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Survival Improvement with Combined Radio-chemotherapy in the Primary Central Nervous System Lymphomas

The benefits of radio-chemotherapy in HIV-negative primary central nervous system (CNS) lymphomas were analyzed in 40 patients, who received radiotherapy to the brain or craniospinal axis with the total dose of 4460-5940 cGy to the primary tumor. Radiotherapy was followed by systemic chemotherapy, mainly with the cyclophospharmide, doxorubicin, vincristine and prednisolone (CHOP) regimen, in 16 of the patients. Follow-up ranged from four to 95 months with a median of 15 months. The relapse rate was 72.5%, and 83% of the relapses occurred within the radiation field. Median survival was 19 months and the two-year survival rate was 41%. Survival was significantly influenced by treatment method and radiation dose when measured by univariate analysis; median survival and the two-year survival rate was 29 months and 63% after radio-chemotherapy, while 13.5 month and 29% after radiotherapy alone (p= 0.027), and 22 months and 49% with doses of 50 Gy or more, but 12.5 months and 13% with doses less than 50 Gy (p=0.009). However, statistical significance was lost in multivariate analysis. These results might suggest the short-term efficacy of radio-chemotherapy, however, cautious observation is needed to confirm long-term effects.

Key Words: *Radiotherapy; Drug therapy; Lymphoma; Central nervous system*

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INTRODUCTION

Primary CNS lymphoma (PCNSL) is rare, however, its incidence is on the rise, not only in immunocompromised populations but also in immunocompetent populations (1). The reason for this increase is unknown. Extent of surgical resection is not correlated with survival in PCNSL and contrary to the excellent survival rate of non-Hodgkin's lymphoma outside the central nervous system, the results of radiation therapy or chemotherapy alone in PCNSL are very poor. Although many investigators have reported that survival improved after combining radiotherapy and chemotherapy, this was not proved by controlled randomized study (2-4). Our previous study showed that combined radio-chemotherapy resulted in better survival when compared to radiotherapy alone (5). We studied a greater number of cases in this study and we present more solid evidence supporting the effectiveness and superiority of combined radio-chemotherapy in PCNSL.

MATERIALS AND METHODS

Forty-four PCNSL patients received radiotherapy alone or combined radio-chemotherapy at the Department of Therapeutic Radiology, Seoul National University Hospital from March 1981 through December 1997. Four of the patients were excluded from this analysis because of incomplete radiotherapy dose of less than 40 Gy.

Ages ranged from 18 to 81 years old with a median of 50 years old. Sixty-nine percent of the patients were between 30 and 50 years old. Twenty-six patients (65%) were male and 14 (35%) were female. Sixty percent were in good host performance status by ECOG scale as shown in Table 1. But distribution of ECOG scale was more favorable in combined chemotherapy and radiation group than in radiation alone group. The most frequent symptom presented at diagnosis was headache (18/40). Others were paralytic symptoms such as paraplegia, hemiplegia, and paraparesis (15/40). Most of the symptoms were caused by increased intracranial pressure (Table 2).

At diagnostic work-up, computerized tomography (CT) or magnetic resonance imaging (MRI) (40/40), cerebrospinal fluid examination (CSF) (25/40), and whole spine MRI (18/40) were performed. Bone marrow aspiration and biopsy was performed for all patients to rule out systemic involvement of non-Hodgkin's lymphoma. Twenty-four patients (60%) had a single lesion on imaging study and the other 16 patients (40%) showed multiple lesions. Single lesions were located in the cerebral hemisphere

Table 1. Characteristics of the patients with primary central nervous system lymphoma treated with radiotherapy alone or with combined radio-chemotherapy

Characteristics	RT alone (%) (n=24)	RT+CTx (n=16)	*p*-value
Age			
<60	18 (75)	15 (94)	0.210
≥60	6 (25)	1 (6)	
Sex			
Male	15 (63)	11 (69)	0.685
Female	9 (37)	5 (31)	
Performance status (ECOG scale)			
0-2	11 (46)	13 (81)	0.047
3-4	13 (54)	3 (19)	
Surgery			
GTR	3 (13)	1 (6)	0.181
STR	7 (29)	2 (13)	
Stereotactic Bx	14 (58)	13 (81)	
CSF cytology			
Positive	1 (4)	2 (13)	0.692
Negative	10 (42)	12 (74)	
Not done	13 (54)	2 (13)	
No. of lesions			
Solitary	17 (71)	7 (44)	0.087
Multiple	7 (29)	9 (56)	
Histology			
DL	9 (37)	10 (63)	0.147
DPDL	3 (13)	1 (6)	
DM	3 (13)	2 (13)	
NOS	9 (37)	3 (18)	

GTR, gross total resection; STR, subtotal resection; Bx, biopsy; DL, diffuse large cell type; DPDL, diffuse poorly differentiated lymphocyte type; DM, diffuse mixed type; NOS, not otherwise specified non-Hodgkin's lymphoma; RT, radiation therapy; CTx, chemotherapy

(19/24), cerebellum (3/24), and brain stem (2/24). Malignant cells were found on CSF examination in three of 25 patients. Four of 18 patients showed spinal metastases on whole spine MRI, and two cases were also histologically confirmed on CSF examination.

All PCNSL was histologically confirmed. Surgical procedures were performed as follows: gross total removal (4), subtotal removal (9), and stereotactic biopsy (27). According to the Working Formulation, 19 patients were classified with diffuse large cell type, four with diffuse poorly differentiated lymphocytic type, five with diffuse mixed type, and 12 patients were not specifically classified.

Corticosteroids were administered to all patients as part of the initial management strategy.

Radiotherapy, comprised of brain or spinal irradiation, was delivered with Co-60 Gamma or 4 MV X-ray. In the brain, whole brain irradiation by parallel opposing technique was followed by a boost to the primary tumor site with adequate margins. Radiation doses to the whole brain ranged from 3,600 cGy to 5,040 cGy with a total dose of 4,460 cGy to 6,120 cGy (median of 5,400 cGy). The spinal field was irradiated with one posterior field. Five of eight patients received spinal irradiation prophylactically without evidence of disease, with dose of 1,500 cGy to 3,000 cGy. Doses to the other three patients with spinal seeding detected by MRI ranged from 4,500 cGy to 5,000 cGy.

Table 2. Presenting symptoms

Symptom	Number (%)*
Headache	18 (45)
Paralysis	15 (38)
Nausea / vomiting	10 (25)
Dysarthria	10 (25)
Altered mentality	7 (18)
Seizure	1 (3)
Facial palsy	1 (3)
Personality change	1 (3)
Other	3 (8)

* Twenty-five patients had multiple symptoms

Chemotherapy was administered to 16 patients. There was no statistically significant difference in histologic type or performance status by the treatments given; radiotherapy alone vs. combined radio-chemotherapy. The chemotherapy regimen, CHOP (cyclophosphamide, dexorubicin, vincristin, prednisolone) was used in 13 cases, high dose methotrexate in one, five cycles of MOP (methotrexate, vincristine, procarbazine) in one, and six cycles of CEVBP (cyclophosphamide, epirubicin, vincristine, bleomycin, prednisolone) in one. Almost all of the patients received chemotherapy after the completion of radiotherapy (Table 3).

The response to treatment was assessed by imaging study immediately or one month after completion of treatment. CT and/or MRI scans were repeated immediately and/or one month after radiation therapy and chemotherapy. Further imaging studies were performed every four to six months during follow-up evaluation for the first two years and then annually. Complete response (CR) was defined as the disappearance of all enhancing tumor as well as improvement or stability of neurologic signs and symptoms. Partial response (PR) was defined as the disappearance of more than 50% of contrast-enhanced tumor with no increase in corticosteroid doses, as well as improvement or stability of neurologic signs and symptoms. Progressive disease (PD) was defined as a more than 25% increase in the tumor-enhanced area or any new tumor. Stationary disease (SD) was defined

Table 3. Detailed features of cases treated with combined radio-chemotherapy

No.	Age (yr)	Sex	Functional status	Agent	Cycle	Histology	Sequence	Outcome
1	50	M	2	CHOP	6	DL	post-RT	22MoDOD
2	39	F	2	CHOP	6	NOS	post-RT	69MoNED
3	33	M	1	CHOP	6	NOS	post-RT	60MoNED
4	39	M	0	CHOP	6	DL	Concurrent	60MoNED
5	34	M	3	CHOP	6	DL	post-RT	48MoNED
6	33	M	1	CHOP	6	DL	Concurrent	36MoDOD
7	26	F	2	CHOP	6	DM	post-RT	24MoDOD
8	44	M	1	MTX	2	DL	pre-RT	10MoDOD
9	61	M	1	CHOP	5	DPDL	post-RT	26MoDOD
10	50	F	1	CHOP	6	DM	post-RT	29MoDOD
11	55	M	1	CEVBP	6	DL	post-RT	22MoDOD
12	53	M	2	CHOP	5	DL	post-RT	19MoDOD
13	23	M	4	CHOP	6	DL	post-RT	12MoDOD
14	32	F	1	CHOP	6	DL	post-RT	12MoNED
15	52	F	2	CHOP	6	DL	post-RT	10MoNED
16	58	M	3	MOP	5	DL	post-RT	6MoNED

Functional status: ECOG scale
CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; MTX: methotrexate; MOP: methotrexate, vincristine, procarbazine; CEVBP: cyclophosphamide, epirubicin, vincristine, bleomycin, prednisone; DL: diffuse large cell type; NOS: not otherwise specified non-Hodkin's lymphoma; DPLD: diffuse poorly differentiated lymphocyte type; DM: diffuse mixed type; DOD: dead of disease; NED: no evidence of disease

as between PR and PD.

The duration of follow-up ranged from four to 95 months with a median of 15 months. Survival rate was calculated from the first day of treatment using the Kaplan-Meier method. The log-rank test was used for comparison of survival rates and the chi-square test was used for comparison of distribution of prognostic factors between two treatment groups.

RESULTS

Although it was not statistically significant, the response rate was higher in combined treatment group than in RT alone group after completion of all treatment: 13 CR and 3 PR in combined treatment group; 14 CR, 6 PR, 2 SD, and 2 PD in RT alone group (p=0.068).

Two-year disease free survival rate was 40.6% for combined treatment group and 21.6% for RT alone group (p=0.26). Overall survival rates at one, two, and five years were 66%, 41%, and 22%, respectively, and median survival was 19 months for all the cases (Fig. 1). Significant prognostic factors for overall survival were found to be radiation dose and treatment method on univariate analysis. However, no significant factor was found by multivariate analysis, partly due to the small number of patients and difference of prognostic factor between two groups. Median survival was 22 months, and the two-year survival rate was 49% with a radiation dose greater than 50 Gy. It was 12.5 months and 13% with less than 50 Gy (p=0.009) (Fig. 2). Median survival was 29 months and there was a two-year survival rate of 63% with combined radio-chemotherapy, but were 13.5 months and a two-year survival rate of 29% (p=0.027) after radiotherapy only (Fig. 3). Age, sex, performance status, or histology was not found to affect survival.

One patient, treated with six cycles of high dose methotrexate after relapse, had no evidence of disease after 26 months.

Twenty-nine patients experienced treatment failure, including initial failure to achieve complete response. Three patients showed progressive disease to the extracranial site. The most common site of failure (25/29) occurred within the radiotherapy field (Table 4). All patients who received radiation dose less than 50 Gy

Table 4. Patterns of relapse

Relapse	Number (%)
Local (within field)	24 (82.8)*
Local (outside field)	3 (10.3)*
Local + Distant	1 (3.4)
Distant metastasis	2 (6.9)
Total	29 (100)

* One case in each group recurred both within and outside the radiation field

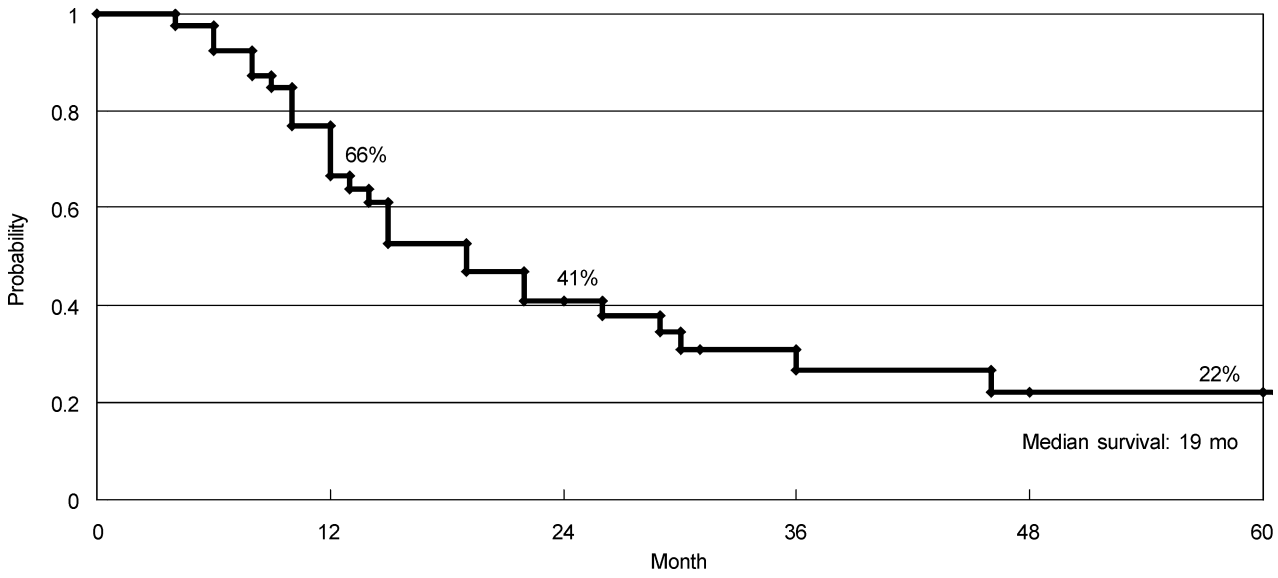

Fig. 1. Overall survival rates of primary central nervous system lymphoma after radiotherapy with or without chemotherapy (n=40).

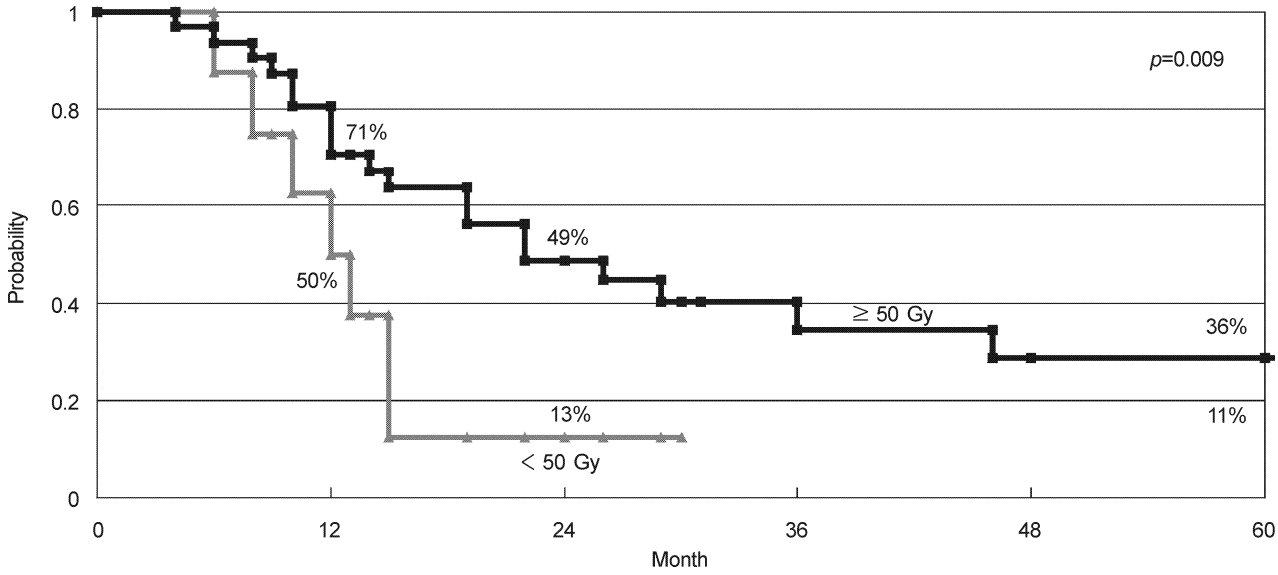

Fig. 2. Overall survival rates of primary central nervous system lymphoma by total radiation dose to the primary site.

suffered from local recurrence.

The toxicity of the chemotherapy was tolerable. The most common toxicity was cytopenia, however, none of our patients experienced neutropenic fever, treatment interruption, or grade III or IV toxicity. We also found no severe acute toxicity related to the radiotherapy. However, two patients did show late toxicity. Both became bedridden after radiotherapy at 12 months and 16 months, but did not show any signs of recurrent disease. One patient who received radiotherapy alone, developed cerebromalacia without any mass or contrast-enhancing lesion on MRI. The imaging results were not available for one patient who received radiotherapy and intrathecal methotrexate.

DISCUSSION

PCNSLs are rare tumors and have a very dismal prognosis, similar to that of glioblastoma. Until recently, the treatment of choice has been radiotherapy. Between 70% and 90% of the patients treated with radiotherapy alone for PCNSL showed neurologic or radiologic improvement (6-8). But long-term survival or quality of life after radiotherapy alone was not satisfactory (6, 8-10). According to a randomized trial by RTOG, the median survival was 11.6 months and the two-year survival rate was 28%. Age and Karnofsky performance status were seen to be significant prognostic factors (11). Murray et al. reported that there were only 21 five-year survivors in their group

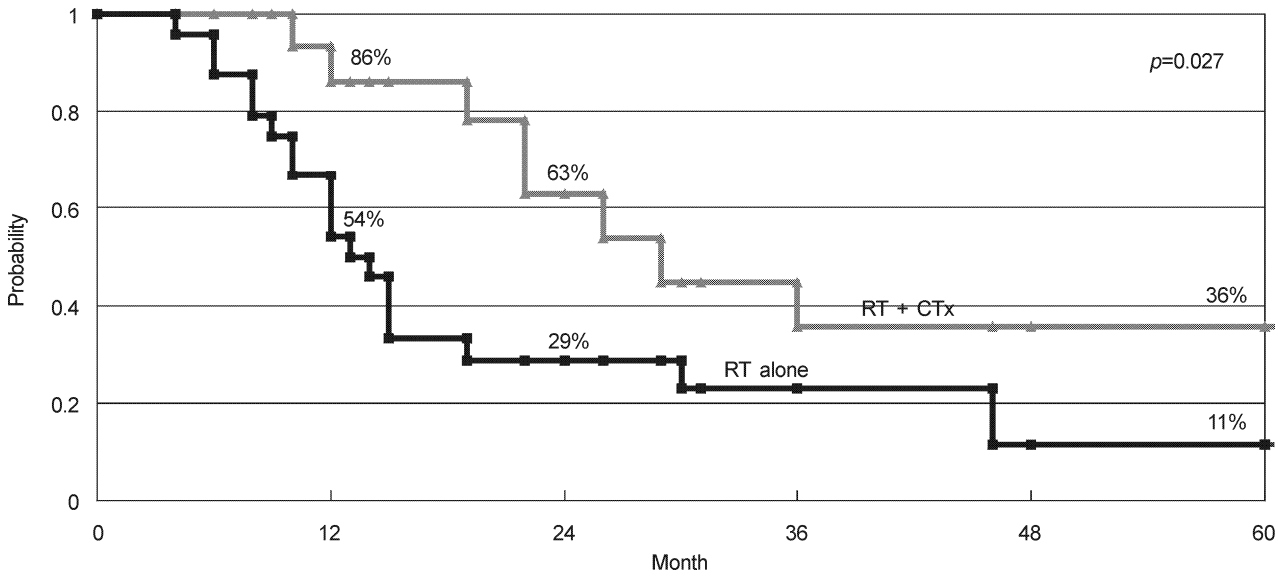

Fig. 3. Overall survival rates of primary central nervous system lymphoma by treatment methods: radiotherapy vs. combined radiochemotherapy.

of 693 patients with HIV-negative PCNSL (12). Hayabuchi et al. performed a multi-institutional retrospective analysis of a total of 544 patients. They reported a 5-year survival rate of 16.9% (13). Most of these patients were treated with radiotherapy alone, and chemotherapy was used in only a limited number of patients.

Recent studies, however, have established the chemosensitivity of PCNSL and strongly suggest improved survival in those receiving chemotherapy in addition to cranial irradiation (14-18). We previously reported the results of six patients treated with cranial irradiation and post-radiation chemotherapy with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The two-year survival rate was 80%, and it has not yet reached its median survival level at the last follow-up (5). Chamberlain et al. reported a median survival of 30 months with concomitant hydroxyuria and adjuvant procarbazine and lomustine (CCNU) (3). O'Neill et al. reported the results of pre-radiation CHOP chemotherapy and post-radiation high-dose cytosine arabinoside. The response rate was 63% and the two-year survival rate was 29%. But in that study, only 37% of the patients completed the planned treatment schedule (19). Pollack et al. also reported good results with systemic chemotherapy in addition to radiotherapy (20). Shibamoto et al. reported 10- to 100-months survival in eight out of ten patients treated with post-radiation VEPA (vincristine, doxorubicin, cyclophosphamide, and prednisolone). But there were significant amounts of mortality and morbidity related to combined treatment (2). They concluded that the high complication rate was due to the sequencing of radiotherapy and chemotherapy. Selch et al. reported a median survival of eight months and a three-year survival rate of 36% with several chemotherapeutic regimens (21). DeAngelis et al., using pre-radiation systemic and intrathecal methotrexate and post-radiation cytosine arabinoside, reported a median survival of 41 months with combined treatment and 10 months with radiotherapy alone (4).

There have also been many studies that reported no benefit of chemotherapy. Brada et al. investigated the effect of pre-radiation MACOP-B, but could not find any difference from radiotherapy alone (22).

In our study, we found that systemic chemotherapy combined with radiotherapy for the initial treatment of PCNSL, significantly prolongs overall survival. Our two-year survival rate was 63%. There was no significant treatment-related toxicity. This is one of the best results that has been reported as of yet. According to recent investigations, there are abnormal blood-brain-barriers (BBBs) in the PCNSL area (23). We think this abnormality of BBB could be related to our good results.

Another controversy regarding the treatment of PCNSL concerns the radiation field. Most investigators agree on the necessity of whole brain irradiation. But there is debate over the use of whole spine irradiation. Loeffler et al. reported better survival rates with whole spine irradiation in addition to whole brain irradiation. Median survival was 41 months with whole spine irradiation and 19 months with whole brain irradiation alone (9). Many studies support these results (8, 24), but whole spine irradiation can not improve the survival rate unless the primary disease can be controlled (21). Prophylactic whole spine irradiation should be indicated in multiple

lesions, lesions located on posterior fossa, or involvement of cerebrospinal fluid (8, 9, 14, 17).

A major component of patterns of relapse in PCNSL is local relapse. As in our current study, where 90% of relapses had local components, most studies have reported that almost all of the relapses are intracranial. According to the Radiation Therapy Oncology Group (RTOG) report, radiation doses for 22 patients experiencing a total of 25 local relapses were below 60 Gy. However, significant toxicity, such as brain necrosis, is predicted with radiation doses above 60 Gy with conventional fractionation (11).

In conclusion, although our current study was not a prospective randomized trial, it does show that better results can be achieved with combined radio-chemotherapy without significant toxicity, although our follow-up period was rather short. Because of the low incidence of this dreaded tumor, a multi-institutional prospective trial would be a good method to confirm the long-term efficacy of combined radio-chemotherapy for PCNSL. In addition, a new approach should be sought to decrease the high recurrence rate within the radiation field.

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