotherapy were treated with the chemotherapy. Furthermore, patients who did not receive MTX-containing chemotherapy in the most recent period had poorer prognosis. This would suggest that many patients regarded as ineligible for MTX-containing chemotherapy were not in favorable conditions and had poor prognosis. As a result, the increase of patients undergoing MTX-containing chemotherapy in the most recent period did not lead to improved survival when all patients were analyzed.

Age, PS, and tumor multiplicity are well-known prognostic factors for PCNSL,[22,23,27,29] and high LDH level and presence of B symptom or cerebrospinal fluid dissemination may also adversely affect prognosis.[19,22,26,30] The present study with a large number of patients seen between 1985 and 2004 suggested that age and LDH level are the most important prognostic factors followed by tumor number. However, tumor multiplicity was not associated with prognosis in the most recent series; the increase in patients with multiple tumors might be a reason for this discrepancy.

Chemotherapy is being increasingly used in the treatment of PCNSL, as is some advocate deferred radiation therapy in elderly patients.[2,16] Since the questionnaires were sent to radiation oncologists in the present study, all patients had received radiation. To our knowledge, however, very few patients are treated by chemotherapy alone in Japan, and results of the present study appear

to represent the status of treatment for PCNSL in our country. The prognosis of the patients did not differ significantly by the radiation field and total dose. Partial-brain radiation was not associated with decreased survival. Moreover, patients receiving whole-brain doses lower than 40 Gy had better survival than those receiving higher doses; those treated with partial-brain fields are included in the former group. Reni et al.[31] reported that whole-brain doses of 40 Gy or higher were associated with better prognosis, but later the same group found that they did not seem to improve prognosis.[11] The result of the present study would suggest that the whole-brain dose may not be important, and it is not contradictory to the proposal made by Shibamoto et al.[28] that partial-brain irradiation may be considered, especially in patients with a single lesion. With respect to the total radiation dose, Nelson et al.[32] did not find improved survival with the use of 60 Gy versus 50 Gy. Comparing two series of prospective studies, however, Bessel et al.[33] reported that a dose of 45 Gy appeared to be better than 30.6 Gy. In the present study, influence of total radiation dose was not clear when 50-Gy or higher doses were compared with lower doses. It seems difficult to draw any conclusions on optimal radiotherapy from retrospective studies; prospective studies should provide better answers.

There have been no randomized studies showing the benefit of chemotherapy as compared with radiation alone. A small randomized study failed to show the efficacy of CHOP chemotherapy when added to radiotherapy.[34] In the present study, the effect of chemotherapy, especially MTX-containing chemotherapy, was suggested in patients treated between 1995 and 1999 and between 2000 and 2004. The effect of MTX-containing chemotherapy was supported by multivariate analysis of patients seen during the 20-year period. In addition, patients receiving MTX-based regimens had better prognosis than those receiving other regimens in the group seen during 1995–2004 with ages <70 years and PS 0–2. The discrepancy from the results of the preceding decade may be due to improvement of chemotherapy. Although full details of chemotherapy regimens were not necessarily reported in many patients, especially in the oldest survey, MTX-containing regimens in the oldest period appeared to be less intensive than those used in the more recent periods. Another reason may be improvement of management of patients undergoing chemotherapy. Before 1994, MTX-containing chemotherapy was not popular in our country and neuro-oncologists might not have been familiar with performing it. Shibamoto et al.[30] recently reported an improved survival for patients undergoing radiotherapy alone in the 1990s with a 5-year survival of 18%, but in the present study, patients undergoing MTX-based chemotherapy and radiation had a 5-year survival of around 50% during 1995–2004. The lack of randomized trials regarding the effect of MTX-based regimens is a flaw in neuro-oncology, but at the present time, conducting a randomized study of radiation versus radiochemotherapy may not be possible in view of the results of the present as well as other phase II studies.

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