Preliminary Results of Management for Primary CNS Lymphoma

Seung Do Ahn, M.D., Hye Sook Chang, M.D., and Eun Kyong Choi, M.D.

Department of Therapeutic Radiology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea

From October 1989 to March 1992, ten patients diagnosed as primary central nervous system (CNS) lymphoma were treated with radiation therapy at Asan Medical Center. To obtain pathologic diagnosis, five patients had stereotactic biopsy and the others underwent craniotomy & tumor removal.

According to the classification by International Working Formulation, seven of 10 patients showed diffuse large cell types and the remaining 3 had diffuse mixed cell types. Computed tomographic scans of the brain disclosed solitary (6 cases) or multiple (4 cases) intracranial lesions. All patients received 4000 cGy/20 fx to the whole brain followed by an additional 2000 cGy/10 fx boost to the primary lesion. Six patients with initial cerebrospinal fluid (CSF) involvement were treated with whole brain irradiation and intrathecal Methotrexate (IT-MTX) chemotherapy. One of them received an additional spinal irradiation after 3 cycles of IT-MTX chemotherapy because of MTX induced arachnoiditis. One patient received 3 cycles of systemic chemotherapy prior to rodiation therapy and one received 5 cycles of salvage chemotherapy for recurrence. With a median follow up time of 8 months, all patients were followed from 7 to 26 months.

Radiologically seven patients showed complete remission and the remaining three showed partial remission at one month after radiotherapy. The 1 and 2 year survival rate was 86% and 69% respectively. Until now, two patients expired at 7 and 14 months. These patients developed extensive CSF seeding followed by local failure. Considering initial good response to radiation therapy and low incidence of extraneural dissemination in primary CNS lymphoma, we propose to increase total tumor dose to the primary lesion by hyperfractionated radiotherapy or stereotactic radiosurgery. For the patients with CSF involvement at diagnosis, we propose craniospinal irradiation with IT MTX chemotherapy.

Key Words: CNS lymphoma, Radiation therapy

INTRODUCTION

Primary CNS lymphoma constitutes a rare group of neoplasms. In large collected series, it accounts for approximately 0.7% of all malignant lymphomas[1], 1.6% of all extranodal malignant lymphomas[2], and less than 1% of all primary intracranial neoplasms. Because of its rarity, few institutions have a large experience with malignant lymphoma of the CNS. Since Bailey's original description in 1929[3], numerous reports have discussed the epidemiologic, biologic, and therapeutic aspects of this unusual tumor. Dose response curve in lymphoma showed that 40-50Gy can achieve 90% local control rate, but 50% of patients developed a relapse outside of the treated volume[4~10].

In contrast to the natural history of lymphoma, primary CNS lymphoma treated with doses of 40 -50Gy showed that 90% of the patients died of local recurrence and only approximately 10% died of disseminated disease[11]. Local control of primary CNS lymphoma is more important and closely correlates with long-term survival. To explore the role of radiation therapy in primary CNS lymphoma, we analyzed 10 patients treated in Asan Medical Center.

MATERIALS AND METHODS

Between October 1989 and March 1992, 10 patients diagnosed as primary CNS lymphoma were treated with radiation therapy at Asan Medical Center. Five patients were referred following stereotactic biopsy and 5 had tumor resection by open craniotomy. Prior to radiation therapy complete staging work-ups were performed with chest X-ray,

CT scan of chest and abdomen, and bone marrow aspiration and biopsy. Age of the patients ranged from 28 to 71 years old and male to female ratio was 5 : 5 (Table 1).

Histology was classified according to the International Working formulation, seven showed a diffuse large cell type and the ramaining 3 had a diffuse mixed cell type (Table 2). Computed tomographic scans of the brain disclosed solitary (6 cases) or multiple (4 cases) intracranial lesions. None of the patients had feature of AIDS or collagen vascular disease and 8 had negative HIV test.

All 10 patients received brain irradiation. Radiation therapy was delivered by 4 MV linear accelerator (Table 3). Initially the whole brain to the bottom of C2 was irradiated by parallel opposed portals to 40 Gy in 20 fractions followed by 20 Gy boost to the primary lesion. Six patients received 3 to 16 cycles of IT-MTX for initially positive CSF. One patient received spinal axis irradiation for initially positive CSF because of MTX induced arachnoiditis. One patients received 3 cycles of systemic chemotherapy prior to radiotherapy and one received 5 cycles of salvage chemotherapy for recurrence. Response was judged by radiological and clinical finding and CT/MRI scan was performed in 4~6 weeks after completion of radiotherapy.

Complete radiological response was defined as complete disapperarance of all previously enhancing lesions with accompanying reduction of mass effect and partial response was defined as ≧50% reduction in size of enhancing lesion.

Table 1. Patient Characteristics (n=10) (I)

Sex: Male	5
Female	5
Age: Range	28-71 yr
Median	46 yr
Diagnostic method	
Operation	5
Gross total removal	2
Partial removal	3
Stereotactic biopsy	5

Table 2. Patient Characteristics (N=10) (II)

Pathology (by International Working Formulation)	
Diffuse large cell	7
Diffuse mixed	3
CSF cytology before treatment	
positive in	6
Negative in	4
Predisposing factors	
HIV test (n=8): negative in all patients	
No history of collagen-vascular disease	
No history of immunosuppression in all	

Table 3. Treatment Modality

Radiation therapy (n=10)
Whole brain 4000 cGy/20 fx
reduced field 2000 cGy/10 fx
Total dose to primary site 6000 cGy/30 fx
Whole spine 3000 cGy/20 ffx in one case
Systemic chemotherapy (n=2)
PreRT CHOP with high dose MTX 3 cycles
PostRT EDAP 5 cycles (as salvage therapy)
IT MTX (n=6): if CSF cytology (+)
3-16 cycles (median 8 cycles)

Table 4. Summary of Treatment Results

Case No.	Tumor		Treatment				Failure@ Pattern	Tx** Rec.	Surv. Status	DFS
	S/M*	CSF	WBRT	SPRT	ITMTx	CT#				
1	S	+	+	−	+	−	CSF	ITMTx	14 M (D)	0 M
2	M	+	+	+	+	−			26 M (A)	
3	S	+	+	−	+	−			19 M (A)	
4	S	+	+	−	+	−			9 M (A)	
5	M	+	+	−	+	−			8 M (A)	
6	M	+	+	−	+	−			8 M (A)	
7	S	−	+	−	−	−	CSF	CT	7 M (D)	2 M
8	S	−	+	−	−	−			27 M (A)	
9	S	−	+	−	−	+			15 M (A)	
10	M	−	+	−	−	−			8 M (A)	

*Multiplicity of lesion: S-Single, M-Multiple
#CT: Chemotherapy, @: initial failure site, **: Salvage treatment
WBRT: Whole brain radiotherapy, SPRT: Spinal radiotherapy

RESULTS

With a median follow-up time of 8 months, all patients were followed from 7 to 26 months. Seven patients showed complete remission at one month after radiotherapy and three showed partial remission. One of three partial responders is alive with disease now. The remaining two partial responders showed local failure following extensive CSF seeding. One of them received IT MTX chemotherapy and the other received systemic salvage chemotherapy. But ultimately these two partients died 7 and 14 months after radiotherapy (Table 4). The 1 and 2 year survival rate was 86% and 69% respectively. One patient showed IT MTX induced arachnoiditis but recovered spontaneously without neurologic sequelae.

DISCUSSION

In a recent review of 693 cases, Murray et al[11] found that only 8% of the patients of CNS lymphoma survived for more than 3 years and that only 3% became long term survivors. Major site of failures after radiation therapy is locoregional recurrence and only 10% can eventually spread beyond the CNS[12]. So the control of neuraxis dissemination is a goal of the treatment. Primary CNS lymphoma has been shown to be radioresponsive, but it is rarely radiocurable with conventional radiation dose and technique[13,14]. Radiation therapy in this study with 40 Gy to the whole brain and meninges plus a boost to gross disease to 60 Gy achieved complete disappearance of disease in 70% of the patients.

Cytologic examination of CSF is not routinely performed in patients with increased ICP due to space occupying lesion in the brain. However, Jellinger et al[15] considered CSF cytology as a useful and reliable tool for clinical diagnosis. In our study, the CSF cytology was examined in all cases and 60% showed positive cytology. Comparing with other studies, the proportion of CSF positive patients is very high. However, it must be taken into account that only a few patients in each series could have such an exploration because of increased intracranial pressure. The patients who showed CSF involvement received IT methotrexate chemotherapy in addition to whole brain irradiation and one of them received whole spinal irradiation after 3 cycles of MTX chemotherapy due to IT MTX induced arachnoiditis. One patient who received IT MTX ultimately developed CSF seeding, however one who received whole spinal irradiation has survived without disease at 26 monts.

Neuwelt et al[16] reported 75% of 1 year survival and 75% of initial radiological response in 12 patients with primary and recurrent CNS lymphoma treated with systemic chemotherapy. But chemotherapy for primary CNS lymphoma is still in the developmental stage and long-term results have not been reported. Considering initial good response to irradiation and low incidence of extranodal dissemination in primary CNS lymphoma, we propose to increase the total tumor dose with hyperfractionated irradiation or stereotactic radiosurgery. For the patients with CSF involvement at diagnosis, we also propose to treat with whole craniospinal irradiation and concomitant IT methotrexate chemotherapy.

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= 국문초록 =

원발성 중추신경계 림프종의 치료에 관한 예비적 결과

울산대학교 의과대학 서울중앙병원 치료방사선과학 교실

안 승 도·장 혜 숙·최 은 경

본 연구는 1989년 10월부터 1992년 3월까지 아산재단 서울중앙병원에서 원발성 중추신경계 림프종으로 진단 받은 10명의 환자를 대상으로 하였다. 병리적 진단을 위한 조직은 5명에서 개두술에 의한 종양절제술로 얻어졌으며 나머지는 정위적 조직생검에 의해 얻어졌다. 성별분포는 남녀가 각 5명이었고 연령분포는 28세부터 72세로 평균연령은 45세로 나타났다. Working Formulation에 의한 세포아형은 7명에서 diffuse large cell type이었고 3명은 diffuse mixed cell type이었다. 전산화 단층촬영 결과 6명은 단일병소로 나타났으며 4명은 다발성병소로 나타났다. 치료는 전 환자가 전뇌 방사선 조사를 4000 cGy/20 fx을 받은 후 원발병소에 2000 cGy/10 fx을 조사하여 총 6000 cGy를 시행하였다. 척수액 검사상 양성인 6명은 전뇌조사와 척수강내 항암제 투여를 받았으며 그중 1명은 척수강내 항암제 투여 3회 실시후 척수방사선 조사를 받았다. 척수액 검사상 음성인 4명중 3명은 전뇌조사만 실시했고 나머지 1명은 방사선 조사전 전신 항암제 투여를 받았다. 추적관찰기간은 7개월에서 26개월이었으며 평균 추적기간은 8개월 이었다. 1년 생존율은 86% 이었고 2년 생존율은 69%로 나타났다.

현재까지 2명이 척수강내 재발 후 뇌실질내 재발로 사망했으며, 반면 7명의 환자는 방사선 치료후 병소가 완전히 없어졌다. 위의 결과로 볼때 원발성 중추신경계 림프종의 방사선 치료에 대한 월등한 초기반응과 원격 전이가 적은 것을 고려하여 원발병소에 분할치료 방법들을 통한 전체 조사량을 증가시키는 것이 효과적이라고 생각되며 척수액 검사상 양성인 경우는 척수 방사선 조사와 척수강내 항암제를 함께 쓰는 좀더 적극적 치료가 필요하리라 생각된다.