

Primary CNS Lymphoma in Children and Adolescents: A Descriptive Analysis from the International Primary CNS Lymphoma Collaborative Group (IPCG)

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Abstract

Purpose: To describe the demographic and clinical features and outcomes for children and adolescents with primary CNS lymphoma (PCNSL).

Experimental Design: A retrospective series of children and adolescents with PCNSL was assembled from 10 cancer centers in 3 countries.

Results: Twenty-nine patients with a median age of 14 years were identified. Sixteen (55%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or greater. Frontline therapy consisted of chemotherapy only in 20 patients (69%), while 9 (31%) had chemotherapy plus cranial radiotherapy. Most patients received methotrexate (MTX)-based regimens. Overall response rate was 86% (complete remission 69%, partial remission 17%). The 2-year progression-free survival (PFS) and overall survival (OS) rates were 61% and 86%, respectively; the 3-year OS was 82%. Univariate analyses were conducted for age (≤ 14 vs. >14 years), PS (0 or 1 vs. >1), deep brain lesions, MTX dose, primary treatment with chemotherapy alone, intrathecal chemotherapy, and high-dose therapy. Primary treatment with chemotherapy alone was associated with better overall response rates with an odds ratio (OR) of 0.125 ($P = 0.02$). There was a marginally significant relationship between higher doses of MTX and response (OR = 1.5, $P = 0.06$). ECOG-PS of 0 to 1 was the only factor associated with better outcome with hazard ratios of 0.136 ($P = 0.017$) and 0.073 ($P = 0.033$) for PFS and OS, respectively.

Conclusion: This is the largest series collected of pediatric PCNSL. The outcome of children and adolescents seems to be better than in adults. PS of 0 to 1 is associated with better survival. *Clin Cancer Res*; 17(2); 346–52. ©2011 AACR.

Introduction

Primary CNS lymphoma (PCNSL) is a rare brain tumor in childhood. The incidence is unknown; however, among 596 cases of PCNSL reported to the Brain Tumor Registry of

Japan (1969–1990), only 9 pediatric cases (1.5%) were documented (1). In the Surveillance, Epidemiology and End Results (SEER, USA, 1973–1998) program, 1% of all reported PCNSL cases were in patients younger than 19 years, giving an estimated incidence of 15 to 20 cases per year in North America (2). Patients with congenital or acquired immune deficiencies are at increased risk for developing PCNSL (3, 4), although most of the 50 pediatric cases reported over the last decade were immunocompetent (5). Because of the rarity of the disease and the lack of large prospective studies, the most appropriate therapy for pediatric PCNSL has not yet been determined. Sporadic case reports have shown long-term survival with chemotherapy alone (6, 7). The largest pediatric PCNSL case series suggested that most children could achieve long-term remission with chemotherapy-based regimens, without whole brain radiotherapy (WBRT). However, this study was limited because of the small number of patients ($n = 12$), its retrospective nature, the heterogeneous patient population (one-third were immunodeficient), and individualized treatment regimens (8). The International PCNSL Collaborative Group (IPCG) is a multidisciplinary group of neuro-oncologists, neurologists, neurosurgeons, radiation oncologists, hematologists, pathologists, and

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Translational Relevance

The outcome of children and adolescents with primary CNS lymphoma (PCNSL) seems to be better than in adults. Frontline therapy with chemotherapy alone, mainly high-dose methotrexate-containing regimens, is associated with better overall response rates. This is the first study that correlates Eastern Cooperative Oncology Group (ECOG) performance status (PS) with outcome in pediatric PCNSL. An ECOG-PS of 0 to 1 at diagnosis was associated with better progression-free survival and overall survival. Children and adolescents with PCNSL could be treated initially with chemotherapy only, and cranial irradiation may be reserved to refractory or relapsed patients. Furthermore, patients with an ECOG-PS of greater than 1 at diagnosis may benefit from more intensive therapy including autologous stem cell transplantation. Multinational prospective studies are needed for this rare entity.

pediatric oncologists from North America, Europe, Australia, and New Zealand. We report a large retrospective analysis of 29 children and adolescents with PCNSL assembled from 10 institutions in 3 countries.

Patients and Methods

Study population

A data collection form regarding PCNSL was sent to investigators affiliated with the IPCG and to selected pediatric oncology centers. Requested information from each participating institution included patient characteristics (age, gender), Eastern Cooperative Oncology Group (ECOG) performance status (PS), immune status, presenting symptoms, initial lactate dehydrogenase (LDH) levels, pathology, cerebrospinal fluid (CSF) cytology and protein, ocular involvement, number of brain lesions and location, treatment, site and date of progression, second-line therapy, long-term neurotoxicity, and survival. Ten cancer centers with at least 1 case of pediatric, adolescent, or very young adult (≤ 21 years of age) PCNSL responded. Each center received ethics committee approval for the release of anonymized patient information. The inclusion criteria were histologic or cytologic diagnosis of lymphoma localized exclusively to the brain, meninges, or spinal cord. Central pathology review was not feasible due to logistics and time elapsed from initial diagnosis. In 23 cases, the original pathology reports were available for central review. Cytologic features, immunophenotyping, and final diagnosis were abstracted from these reports.

Statistical analyses

Logistic regression models were used to assess predictors of radiographic response. Univariate Cox regression models were used to assess predictors of overall survival (OS) and progression-free survival (PFS). Kaplan–Meier curves were calculated to display the distributions of OS and PFS.

Stratification variables included gender, age (≤ 14 years vs. > 14 years), ECOG-PS (0–1 vs. > 1), number of brain lesions (multiple vs. single), lesion location (deep brain vs. cerebral hemisphere), CSF cytology for lymphoma cells (positive vs. negative), initial LDH levels (high vs. normal), primary treatment (chemotherapy only vs. chemotherapy plus WBRT), receipt of intrathecal (IT) therapy (no vs. yes), high-dose therapy (no vs. yes), and methotrexate (MTX) dose.

Results

Case identification

A total of 29 cases were identified from 6 IPCG centers and 4 pediatric oncology centers. All cases were diagnosed between 1978 and 2008. All patients had their disease confined to the brain ($n = 26$) or meninges ($n = 3$), with no evidence of systemic lymphoma at presentation. Three patients described in a previous pediatric PCNSL report (8) were included in this series.

Demographics and clinical features

There were 21 males (73%) and 8 females (27%). Median age at diagnosis was 14 years (range = 2–21). Three patients were immunodeficient; 1 had congenital combined immunodeficiency, 1 had acquired immunodeficiency with PCNSL developing 4 months post-renal transplant, and 1 patient with lupus erythematosus had immunosuppressive therapy with mycophenolate for 1 year before developing PCNSL. ECOG-PS was available in 19 cases (65%) and was abnormal in 16 (84%), 3 of whom had an ECOG-PS of 2 or worse. Slit-lamp examination of the eyes was recorded in 7 patients (24%); 2 had positive findings. Initial LDH was available in 17 cases, 9 of whom (53%) had elevated levels defined as above-institutional normal values. CSF cytology was documented from 26 patients (90%) and was positive for lymphoma in 8 cases (31%); 3 of these had primary leptomeningeal lymphoma (PLML). The CSF protein was available in 11 cases (38%) and was high in 8. Baseline computed tomography and/or magnetic resonance imaging (MRI) of the brain with gadolinium contrast enhancement were obtained in all patients before starting therapy. Eleven patients (38%) had multiple lesions at diagnosis. Twelve patients (41%) had involvement of deep brain structures (basal ganglia, cerebellum, or brain stem), 14 had cerebral hemispheres involved, and 3 had isolated meningeal involvement. The most common presenting symptoms were those of increased intracranial pressure (headaches, nausea/vomiting), followed by cerebellar symptoms such as ataxia, dysarthria, and dysmetria. Seizures and hemiparesis were also common. Some patients had associated blurring of vision, photophobia, nystagmus, diplopia, and proptosis. One patient presented with cranial polyneuropathy, and another patient, diagnosed with pineal PCNSL, presented with Parinaud syndrome. One patient presented at age 14 years with short stature, diabetes insipidus, and a thickened pituitary stalk on brain MRI. She was treated with growth

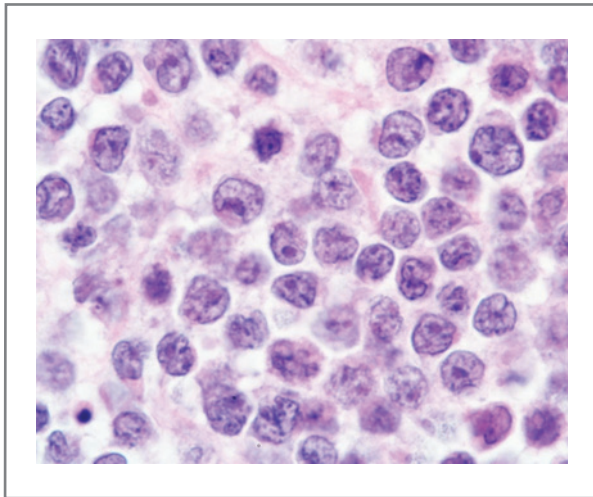


Figure 1. Primary diffuse large B-cell lymphoma of the CNS in a 12-year-old patient. High magnification (100×): homogeneous tumor cell population, cells medium sized to large, prominent nucleoli, CD20⁺, kappa-light chain restricted, CD10⁻, CD30⁻, K167⁺ >90%.

hormone therapy for 1 year and repeat MRI showed progression of the lesions, which on biopsy were confirmed to be diffuse, large B-cell lymphoma (DLBCL)-PCNSL. Another patient had a 4-year prodrome with headaches and dysarthria; meningeal biopsy showed a DLBCL-PLML after being treated for hydrocephalus and shunt infections for years. None of the 29 patients had initial "B" symptoms.

Pathologic features

Diagnosis was confirmed by stereotactic brain biopsy in 59% (17 patients), by surgical resection in 31% (9 patients, 4 total and 5 subtotal), and by cytologic and immunophenotypic analyses of the CSF in 10% (3 patients). In 6 cases, the diagnosis of PCNSL was retrieved from lymphoma databases at individual institutions. The original anonymized pathology reports were available in the other 23 cases. All patients were diagnosed as primary CNS non-Hodgkin's lymphoma (NHL). A total of 20 patients (69%) had DLBCL (Fig. 1), 5 patients (17%) had anaplastic large T-cell lymphoma (ALCL), 2 patients (7%) had lymphoblastic lymphoma (1 precursor-B and 1 not specified), and 2 patients (7%) with a diagnosis of Burkitt-like lymphoma. The diagnosis of PCNSL was confirmed by immunophenotyping in all patients, combined with immunoglobulin (IgH) gene rearrangement RT-PCR in 2 cases.

Therapeutic strategies

Treatment data were available for all 29 patients. Steroid use before primary therapy was documented in 12 patients (41%). Dexamethasone dose ranged from 4 to 16 mg/d. Primary treatment consisted of chemotherapy alone in 18 patients (62%), 2 of whom had intra-arterial chemotherapy with blood-brain barrier disruption (BBBD). Two patients (7%) had chemoimmunotherapy; 9 patients (31%) had chemotherapy followed by WBRT. Nine patients had initial surgical resection, followed by che-

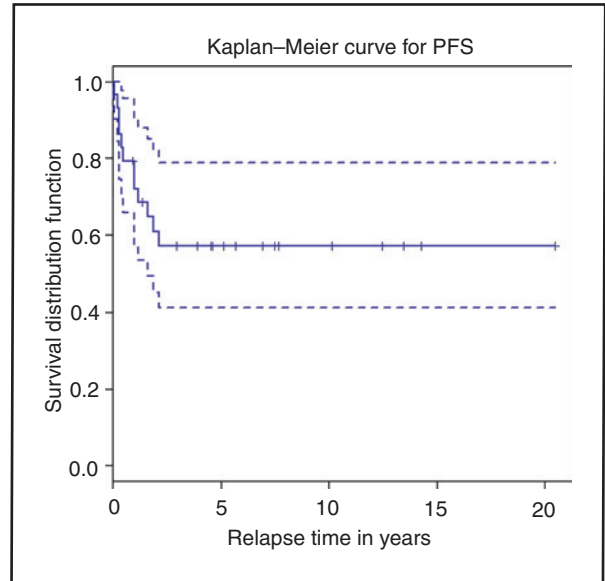


Figure 2. Progression-free survival for all patients with primary CNS lymphoma.

motherapy or chemoradiotherapy combinations (Table 1). Details of primary treatment strategies are summarized in Table 2. MTX was the most commonly used drug in combination with other agents (n = 27). The intravenous (or intra-arterial) MTX dose ranged from 60 mg/m² to 8 g/m² per course, and the most common intravenous doses ranged from 5 to 8 g/m². In 4 patients, the MTX dose was unknown. MTX therapy was interrupted in 2 patients due to anaphylaxis and severe hepatitis, respectively. Two patients had non-MTX-based regimens. Intrathecal chemotherapy was given to 17 patients (59%), 1 had IT cytarabine (Ara-C) alone and 16 had IT MTX either alone (n = 4) or in combination with Ara-C (n = 3), hydrocortisone (n = 1), or both (n = 8). Two patients had intraventricular MTX and Ara-C/rituximab, respectively. Two patients had frontline high-dose chemotherapy and autologous stem cell transplantation (ASCT) following MTX-based regimens. Primary treatment with cranial irradiation combined with chemotherapy was administered to 9 patients and consisted of whole brain irradiation

Table 1. Frontline treatment of PCNSL patients

Treatment	Patients, n (%)
Chemotherapy only	18 (62)
Chemoimmunotherapy (rituximab) only	2 (7)
Chemotherapy and WBRT	9 (31)
Surgical resection	9 ^a (31)
ASCT	2 (7)

^aThese patients had surgical resection prior to definitive treatment.

Table 2. Chemotherapy regimens at PCNSL presentation

Treatment	Patients, <i>n</i>
MTX-based	27
FAB/LMB 96 ^a	9
Bonn protocol ^b	2
CALGB-50202 ^c	1
POG-9906 ^d	1
COG-ANHL0131/A ^e	1
IA-MTX/IV Cy + BBBD ^f	2
MTX (225 mg) + vincristine (2.5 mg)	1
MTX/vincristine + other regimens ^g	3
HD-MTX (5 g/m ²) + HD-Ara-C (3 g/m ²)	3
HD-MTX (3.5–5 g/m ²) + other chemotherapy drugs ^h	4
Non-MTX based	2
CCNU	1
Vincristine/prednisone/doxorubicin	1

^aFAB (French-American-British) LMB 96 = COPADM × 2: cyclophosphamide, vincristine, prednisone, cytarabine, doxorubicin, intravenous MTX (5–8 g/m²); CYVE × 2: cytarabine (3 g/m²), etoposide.

^bMTX (3 g/m²), vincristine, ifosfamide, dexamethasone, intra-omaya chemotherapy, cytarabine (3g/m²), and vindesine.

^c MTX (3.5 g/m²), rituximab, temozolomide, cytarabine, and etoposide.

^dPOG (Pediatric Oncology Group) 9906-Acute Lymphoblastic Leukemia Protocol: vincristine, prednisone, doxorubicin, L-asparaginase; cyclophosphamide, cytarabine, 6-mercaptopurine plus IT MTX; intravenous MTX (5 g/m²), vincristine; oral 6-mercaptopurine plus oral MTX in maintenance. Patient also received 1,200 cGy WBRT.

^eCOG (Children's Oncology Group) ANHL0131-Regimen A-Anaplastic T-Large Cell Lymphoma Protocol: vincristine, prednisone, L-asparaginase, doxorubicin plus IT MTX; oral MTX plus 6-mercaptopurine/prednisone in maintenance.

^fIA-MTX: intra-arterial MTX (1.5–2.5 g/m²) × 2 days, IV Cy: intravenous cyclophosphamide (15 mg/kg/d) × 2 days, BBBD for a total of 12 months.

^gOther regimens included cyclophosphamide, doxorubicin, ifosfamide, cytarabine, and etoposide.

^hOther chemotherapy drugs included thiotepa (35 mg/m²)/cytarabine (n = 1), vincristine/procarbazine (n = 1), vincristine/cyclophosphamide/dexamethasone (n = 1), rituximab/ifosfamide/carboplatin/etoposide (n = 1).

tion in all; in one, the irradiation field also included the eyes. In 8 of these 9 patients, WBRT was delivered after chemotherapy; in 1 patient, WBRT was given initially alone without any response. This patient was subsequently switched to a MTX-based chemotherapy regimen. The irradiation dose in all patients ranged from 12 to 50 Gy (median = 24 Gy).

Response rate was determined on the basis of consensus criteria for brain tumors at the time of assessment: Macdonald criteria (9) prior to 2006 and IPCG criteria (10) after 2006.

Outcome

The median time to end of follow-up is 5.7 years (95% CI, 4.3–10.1 years). Overall response rate was 86%, with 20 patients (69%) achieving complete remission (CR) and 5 patients (17%) partial remission (PR). One patient had stable disease after initial therapy, and 3 had progressive disease. Six patients have died, 5 due to lymphoma (1 progressive disease and 4 relapses) and 1 as a result of infectious toxicity. The 5- and 10-year OS were not estimable, as the longest time to death from diagnosis was slightly over 3.5 years. Similarly, the 5- and 10-year PFS were not estimable, as all patients who relapsed did so within slightly over 2 years. The 2-year PFS (Fig. 2) and OS (Fig. 3) were 61% (95% CI, 40–76) and 86% (95% CI, 66–94), respectively. The 3-year OS was 82% (95% CI, 61–92). Ten patients (35%) have relapsed at a median 12 months from diagnosis (range, 1–25 months); 8 relapsed in the brain alone, 1 in the leptomeninges alone, and 1 in the brain and leptomeninges. One patient was salvaged with WBRT alone, and 1 had no further treatment. Eight patients received systemic chemotherapy-based regimens as salvage therapy; 3 of them had systemic chemotherapy alone, while WBRT followed chemotherapy in 4 patients and partial brain irradiation in 1. High-dose chemotherapy with ASCT was used in 4 patients as part of their salvage strategy; all are alive at a median 45 months from diagnosis (range = 18–56 months) and 26 months from relapse (range = 14–30 months). Among the 6 patients who relapsed after primary treatment with chemotherapy alone, 5 were salvaged with either WBRT alone or chemotherapy

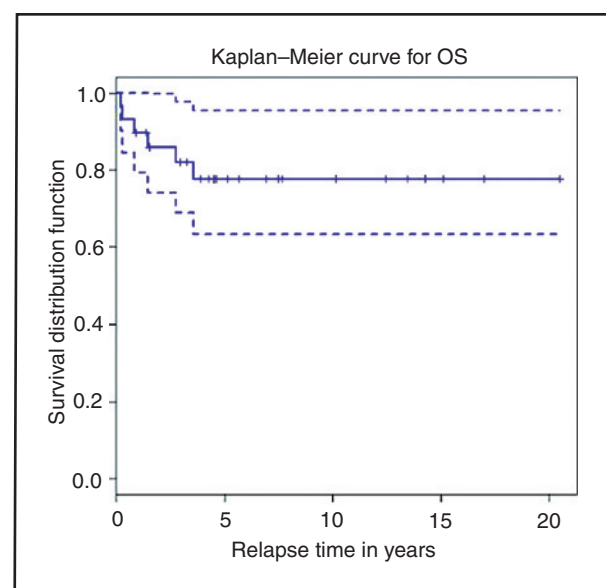


Figure 3. Overall survival for all PCNSL patients.

Table 3. Treatment of PCNSL relapses

Modality	Outcome
WBRT only: 1 patient (54 Gy)	(alive)
WBRT + chemotherapy: 5 patients	
MTX/Ara-c/Ritux/Ifos/VP16 → 24 Gy + boost 12 Gy	(died)
ICE (× 4) → 45 Gy	(died)
ICE (× 3) + BEAM-ASCT → 50 Gy	(alive)
BEAM + Ritux → ASCT + partial brain 45 Gy	(alive)
MTX/Gem/Ritux/Ifos + IO → BEAM-ASCT + WBRT	(alive)
Chemotherapy only: 3 patients	
HD-MTX → Bu/Cy/Thio → ASCT	(alive)
MTX (IA) + Cy + BBBD + IO (2)	(1 died and 1 alive)
No further therapy: 1 patient	(died)

Abbreviations: Ritux, rituximab; Ifos, ifosfamide; VP16, etoposide; ICE, ifosfamide, carboplatin, and etoposide; BEAM, BCNU, etoposide, cytarabine, and melphalan; Gem, gemcitabine; IO, intra-omaya chemotherapy; HD-MTX, 8 g/m² MTX; Bu, busulfan; Cy, cyclophosphamide; Thio, thiotepa; IA, intra-arterial.

followed by ASCT plus irradiation. Overall, 6 of the 10 relapsed patients were still alive at the time of data submission. Details on salvage treatment of the relapsed PCNSL patients are summarized in Table 3. Univariate analyses of 12 predictor variables showed that the only variable that had significant association with response was primary treatment with chemotherapy alone, which had an odds ratio (OR) of 0.125 (chemotherapy plus WBRT vs. chemotherapy alone; $P = 0.02$). Higher doses of MTX, analyzed as a continuous variable, had a marginally significant relationship with response rate, with an OR of 1.5 ($P = 0.06$). Univariate Cox models showed that only ECOG-PS was significantly associated with PFS, where a lower ECOG-PS (0–1) was associated with a hazard ratio (HR) of 0.136 for progression or death than is higher ECOG-PS (>1 ; $P = 0.017$). Age older than 14 years did not have any impact on response rates, PFS, or OS (RR: OR = 1.63, $P = 0.55$; PFS: HR = 0.85, $P = 0.79$; OS: HR = 1.21, $P = 0.81$). Lesions involving deep brain structures have been previously associated with a worse outcome (9). In our cohort, this was not shown (RR: OR = 2.5, $P = 0.33$; PFS: HR = 2.3, $P = 0.20$; OS: HR = 0.46, $P = 0.50$). Other well-known adverse prognostic factors for PCNSL are high LDH and elevated CSF protein levels (9); data regarding these 2 factors were available in only few patients. The IELSG score (ECOG-PS, tumor location, CSF protein, age, and serum LDH) could not be assessed, as data on all 5 parameters were missing in few patients. Furthermore, the collection of data on treatment-related acute toxicities was not feasible due to the retrospective nature of the study and time from diagnosis in most patients.

Neurotoxicity

Long-term neurotoxicity data was available in 7 patients (24%). Three have developed learning disability, 1 of them with chronic headaches, depression, and aggressiveness. Only 1 of these had received cranial irradiation (1,200

cGy) as part of his primary treatment. Other neurologic symptoms included seizures and visual field loss ($n = 1$), hearing loss ($n = 1$), esotropia and tremors ($n = 1$), and periodic stroke-like migraine after radiation therapy (SMART; $n = 1$). The 2 patients who presented with diabetes insipidus and Parinaud syndrome, respectively, have persistent symptoms in the presence of radiographic complete remission.

Discussion

The exact incidence of pediatric PCNSL is unknown, and it is likely that many cases are not being reported. Although mostly retrospective, our international collaboration within the IPCG allowed us to collect the largest series of pediatric and adolescent PCNSL to date. The data set was not comprehensive and contained missing values and heterogeneous treatments across different centers and throughout 3 decades. Nevertheless, some patient characteristics and treatment-related findings can be helpful for clinicians managing very young patients with PCNSL. The median age of our cohort was 14 years and, similar to previous reports (5, 8), there was male predominance. The majority of patients (49%) presented with lesions in the cerebral hemispheres, and, unlike the situation in adult PCNSL (11), involvement of deep brain structures was not associated with a difference in outcome. The most frequent pathologic subtype was DLBCL (69%), which is consistent with previous pediatric PCNSL reports (5, 8). In adults, 90% of PCNSL are represented by DLBCL (12). The pathology subtype, however, did not affect response rates or survival in our series.

Age and PS have been reported as the 2 most important prognostic factors in PCNSL (11, 13). Furthermore, age 15 years or older was associated with worse outcome in adolescents with systemic NHL treated on the French-LMB 89 study (14) and the international French-American-British (FAB)-LMB 96 study (15). In our series, only ECOG-PS was a

strong predictor of survival, whereas age older than 14 years was not. High-dose methotrexate (HD-MTX) has been the single most active agent in PCNSL to date (16). Use of MTX did not have an influence on PFS or OS in this series, however, there was a marginally significant relationship between higher doses of this drug and response ($P = 0.06$).

The prognosis of childhood PCNSL depends on the intensity and type of CNS-directed therapy. A previous review of cases treated between 1975 and 1991 showed a mean survival time of 17 months with WBRT alone or combined with chemotherapy (1). A more recent pediatric PCNSL retrospective series showed improved survival with a 5-year event-free-survival (EFS) of 70% in patients treated with chemotherapy alone, mostly consisting of HD-MTX and HD-Ara-C combinations (8). In the present study, the 3-year OS was 82% and at least 15 patients received HD-MTX plus HD-Ara-C. Two of these received the Bonn protocol (consisting of HD-MTX, Ara-C, vinca alkaloids, ifosfamide, and cyclophosphamide with intraventricular MTX, prednisolone, and Ara-C), and 9 had FAB-LMB 96-based regimens (Table 2); both protocols contain MTX and Ara-C in high doses. The Bonn protocol in adulthood PCNSL has a 5-year survival of 75% (17). Children and adolescents with CNS-positive B-NHL who were treated on the FAB-LMB 96 study received therapy that included HD-ARA-C as well as 8 gm/m² of MTX plus IT therapy without WBRT. The 4-year EFS for CNS-positive patients in this study was 75% (18).

In our study, primary treatment with chemotherapy did not have a statistically significant effect on PFS (OR = 0.51, $P = 0.31$) and OS (OR = 1.75, $P = 0.49$). The response rate for PCNSL in patients who received chemotherapy alone, however, was better than that seen in patients who received combined chemoradiotherapy. The likely explanation for this finding is the lower doses of chemotherapy, particularly of MTX, given to patients receiving combined therapy. In addition, 5 of the 6 patients who relapsed after initial treatment with chemotherapy were salvaged with either chemotherapy alone or with chemoradiotherapy combinations and ASCT. These results, together with the well-known devastating late effects of cranial irradiation in children including secondary brain tumors, neurocognitive deficits, hypothyroidism, early puberty, and short stature (19, 20) suggest that young patients with PCNSL could be treated initially with chemotherapy, without WBRT, as a single modality.

The prognosis of childhood and adolescent PCNSL seems to be better than most adult series (25%–40% 5-year EFS; ref. 21). This could be due to the fact that very young patients can tolerate higher doses of MTX more than

adults, as well as to different biology. Pediatric DLBCL has a moderate to high proliferation index, decreased Bcl2 protein expression, and an increased frequency (75%) of the germinal center (GC) phenotype (Bcl6+), which may contribute to the excellent prognosis (22). As most cases of childhood PCNSL are pathologically DLBCL (69% in our study) and if most of them are of the GC phenotype, then this could explain, at least partially, the favorable outcome in children. Where data were available, all DLBCL cases had moderate to high proliferative indices (60%–90%); Bcl2 showed weak focal expression in 2 patients, and Bcl6 was strongly positive in these.

Our descriptive study has some limitations. Not all IPCG members had treated pediatric cases of PCNSL, and some did not reply. Most cases were retrospectively collected (only 2 were prospective) and detailed data were not available. Pathology slides were not reviewed centrally and treatments were not standardized among the individual patients. Nevertheless, this study confirms our previous observation that children with PCNSL can be treated initially with chemotherapy only and that cranial irradiation can be reserved for refractory or relapsed disease. Of interest, there was also the correlation (although not statistically significant) between higher doses of MTX and response rates. Finally, our study is the first to show a correlation between ECOG-PS and outcome in pediatric and adolescent PCNSL. This may suggest that patients with an ECOG-PS of greater than 1 at diagnosis could benefit from more intensive therapy including frontline ASCT.

Because of the rarity of pediatric PCNSL and the need for many years of follow-up to detect late relapses, it is clear that no meaningful prospective phase III trials can be conducted through the North American Children's Oncology Group (COG) alone. Thus, a prospective collaboration between IPCG members and the international pediatric lymphoma groups (French-LMB, German NHL-BFM, and COG-NHL committee) might lead to better therapeutic strategies for pediatric and adolescent PCNSL. Furthermore, biology and molecular studies are warranted for this rare entity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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