Primary central nervous system lymphoma in children

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✓Primary central nervous system lymphoma (PCNSL) is a very rare brain tumor in children, and the optimal management and prognosis of such patients have yet to be defined. In this study, the incidence rate, clinical features, diagnosis, and treatment of childhood PCNSL are reviewed. Except for human immunodeficiency virus–related PCNSL, the prognosis for patients with this tumor type is significantly better in children than in adults. In the absence of prospective studies, it is very difficult to determine the true incidence and the best therapeutic strategy for this rare entity. The majority of children with PCNSL, however, can achieve long-term remissions with intensive chemotherapy alone (an estimated 70% 5-year event-free survival rate), and cranial irradiation can be reserved for relapse of the disease. Further progress in the management of childhood PCNSL will require prospective multinational studies.

KEY WORDS • primary central nervous system lymphoma • chemotherapy • radiotherapy • children

P RIMARY central nervous system lymphoma is an extranodal malignant lesion that is confined to the brain, eyes, and/or leptomeninges. Cases of PCNSL represent 4 to 7% of primary brain tumors, and its incidence has been increasing in the last three decades.⁷⁴ The incidence is increased 3600-fold in patients with AIDS.²² It can affect all age groups, with a median age in the sixth decade in patients without AIDS.³⁹ This tumor is rare in childhood; thus, the incidence and prognosis in this age group are not well defined and the best treatment strategy remains unclear. The aims of this review are to describe the incidence rate, clinical features, therapy, and outcome of childhood PCNSL and to discuss the issues pertinent to therapeutic decision making in a young patient.

Epidemiology

Among 596 cases of PCNSL reported to the Brain Tumor Registry of Japan between 1969 and 1990, only nine pediatric cases (1.5%) were observed.⁴¹ In the US, the Surveillance, Epidemiology, and End Results program (which ran from 1973 to 1998) found 1% of all PCNSLs in patients younger than 19 years of age,⁴⁰ giving an estimated incidence of 15 to 20 cases per year in North America. It is estimated that 14 cases of pediatric PCNSL will be reported annually to the newly opened rare non-Hodgkin lymphoma registry of the Children's Oncology

Group.² This tumor tends to occur more frequently in immunodeficient children, with an incidence of 0.57 to 1% in HIV-infected children⁶¹ and 4% in patients with congenital immunodeficiency.⁶⁴ Nevertheless, most of the 43 pediatric patients with PCNSL reported during the last decade were immunocompetent. These 43 cases include 31 previously reported ones and 12 cases from our recent multiinstitutional series.² The median age of the 43 patients was 9 years (range 2–18 years) at diagnosis. In an earlier review, however, PCNSL was reported in infants as young as 1 month old.⁴¹ In the present review, PCNSL was more common in male than in female patients (26 compared with 17).

Clinical Presentation

Clinical findings at presentation include increased intracranial pressure (severe headaches, vomiting, and papilledema), facial nerve palsy, diplopia, dysarthria, ataxia, bulbar palsy, quadriparesis, and obtundation.^{1,2,75,79,81} Less frequent findings include seizures, acute blindness, proptosis, lower- and upper-limb muscle weakness, nystagmus, paresthesias, personality change, lethargy, and somnolence.^{2,9,15,29,44,67,77,78} Children with PCNSL may also present solely with diabetes insipidus and progressive panhypopituitarism due to pituitary and hypothalamic involvement.^{9,17,70}

Radiographic Features

Pediatric PCNSL may present as a solitary mass or as a multifocal tumor. The most frequent tumor locations in children are the parietal and frontal lobes, cerebellum, pituitary stalk, and hypothalamus,² whereas PCNSL in adults most commonly involves the periventricular re-

Abbreviations used in this paper: ALCL = anaplastic large cell lymphoma; AraC = cytarabine; BBB = blood-brain barrier; CHOP = cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone; CNS = central nervous system; CSF = cerebrospinal fluid; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; EFS = event-free survival; MTX = methotrexate; PCNSL = primary CNS lymphoma.

gion, basal ganglia, corpus callosum, and the deep white matter.¹⁹ In children with PCNSL, contrast-enhanced computed tomography scanning usually shows a characteristic heterogeneous pattern, marked edema, and a prominent mass effect with a ring-like peripheral pattern of enhancement.⁶⁵ Heterogeneous and ring-like enhancement are less common in adults.¹⁹ Occasionally, pediatric cases have predominant leptomeningeal involvement and no evidence of an intracranial mass. Eight (18%) of the 43 pediatric cases reported in the last 10 years were primary leptomeningeal lymphomas.

Pathological Features

Reports on 43 pediatric patients with PCNSL were reviewed. The diagnosis was established either by stereotactic biopsy (24 cases), leptomeningeal biopsy (two), open biopsy (three), autopsy (two), or by immunocytochemical, cytogenetic, and polymerase chain reaction analysis of CSF (nine). In the other three children the diagnostic method was not reported. The DLBCL is the most common subtype (13 [30%] of 43), followed by ALCL (21%; seven T-cell and two null-cell tumors), lymphoblastic lymphoma (16%; five precursor-B and two T-cell lesions^{6,78}), Burkitt (12%), histiocytic (5%, confirmed by immunohistochemical findings), and other (6%) lesions. Histological findings were not reported in 10% of cases. The most common immunophenotype was mature B-cell (43%), followed by T-cell (21%), precursor B-cell (12%), null-type (10%), and histiocytic (5%) tumors. By contrast, T-cell lymphomas comprise less than 5% of all cases of adult PCNSL,⁷⁶ and to the best of our knowledge precursor B-cell lymphomas have not been reported in adults.

Prognosis and Biology

The prognosis of adult patients with PCNSL is poor, with an estimated 5-year EFS of 25 to 40%.⁴⁹ In pediatric patients with PCNSL, however, the prognosis has improved over the last 10 years. A review by Kai, et al.,⁴¹ of pediatric cases treated between 1975 and 1991 found a mean survival time of 17.1 months (range 0.3–78 months), with the majority of cases treated with cranial radiotherapy alone or combined with moderate chemotherapy. In our more recent pediatric series, the 5-year EFS was 70% in children with PCNSL who were treated with chemotherapy alone.² The use of more intensive chemotherapy regimens based mainly on high-dose MTX and high-dose AraC may have contributed to this improvement. Young age is considered to be a favorable prognostic factor in PCNSL in adults,¹³ which may reflect differing biology or the ability to tolerate more intensive therapy. Performance status (Karnofsky Performance Scale or Eastern Cooperative Oncology Group score) is another prognostic indicator that was not assessed in any of the pediatric studies.

A correlation between histological findings and prognosis can be inferred, with the histiocytic subtype being the most aggressive among published pediatric cases of PCNSL; the overall survival was only 3 to 4 months.^{18,77} Lymphoblastic lymphoma, which occurred more frequently in children, was thought to have a worse prognosis

with a high relapse rate and a tendency toward leukemic transformation.⁴¹ In the present review, however, all patients with B-lineage lymphoblastic lymphoma were alive 22 or more to 77 or more months after treatment with an intensive chemoradiotherapy combination.^{1,29,69} Among the children in whom an ALCL was diagnosed, a better outcome was associated with ALK-1 positivity, lack of necrosis, and unifocal tumor.³⁵ Within the most common subtype of DLBCL, studies in adults have demonstrated the prognostic importance of the germinal center stage of systemic DLBCL.²³ Coupland, et al.,²³ showed that most PCNSLs in adults were late germinal center or postgerminal center stage, and Braaten, et al.,¹⁴ demonstrated a median survival duration of 101 months for those with *BCL-6* expression (reflecting the germinal center stage) compared with 14.7 months in patients whose tumors were *BCL-6*-negative. In pediatric cases of DLBCL, most tumors have been shown to be late germinal center stage.⁶⁰ If this is true for pediatric cases of PCNSL as well, it may, at least in part, explain the better prognosis in children.

Treatment

The best treatment strategy for pediatric PCNSL has yet to be established, although many reports have shown long-term survival with chemotherapy alone without cranial radiotherapy.^{2,21,38,75,82} Possibilities for therapy include surgery, cranial radiotherapy alone, chemotherapy followed by cranial radiotherapy, chemotherapy alone, BBB disruption-enhanced chemotherapy, high-dose chemotherapy with stem cell rescue, and various new experimental therapies. All authors agree that cranial radiotherapy prior to chemotherapy significantly increases neurotoxicity, and therefore it is not recommended.

Surgery Alone

Because the overall survival after surgery alone is 3 to 5 months,⁵¹ the utility of surgery in both pediatric and adult patients with PCNSL is limited to biopsy sampling. Aggressive surgery has been shown to worsen the neurological deficit with no increase in the survival rate. As a result, the recommended approach to diagnosis is CSF examination when safe, followed by a stereotactic biopsy procedure if the CSF findings are negative.

Cranial Radiotherapy Alone

Due to the extreme radiosensitivity of this tumor, cranial radiotherapy has been the mainstay of treatment for PCNSL for many years,⁵² with doses ranging from 36 to 45 Gy. Earlier studies demonstrated a 90% response rate to cranial radiotherapy alone, with a median survival duration of 11.6 to 18 months; a 5-year overall survival rate of 4%; a high relapse rate (80%) over 10 to 14 months; and severe neurotoxicity, particularly in elderly adults.¹² In the study of cranial radiotherapy alone published by Nelson, et al.,⁵³ 61% of patients suffered a relapse of the tumor within the radiation field. Among the pediatric cases reported in the last decade, three were treated with cranial radiotherapy alone: two patients were alive at 56 and 60 months, respectively, and the third suffered a relapse at 12 months.^{19,35,41} The numbers are too small for meaningful

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assessment of treatment efficacy, but in children there are even greater concerns about the use of cranial radiotherapy due to the high risk of secondary brain tumors⁴⁸ as well as the risk of severe neurocognitive dysfunction.⁶² Treatment of pediatric PCNSLs with cranial radiotherapy alone is therefore not indicated, except in the palliative setting.

Chemotherapy Followed by Cranial Radiotherapy

Early attempts to improve the survival rate by adding standard chemotherapy such as CHOP to cranial radiotherapy failed, probably due to the inability of component drugs such as vincristine and doxorubicin to cross the BBB.⁵⁰ The combination of high-dose MTX and cranial radiotherapy resulted in better survival rates (30–60 months) but worse neurotoxicity in adult patients.³ Twelve children of the 43 in this review received chemoradiotherapy; eight (66%) of the 12 were alive at the time of this report (22–98 months after diagnosis). Chemotherapy regimens were mostly based on high-dose MTX and high-dose AraC combined with dexamethasone or prednisone, plus or minus other drugs. Radiotherapy consisted of either cranial radiotherapy or craniospinal radiotherapy, with doses ranging from 12 to 50 Gy. No long-term late effect data are available in this group of patients.

Chemotherapy Alone

A number of studies conducted in adult patients support the suggestion that when drugs that cross the BBB are used, patient survival is equivalent to that seen after combined therapy, with significantly fewer cognitive defects.^{33,34,59,63} Based on results of the largest single case series of pediatric PCNSL, consisting of 12 patients, we would suggest that most children with PCNSL can achieve long-term remissions with chemotherapy alone and without cranial radiotherapy.² Ten children underwent first-line treatment with chemotherapy alone (mostly high-dose MTX and high-dose AraC combinations), with a 5-year EFS of 70% and a median follow-up time of 79 months (range 31–122 months). Two children received chemotherapy and cranial radiotherapy, one of whom experienced a relapse and died of his disease, whereas the other remains in continuous complete remission more than 98 months from diagnosis.

These results are concordant with the international FAB LMB-96 study results in children and adolescents with CNS-positive B-cell non-Hodgkin lymphoma, in whom the abandonment of cranial irradiation and an additional course of systemic high-dose MTX (8 g/m²) and intrathecal chemotherapy resulted in a 70% 4-year EFS rate.³⁶ Among the total group of 43 pediatric patients with PCNSL, 23 were treated with chemotherapy alone; 18 (78%) of the 23 were alive at the time of this report. It is noteworthy that two of the patients who experienced a relapse without prior radiation therapy underwent salvage treatment with autologous stem cell transplant combined with cranial radiotherapy in one,² and EBV-cytotoxic immunotherapy followed by allogeneic stem cell transplant⁸¹ in the other.

High-dose MTX is the single most important drug for the treatment of PCNSL.⁵ It has been established that MTX has a lymphoblastolytic action and the ability to

penetrate the CNS at doses of 1 g/m² or more.⁴⁹ At doses of 3.5 g/m² or more it yields tumoricidal levels in the CSF.¹⁰ The optimal dose of MTX in PCNSL is not well defined, although in most trials investigators used doses ranging from 1 to 5 g/m², with 3.5 g/m² being the most common dose.³⁰ Intensifying the MTX dose to 8 g/m², an amount commonly used in pediatric systemic non-Hodgkin lymphoma, was found to be beneficial in one study.⁸⁰ High-dose MTX produces a response rate of 52 to 88% when given as a single agent and 70 to 94% when administered with other drugs and cranial radiotherapy.²⁴ However, single-agent therapy, even with very-high-dose MTX (8 g/m²) leads to a higher risk of relapse, at least in adult patients.¹² In agreement with this, one HIV-positive child with PCNSL, who was treated with high-dose MTX monotherapy, suffered a relapse and died 4 months after diagnosis.²

Cytarabine also has a proven efficacy in PCNSL, especially at doses of 3 g/m² or more.⁷¹ Adding high-dose AraC to high-dose MTX has given better overall survival rates compared with high-dose MTX alone (2-year overall survival 64% compared with 18%).³¹ The combination of MTX and AraC at high doses has a synergistic action.³² Pels, et al.,⁵⁹ have shown a benefit from the combination of high-dose MTX (5 g/m²) and high-dose AraC (3 g/m²) in one prospective study performed in adults. Furthermore, the LMB and Berlin–Frankfurt–Münster studies have confirmed a benefit from the introduction of high-dose AraC (CYVE protocol) together with an increased dose of MTX (8 g/m²) in CNS-positive childhood systemic B-cell lymphomas.⁵⁷ In our review, 16 children with PCNSL who received high-dose AraC combined with other agents had long-term remissions.

Other Chemotherapeutic Agents

Drugs with poor BBB penetration, such as CHOP, are very active against systemic non-Hodgkin lymphoma but have little role in the treatment of PCNSL. Four trials have failed to show any benefit of CHOP plus cranial radiotherapy compared with cranial radiotherapy alone.^{46,66,68,73} Furthermore, these agents usually cause significant myelosuppression, peripheral neuropathy, and potential cardiomyopathy. Etoposide and ifosfamide have a good CNS penetration and were used in combination with AraC as salvage chemotherapy in recurrent PCNSL, with a 1-year overall survival rate of 41%.⁸ Etoposide is also given in the intensification phase of the LMB-89 protocol, a therapy that was used successfully in some pediatric PCNSL cases (Table 1).⁵⁸ High-dose busulfan, cyclophosphamide, and thiopeta have good CNS penetration. Studies in adults have shown superiority of this combination as conditioning therapy for stem cell transplant in refractory PCNSL.⁷²

Blood–Brain Barrier Disruption

The normal BBB prevents passage of ionized water-soluble substances with molecular weights more than 180, and most chemotherapy drugs have a molecular weight between 200 and 1200. Even if the BBB is disrupted by the tumor, the disruption is variable and dependent on tumor type. In addition, most investigators agree that dose intensity is a significant predictor of longer survival time in PCNSL.⁴⁵ With these points in mind, Neuwelt, et al.,⁵⁵

TABLE 1
Literature review of pediatric PCNSL cases reported between 1996 and 2006*

Authors & Year	Age (yrs), Sex	Lesion Site	Histology/ Immunophenotype	Immune Status	Lepto Involvement	Chemo	RT (dose)	Outcome (mos)
Torres et al., 1996	2, M	primary lepto	histiocytic	normal	yes	cyclo, ida, VCR, dex, IT AraC	none	dead (3)
Rodriguez et al., 1997	3, M	multifocal frontal, periventricular	DLBCL	HIV-pos	NR	none	none	dead (2)
Ciftci et al., 1998	12, M	corpus callosum	DLBCL	normal	no	none	yes	NR (12)
Kai et al., 1998	5, M	cerebellum	small lymphocytic B-cell	normal	no	none	yes (50 Gy)	alive (60)
Uetsuka et al., 1999	7, M	parietal	lymphoblastic T-cell	normal	no	cyclo, VCR, pred, dauno, asp, 6-MP, IT MTX/AraC	none	alive (19)
Yang et al., 1999	10, M	multifocal cerebral	Burkitt	normal	yes	LMB-89 (C) protocol	none	alive (48)
Al-Ghamdi et al., 2000	10, F	cerebellum	lymphoblastic T-cell	normal	yes	HD-MTX (9 g/m ²), HD-AraC (3 g/m ²), asp	CSRT (50.4 Gy)	dead (57)
Felice et al., 2000	12, F	primary lepto	lymphoblastic pre-B-cell	all normal	all yes	all w/ BFM-ALL tx	CSRT (24 + 6 Gy)	alive (77)
	7, F						(15 + 6 Gy)	alive (67)
	4, M						(18 + 6 Gy)	alive (35)
Kim et al., 2000	18, F	primary lepto	DLBCL	normal	yes	cyclo, adria, VCR	none	NR (36)
Baleyrier et al., 2001	9, M	pituitary	DLBCL	normal	yes	LMB-96 (C) protocol	none	alive (12)
Cheuk et al., 2001	11, M	cerebellum, occipital, frontal	histiocytic	normal	NR	none	none	dead (4)
Silfen et al., 2001	15, M	pituitary	Burkitt	normal	no	CCG-5961 protocol, incl HD-MTX + AraC	none	alive (17)
George et al., 2003	17, M	parietal dura mater	ALCL T-cell	normal	no	none	yes	alive (56)
	18, F	temporal	ALCL T-cell	normal	no	yes	yes	alive (60)
	4, F	multifocal brain, brainstem, & spinal cord	ALCL, indeterminate	normal	yes	yes	yes	alive (71)
	10, F	parietal, falx	ALCL T-cell	normal	no	yes	yes	dead (6)
	13, M	parietal, frontal	ALCL T-cell	normal	yes	yes	none	dead (1)
	12, F	occipital	NR	NR	NR	yes	yes	dead (63)
Shehu, 2003	8, M	rt orbit, lt temporal	Burkitt	normal	no	cyclo, VCR, MTX, IT AraC	none	dead (1)
Abela et al., 2004	6, M	lepto	lymphoblastic pre-B-cell	normal	yes	ALL txs, incl HD-MTX (5 g/m ²)	CRT (12 Gy)	alive (36)
Haldorsen et al., 2004	11, M	NR	NR	NR	NR	AraC, VCR, IT MTX/AraC	none	alive (74)
	13, M	NR	NR	NR	NR	MTX, AraC, VCR, IT MTX	none	alive (63)
Brennan et al., 2005	6, F	cortex deep white matter	DLBCL	PTLD	NR	none	none	alive (26)
Fallo et al., 2005	2, F	multifocal frontal, occipital	DLBCL	HIV+	no	none	none	dead (3)
Neuwelt et al., 2005	10, M	NR	NR	NR	NR	BBB-D-based HD-MTX	none	alive (104)
Shiozawa et al., 2005	9, M	occipital	lymphoblastic pre-B-cell	normal	yes	HD-MTX + AraC, triple IT	CSRT (24 Gy)	alive (22)
Uhlenberg et al., 2005	8, M	primary lepto	DLBCL	NR	yes	none	none	dead (20)
Wynn et al., 2005	8, F	parietal cerebellum	DLBCL	con immun	no	LMB-96 protocol + rituximab → progression→EBV T-cell immunotherapy → allo SCT	none	alive (17)
Abela et al., 2006†	7.5, (Med.) 6, M 6, F	8 multifocal, 4 solitary	5 DLBCL, 1 Burkitt, 3 ALCL T-cell, & 3 indeterminate	8 normal, 2 con immun, & 2 HIV-pos	1 pos, 7 neg & 4 NR	10 w/ chemo alone mostly: HD-MTX + AraC	1 CRT + chemo, & 1 CSRT + chemo	3 dead (4–26), 9 alive (31–122)

(continued)

developed an approach in which intraarterial hyperosmolar agents such as hypertonic saline or mannitol are given

TABLE 1 (continued)
Literature review of pediatric PCNSL cases reported between 1996 and 2006*

Authors & Year	Age (yrs), Sex	Lesion Site	Histology/ Immunophenotype	Immune Status	Lepto Involvement	Chemo	RT (dose)	Outcome (mos)
Taga et al., 2006	11, M	primary lepto	Burkitt	normal	yes	BFM-90 protocol for NHL, incl HD-MTX (5 g/m ²) + HD-AraC (2 g/m ²) + triple IT	none	alive (33)

*Adria = adriamycin; ALL = acute lymphoblastic leukemia; allo SCT = allogeneic stem cell transplant; asp = asparaginase; BBB-D = BBB disruption; BFM = Berlin–Frankfurt–Münster; chemo = chemotherapy; con immun = congenital immunodeficiency; CRT = cranial radiation therapy; CSRT = craniospinal RT; cyclo = cyclophosphamide; dauno = daunomycin; dex = dexamethasone; HD = high-dose; ida = idarubicin; incl = including; IT = intrathecal; lepto = leptomeningeal; Med = median; 6-MP = 6-mercaptopurine; neg = negative; NHL = non-Hodgkin lymphoma; NR = not reported; pos = positive; pre-B = precursor B; pred = prednisone; PTLN = posttransplant lymphoproliferative disorder; tx = therapy; VCR = vincristine.

†This series includes the patient reported by Capra, et al.

to cause BBB disruption, therefore enhancing chemotherapy delivery to microscopic tumoral areas.

To date, more than 3000 procedures have been performed in more than 300 adult patients by the BBB Disruption Consortium. In one such study, intraarterial MTX (2.5 g/day, 2 days) in conjunction with BBB disruption and without cranial radiotherapy gave an estimated 5-year survival rate of 42% when used as first-line therapy, without causing cognitive impairment.⁴⁹ No survivors were seen among patients in whom previous cranial radiotherapy had failed. These results were believed to be equal to those of non-CNS lymphoma in adults, but they are nonetheless significantly inferior to the results found in pediatric patients treated with systemic chemotherapy alone.

One of the pediatric patients with PCNSL whose case was reviewed was treated with BBB disruption-enhanced MTX chemotherapy and remains well at 104 months with no cognitive dysfunction.⁵⁴ However, there is no evidence that BBB disruption is superior to high-dose systemic MTX therapy, at least in children, and the toxicities associated with BBB disruption, such as seizures (6.8%), strokes (6–8%), nonfatal thromboembolic events (23%), dissections, and edema⁴⁵ cannot be justified in this population, at least with the present state of knowledge. Finally, BBB disruption is a very complex procedure and its use is limited to centers with a specialized team. The BBB disruption-enhanced therapy may be useful in patients who cannot tolerate high systemic doses, in pediatric salvage protocols, or as a means to administer other therapies such as monoclonal antibodies or gene therapies that do not cross the BBB.

Role of Intrathecal Chemotherapy

In children with parenchymal PCNSL, lymphoma cells were detected in the CSF in seven (16%) of 43 cases at diagnosis, and primary leptomeningeal lymphoma without parenchymal CNS disease was identified in eight (18%) of 43. Primary leptomeningeal lymphoma represents 7% of PCNSL cases in adults and usually has a very poor prognosis, with a median survival duration of 8 months.⁴⁷ However, five of eight of the pediatric patients with primary leptomeningeal lymphoma are long-term survivors. Intrathecal chemotherapy is the mainstay of therapy for lymphomatous meningitis; however, the role of both intraventricular and intrathecal therapy is still controversial, especially when high doses of intravenous MTX (> 3 g/m²) are used.⁴³ The major problem is the additional neurotoxicity associated with intrathecal MTX,

particularly when given in conjunction with systemic MTX or cranial radiotherapy. Of the 43 pediatric patients, 26 received intrathecal chemotherapy. Due to the retrospective nature of this review and because of the heterogeneity of treatment strategies, the impact of intrathecal chemotherapy on the outcome in children with PCNSL cannot be truly assessed. In the absence of prospective studies, we suggest reserving intrathecal chemotherapy for CSF-positive patients.

Stem Cell Transplant

Following the study by Soussain, et al.,⁷² in which a 3-year EFS of 53% and an overall survival of 63% were demonstrated in 22 patients with relapses of PCNSL who received high-dose chemotherapy and autologous stem cell transplant, a number of studies were performed in which investigators looked at the role of autologous stem cell transplant as front-line therapy for PCNSL, with survival durations ranging from 50 to 69% at 5 years.^{4,16} Two pediatric patients with PCNSL in this series underwent autologous stem cell transplant. One patient received the transplant as part of her front-line therapy and remains in continuous complete remission at more than 91 months from diagnosis; the second underwent an autologous stem cell transplant combined with cranial radiotherapy after relapse and is in continuous complete remission at more than 55 months.² The patient who underwent allogeneic stem cell transplant after progressive disease is alive at 17 months.⁸¹ The role of stem cell transplant as first-line treatment in pediatric PCNSL is still unclear. However, high-dose therapy with rescue seems a reasonable alternative for slowly responding or refractory disease. Due to the high incidence of neurotoxicity, stem cell transplant may not be feasible in patients who have received previous radiation therapy.^{5,72}

Treatment of Immunocompromised Children

Eight of 43 pediatric patients with PCNSL in this review were immunodeficient. One patient with EBV-positive CNS posttransplant lymphoproliferative disorder remains in continuous complete remission at more than 26 months after withdrawal of immunosuppression and intravenous acyclovir.¹⁵ In four children, HIV-related PCNSL was diagnosed in this review; two were not treated,^{28,61} whereas the other two were treated with monochemotherapy (one with high-dose MTX and the other with hydroxyurea).² All four patients died between 2 and 26 months after their diagnosis. All 10 pediatric patients with HIV-

associated PCNSL reported on since 1986 have died.^{7,20,25–28,37,42,61} Highly active antiretroviral therapy combined with cranial radiotherapy (≥ 30 Gy) improved survival duration for adults with HIV and PCNSL.⁵⁶ Because the outcome in these patients is further compromised by coexisting AIDS-related encephalopathy,³⁷ however, this therapy cannot be recommended for pediatric patients with HIV, and cranial irradiation should be reserved for palliation.³⁷ The utility of highly active antiretroviral therapy and effective multidrug chemotherapy in pediatric HIV-associated PCNSL is unknown. By contrast, three patients with congenital immunodeficiencies and PCNSL are in continuous complete remission at more than 17, 90, and 122 months from initial diagnosis, following treatment with multiagent chemotherapy protocols.^{2,81}

Conclusions

The literature on PCNSL in children is scant and sporadic due to the rarity of this disease. It is very difficult to determine the true incidence of pediatric PCNSL, and it is likely that many cases of this lesion are not being reported. Firm conclusions regarding the best therapeutic options are difficult in the absence of prospective studies. With the exception of HIV-associated PCNSL, review of the published pediatric cases supports the suggestion that the prognosis is significantly better in patients who present with PCNSL in childhood than in their adult counterparts. Whether this difference is due to different biology or better tolerance of chemotherapy is uncertain, but based on our review of the existing literature we suggest that the majority of pediatric patients can be cured with high-dose multidrug chemotherapy and that cranial irradiation can be reserved for refractory or recurrent disease. Intrathecal therapy can be reserved for patients with lymphomatous meningitis, and the role of BBB disruption and ultrahigh-dose therapy and stem cell rescue remain to be elucidated. Due to the rarity of the condition, multinational cooperative trials are essential for progress to be made.

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