Successful Treatment of Primary Central Nervous System Lymphoma without Irradiation in Children: Single Center Experience

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a very rare brain tumor in children. Current estimates are only 14 cases annually in the United States (1), and the exact epidemiology and characteristic of disease are still unknown. The rarity of this disease makes large-scaled prospective studies difficult to perform for establishment of a definitive treatment for this disease. Only a few studies with small numbers of pediatric patients or case series of childhood patients have been documented (1-5). No established, efficacy-proven treatment exists for pediatric PCNSL, and much information regarding treatment has been extrapolated from the results of adult studies (1-3).

In the past, most treatment strategies for PCNSL have been based on radiotherapy (RT) alone with or without steroids, whereas most patients currently receive a combination of chemotherapy and cranial RT or intensive chemotherapy alone (6). However, no report has yet suggested any clear role or advantage for cranial or craniospinal RT for the treatment of childhood PCNSL (1, 3, 5). The recognition of adverse effects of cranial irradiation in young children, also raises concerns about the use of cranial or craniospinal irradiation due to lack of proven efficacy in children (7).

For both adults and children, the prognosis of PCNSL is unfavorable, with a 5-yr event-free survival (EFS) rates ranging from 25% to 40% (8). However, a recent multicenter report that included 31% of patients with whole brain RT showed that the 2-yr EFS and overall survival (OS) rates were 61% and 86%, respectively, and the 3-yr OS rate was 82% for childhood PCNSL (5). Abla et al. (1) reported that 10 patients with PCNSL who were treated with chemotherapy alone, without cranial RT showed better 5-yr EFS rate of 70.0% ± 14.5%. Although the number of patients was small, these data indicate that the survival of the PCNSL patients without irradiation was acceptable and better than previously reported.

In this article, we reviewed the patients with childhood PCNSL...
in our hospital, and evaluated the efficacy of systemic and intrathecal (IT) chemotherapy, without cranial or craniospinal RT, and effects on patient survival.

MATERIALS AND METHODS

From January 1996 to December 2010, six patients who were newly diagnosed with primary CNS lymphoma before 18 yr of age were analyzed from 175 patients with non-Hodgkin lymphoma (NHL) in Seoul National University Children’s Hospital. The patients who were diagnosed with lymphoma in other primary sites with CNS involvement were excluded. Their magnetic resonance imaging (MRI) and medical records, including demographics, symptoms, disease characteristics, laboratory and pathologic findings, patients’ status of Epstein-Barr virus (EBV) or human immunodeficiency virus (HIV) infection, treatments, clinical outcomes and survival status were analyzed retrospectively.

Statistical analysis
Statistical analysis was performed using SPSS software (version 18.0; SPSS, Chicago, IL, USA). For the analysis of survival status, EFS was defined as the duration between diagnosis to occurrence of events such as relapse or treatment-related mortality, and OS as the time between diagnosis and death. Kaplan-Meier methods were used to estimate 5-yr EFS and OS rates. The analyses were descriptive, because the number of the patients was small.

Ethics statement
This study was approved by the institutional review boards at Seoul National University Hospital (IRB number: H-1109-133-380). An informed consent was waived by the IRB.

RESULTS

Patient characteristics
Their male:female ratio was 5:1, and the median age was 10 yr (23 months-11 yr 9 months). The initial symptoms were headache in three patients (one of these also had diplopia), decreased visual power and gait disturbance in two, and clonic movement of right extremities and lethargic features in one. Time intervals from the appearance of symptoms and diagnoses were about two months in two patients, one month in one, one week in two, two days in one. All of the patients showed normal Eastern Cooperative Oncology Group (ECOG) performance scores (0 or 1).

The median value for initial serum lactate dehydrogenase (LDH) level was 289 (range 199–481 IU/L). The primary site was the sellar area in three patients, the parietal area in one, the cerebellum in one, and multiple areas in one. Two patients (patients 2 and 4) had parameningeal involvement of the tumors on brain MRI, and three (patients 2, 3 and 4) showed positivity on cerebrospinal fluid (CSF) cytology examination. Two patients (patient 3 and 5) showed the feature of meningeal seeding on their MRI. The median value of their CSF protein level on diagnosis was 9.5 mg/dL (2-61 mg/dL). The EBV exam showed negative features on tissue in three patients (one patient showed negativity on blood EBV examination), and three patients had no examination about EBV status. Five of these patients had a serology test for HIV infection and all showed negative results. No patient had undergone a previous organ transplantation or immunosuppressive therapy. All patients had the biopsies as confirmative diagnosis. The pathologic diagnoses were diffuse large B-cell lymphoma (DLBL) in three patients, Burkitt lymphoma in two, and undifferentiated B-cell lymphoma in one. Immunohistochemistry of Bcl-6 was performed in four patients (patients 3-6), and 3 (patients 3, 5, and 6) showed a positive finding. No patient had bone marrow involvement of their tumors.

Characteristics of the patients were summarized in Table 1. The rate of the PCNSL in our center was 3.43% (6/175) of pediatric NHL, as mentioned previously.

Table 1. Patient characteristics for children with primary CNS lymphoma (PCNSL)

| Case | Sex | Age (yr) | Primary sites | Histology | Bcl-6 | Initial LDH | HIV | EBV | BM involve | CSF cytology |
|------|-----|----------|---------------|-----------|-------|-------------|-----|-----|------------|-------------|
| 1    | Male| 23 months| Sellar area (pituitary), extend to sphenoid | B-lymphoma, undifferentiated | N/A   | 481         | N/A | -   | -          | -           |
| 2    | Male| 10       | Suprasellar, cerebellum, 3rd ventricle, etc | Burkitt  | -     | 294         | -   | -   | -          | -           |
| 3    | Male| 10       | Cerebellum, 4th ventricle | Diffuse large B-cell | +     | 226         | -   | N/A | -          | -           |
| 4    | Male| 32 months| Sellar area, extend to orbit/sphenoid | Burkitt  | -     | 350         | -   | -   | -          | -           |
| 5    | Female| 13      | Sellar area, extend to sphenoid | Diffuse large B-cell | +     | 199         | N/A | -   | -          | -           |
| 6    | Male| 13       | Left parietal area | Diffuse large B-cell | +     | 284         | N/A | -   | -          | -           |

LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; EBV, Epstein-Barr Virus; BM, bone marrow; CSF, cerebrospinal fluid; N/A, not assessed.
was treated with the Children’s Cancer Group (CCG)-106B treatment protocol (9), and the others were treated with the regimen for Group C disease of French-American-British (FAB)/LMB96 (CCG-5961) treatment protocol (10), with augmented IT chemotherapy. This treatment protocol includes three doses of intravenous high-dose (HD) methotrexate (MTX, 8 g/m²/dose) and eight doses of HD cytarabine (3 g/m²/dose) chemotherapy, with triple IT chemotherapy consisting of cytarabine, hydrocortisone, and MTX. In contrast, the CCG-106B treatment protocol did not include HD MTX. The patient who was treated with the CCG-106B protocol received IT chemotherapy of MTX, but not triple agents. All patients had IT chemotherapy more than 11 times. No patient had cranial or craniospinal RT or HD chemotherapy with autologous stem cell rescue as a first-line treatment. Other supportive care was provided according to the guidelines for treatment of pediatric leukemia/lymphoma of our center (11).

Treatment results
Five patients were alive and in remission at last follow-up and none of these had any relapse of disease. Only one patient (patient 4) had a relapse of the disease at the primary site of the tumor, at six months from initial diagnosis. After relapse, this patient underwent the CCG-106B induction treatment protocol with four rounds of IT chemotherapy (hydrocortisone, MTX, cytarabine), and subsequent craniospinal radiotherapy (600 cGy of spinal irradiation and 1,800 cGy of whole brain irradiation). This was followed by the CCG-106B consolidation and LMB96 reduction chemotherapy consisting of prednisolone, vincristine, and cyclophosphamide, combined with IT chemotherapy. However, disease control was failed and the patient died at nine months after the diagnosis.

Fig. 1. Event-free survival (EFS) of 6 patients with PCNS. Estimated 5-yr EFS rate is 83.3%.

Fig. 2. Patient 2 and patient 6 had their primary tumor in multiples site including cerebellum and third ventricle, and left parietal area, respectively. After systemic and intrathecal chemotherapy, their tumors were completely resolved.
The median EFS and OS were both 72 months. Only one of six patients had relapse, and eventually died of disease, so the estimated 5-yr EFS and OS rates were both 83.3% (Fig. 1). Although one patient (patient 1) had decreased visual power, this was thought to perhaps be a sequel of primary disease rather than the treatment. The other patients showed no other treatment-related toxicity or long-term sequelae.

Fig. 2 shows complete response of the tumors after treatment in the patients 2 and 6, and treatments and clinical outcomes of the patients are summarized at Table 2.

**DISCUSSION**

PCNSL is very uncommon disease in children. The exact incidence of pediatric PCNSL is unknown (12), but it is thought to be lower than the incidence in adults. In the SEER program in the USA, 1% of all reported PCNSL cases were in patients younger than 19 yr, giving an estimated incidence of 15 to 20 cases per year in North America (3). In adults, PCNSL is thought to represent about 3% of the brain tumors and 2%-3% of the NHL (5). However, no exact statistics are available for PCNSL in pediatric patients. A multicenter study of Berlin-Frankfurt-Munster group, in the 2,311 pediatric patients who were diagnosed as NHL without HIV infection, only ten patients had PCNSL (0.43%) (13). In the reports of eastern countries, among 596 cases of PCNSL reported to the Brain Tumor Registry of Japan (1969-1990), only nine pediatric cases (1.5%) were documented (3). In our study, the ratio of PCNSL was 3.43% of the NHL in our hospital, which is similar to the ratio in adult patients. The ratio of PCNSL in pediatric NHL is smaller than that of adults, but our ratio is inconsistent with this. Although the small number of the patients makes estimation of the correct ratio of the PCNSL difficult, we speculate that this discrepancy has two possibilities. The first is that the patients with brain tumors usually want to be evaluated and treated at the larger hospital in Korea, so the ratio obtained at a large, single tertiary center could be overestimated. The second is that the incidence of PCNSL in Korean children is actually higher than that reported in Western reports. Another single-center report of PCNSL in Korea also showed a rate of PCNSL of 4% (five in 125 NHL patients) (4), similar to ours. The actual incidence and ratio in pediatric NHL could be better estimated by a multicenter, nationwide survey.

Although patients with congenital or acquired immunodeficiency (e.g. HIV infection) are known to be at increased risk for developing PCNSL (5, 14, 15), no HIV positivity was detected in our patients. We think that this is related with the somewhat low incidence of congenital HIV infection in Korean children and that PCNSL can arise in children without immunodeficiency. We evaluated of EBV status were performed in three patients and all showed negative results. In spite of the small number of patients, the relationship between PCNSL and EBV infection seemed to be weak, in contrast to the head and neck lymphoma.

From a pathologic aspect, Hodgkin lymphoma rarely involves the brain parenchyma. All of the reported childhood PCNSL cases were NHL and the majority of them were B-cell lymphoma (1-5). Which subtype of NHL is most common in childhood PCNSL is still unknown. A review by Abla et al. (3) indicated that DLBL (30%) was the most common in a previously report of 43 pediatric patients with PCNSL. In a multicenter study of PCNSL in children, the most common subtype was DLBL (68%), followed by anaplastic large T-cell lymphoma (17%), lymphoblastic lymphoma (7%), and Burkitt lymphoma (7%) (5). In our study, all of the patients were diagnosed with B-cell NHL, and DLBL was the most common subtype (3/6), and no patient had T-cell lymphoma. The small number of the patients makes it difficult to explain these differences in subtypes of pediatric PCNSL. No known relationship exists between pathologic subtypes and outcome in pediatric PCNSL (3).

No definite treatment scheme has been established for childhood PCNSL. In adult patients, the backbone of the treatment in PCNSL is CNS irradiation and chemotherapy with HD (> 1,000 mg/m²) MTX (16). Treatment with only CNS irradiation without chemotherapy is not used because of the high rate of relapse and poor survival (17). Many patients with pediatric PCNSL were treated with chemotherapy regimens that included CNS irradiation with usual doses ranging from 12 to 50 cGy (3, 5). In the patients who had chemotherapy, the exact role of the CNS irradiation is still unclear. Some recent reports have indicated

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**Table 2. Systemic and intrathecal treatments for patients with PCNSL**

| Case | Systemic chemotherapy | Intrathecal chemotherapy | HD MTX | HD Ara-C | Salvage treatment | Status | EFS (months) | OS (months) |
|------|-----------------------|--------------------------|--------|----------|------------------|--------|--------------|-------------|
| 1    | CCG-106B              | Ara-C × 1, MTX × 25      | -      | -        | -                | NED    | 87+          | 87+         |
| 2    | FAB/LMB96, Group C    | Ara-C × 1, MTX × 3, triple* × 9 | 3 g/m² × 4 | 3 g/m² × 8 | -                | NED    | 86+          | 86+         |
| 3    | FAB/LMB96, Group C    | MTX × 2, triple × 9      | 3 g/m² × 4 | 3 g/m² × 8 | RT, chemotherapy | DOD    | 6            | 9           |
| 4    | FAB/LMB96, Group C    | MTX × 2, triple × 12     | 3 g/m² × 4 | 3 g/m² × 8 | -                | NED    | 64+          | 64+         |
| 5    | FAB/LMB96, Group C    | Ara-C/HC × 1, MTX × 2, triple × 11 | 3 g/m² × 4 | 3 g/m² × 8 | -                | NED    | 15+          | 15+         |
| 6    | FAB/LMB96, Group C    | Ara-C/HC × 1, MTX × 2, triple × 11 | 3 g/m² × 4 | 3 g/m² × 8 | -                | NED    | 15+          | 15+         |

*Triple means intrathecal combination chemotherapy, consisted of hydrocortisone, cytarabine and methotrexate. HD, high-dose; MTX, methotrexate; Ara-C, cytarabine; EFS, event-free survival; OS, overall survival; NED, no evidence of disease; DOD, died of disease; HC, hydrocortisone; RT, radiotherapy.
that children with PCNSL or CNS-involved NHL were successfully treated with chemotherapy, not RT (1, 4, 5, 18). We cannot compare effects of RT, because we had only six patients and none of the PCNSL patients in our center underwent RT. One patient who was treated with the CCG-106B treatment protocol was scheduled to have RT, but after induction chemotherapy, he showed complete remission of his primary lesion. Irradiation was therefore delayed, and subsequent treatment was completed without irradiation. The other five patients were treated with the FAB/LMB96 treatment protocol, which recommends no RT for primary treatment of lymphoma with CNS involvement. Consequently, our six patients were all treated without irradiation as a primary treatment.

The treatment outcome of PCNSL with the FAB/LMB96 protocol for PCNSL has not been previously reported, but a large-scaled report about the outcome of the FAB/LMB96 protocol in B cell-NHL with CNS involvement showed that the 4-yr EFS rates were 70% ± 4.3% in CNS-positive patients and 83% ± 5.6% in CNS-only positive patients (i.e., without marrow involvement) (18). Although we enrolled only PCNSL patients without other primary sites, our treatment outcome is comparable to these data (EFS rate of 83% in total patients, 80% in LMB96 treatment patients). Considering it is usually thought PCNSL had larger tumor burden than extraneural lymphoma with CNS involvement, our results indicate that larger tumor burden of PCNSL can be cured with intensive chemotherapy without RT.

HD MTX is recognized as the single most important drug for the treatment of PCNSL (19, 20). Many convincing data show that HD MTX is an effective treatment and that improves the survival of PCNSL patients. Although the optimal dose for treatment of PCNSL is unknown, the common dose of HD MTX for PCNSL is higher than 3,500 mg/m²/dose (19-21). In the LMB96 protocol, MTX at 8,000 mg/m²/dose is used for treatment of lymphoma with CNS involvement. Five of six of our patients were treated with chemotherapy at this dose without significant toxicity. HD cytarabine at 3 g/m² or more is another systemic chemotherapy that has a proven benefit for treatment of PCNSL (22-24). A study by Ferreri et al. (22) reported that in PCNSL patients aged 75 yr and younger, the addition of HD cytarabine to HD MTX provides improves outcome with acceptable toxicity when compared with HD MTX alone. No randomized study has been conducted to examine the effect of adding HD cytarabine to HD MTX, but HD cytarabine is widely used for the treatment of acute leukemia without significant toxicity. In small, non-randomized studies of pediatric PCNSL, the outcomes following the use of HD MTX and HD cytarabine are satisfactory (1, 3). Our patients received IT chemotherapy from 11 to 26 times (median 14.5 times), consisting of MTX, cytarabine, and hydrocortisone. The exact role of IT chemotherapy in treatment of PCNSL is still not understood, especially when HD MTX is used (25). IT chemotherapy has been recommended by some for CSF-positive PCNSL patients (3). Considering the patient 1 who was successfully treated without HD MTX or cytarabine, we think that intensive IT chemotherapy is essential for the patients without HD MTX or cytarabine. Further investigations will be needed to determine exact role and optimal numbers, and agents for IT chemotherapy.

Because of the small number of PCNSL cases in children, the exact survival rates and outcomes are not well known. In the report by Abla et al. (5), the 2-yr progression-free survival and OS rates for 21 patients were 61% and 86%, respectively, and the 3-yr OS rate was 82%. Our report, despite the small number of patients, showed tolerable treatment results of both 83% in terms of 5-yr EFS and OS rates. No reports exist on large-scaled studies into the clinical outcome of childhood PCNSL, because of rarity of this disease. However, a review of previously reported cases suggests that the prognosis is significantly better in patients who present with PCNSL in childhood than in their adult counterparts (3).

Although some prognostic factors are indicated in adult PCNSL, such as age, ECOG performance score, response to HD MTX chemotherapy, CSF or serum LDH level, etc (22, 26), none of these is a definite prognostic factor in childhood PCNSL. Some studies suggest that specific markers such as Bcl-6, p53, XBP-1, MUM-1, MMP-9 or Ki-67 are related with prognosis in adult PCNSL (26-28), but their involvement in childhood PCNSL has not been reported. In a study of Bcl-6 in adult PCNSL, Bcl-6 expression in non-deep site DLBCL was related with a favorable outcome (29). In our study, all three of the DLBCL patients showed positive Bcl-6 on immunohistochemistry, and all survived without relapse or progression. In a multicenter study by Abla et al. (5), ECOG performance score was the only prognostic factor and a marginally significant relationship was observed. Because of small number of the patients with good performance score overall, we were unable to analyze any prognostic factors in our study. Numerous larger prospective multicenter studies with molecular investigations will give us exact prognostic factors for childhood PCNSL.

Our study has many limitations. Mainly because PCNSL is a very rare disease, the small number of our patients and the long-term duration of the retrospective patient enrollment were the major obstacles for further analysis and estimation. However, this is the first single center study about treatment outcomes of PCNSL without radiotherapy. Furthermore, all of the patients had confirmative tissue diagnosis, and they were treated with a relatively homogenous treatment protocol (FAB/LMB96-based) except one patient. We think this report would give some information about pediatric PCNSL in eastern countries.

In conclusion, PCNSL is a very uncommon disease in children and was successfully treated by systemic and IT chemotherapy without irradiation. Our results will be additive evidence for favorable clinical outcomes of pediatric PCNSL treatment.
without RT. Large-scaled, prospective studies are still needed that will focus on the feasibility and effects of chemotherapy without irradiation in PCNSL and on risk stratification for initial use of irradiation. In addition, the correct incidence and rate of PCNSL in children should be investigated by a multicenter, nationwide study in Korea and across Asia.

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