Management of primary central nervous system lymphoma in children

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A 14-year-old boy with no significant past medical history presents with headaches and vomiting and is found to have a 2 × 3-cm left parietal lobe mass. A stereotactic biopsy reveals diffuse large B-cell lymphoma (DLBCL). Cerebrospinal fluid cytology, as well as bone marrow biopsies are negative, and a whole-body positron emission tomography/computed tomography scan does not demonstrate other areas of disease. The primary medical team asks how you would treat this patient.

Learning Objectives

- Understand the role for surgery, whole brain radiation therapy, and chemotherapy in the treatment of primary central nervous system (CNS) lymphoma in children
- Describe appropriate chemotherapy regimens for the treatment of primary CNS lymphoma in children and the evidence to support their use

Introduction

Primary central nervous system lymphoma (PCNSL), a rare form of extranodal non-Hodgkin lymphoma (NHL), occurs in adults and children. The disease is typically restricted to the central nervous system (CNS) and can involve the brain, spinal cord, cranial nerves, eyes, and meninges. The exact incidence of PCNSL in children is unknown; however, estimates based on Surveillance, Epidemiology, and End Results Program data suggest that approximately 15 to 20 cases are diagnosed annually in the United States.[1,2] Given the rare occurrence of this tumor, there are no prospective clinical trials in pediatrics to guide management. There have been case reports and case series describing approximately 100 cases over the course of last 20 years.[3-8] In this minireview, we summarize data from recent pediatric series (Table 1), as well as clinical trials in adults, to guide the treatment of PCNSL in children.

Clinical and histologic features

The median age of pediatric patients with PCNSL ranges from 7 to 14 years.[3,5,7,8] The most common presenting symptoms are manifestations of increased intracranial pressure, including headache, vomiting, visual changes, or altered mental status.[4] The optimal modality for neuroimaging in suspected cases is a contrast-enhanced brain magnetic resonance imaging scan. The lesions in PCNSL can be solitary or multifocal and are isointense to hypointense on T2-weighted magnetic resonance imaging scan sequences.[9] Isolated leptomeningeal disease can occur and was reported in 18% of cases in 1 review.[4]

Occasionally, the diagnosis can be made from cytology/flow cytometry/cytogenetic or molecular analysis of the cerebrospinal fluid (CSF); however, the most common and efficient method to obtain a diagnosis is a stereotactic biopsy. In general, brain biopsy should not be deferred in suspected PCNSL cases, as waiting on CSF or vitreous fluid assessment leads to delayed diagnosis. In adults, the histology in more than 90% of cases is DLBCL, which is also the most common subtype in pediatrics, but the incidence of this subtype in children ranges from 30% to 70%.[3-5,7,8] Other common histologic subtypes in pediatrics are anaplastic large cell lymphoma (ALCL), Burkitt lymphoma, and lymphoblastic lymphoma.

The prognosis of PCNSL in adults has improved with the use of high-dose chemotherapy. Although a substantial number of adult patients achieve long-term remission, most are not cured of their disease with contemporary therapies. In pediatrics, less is known regarding prognosis; however, outcomes in recent series are similar to that of systemic NHL with CNS disease with 3-year overall survival (OS) of 62% to 83%.[3,5,7,8,10]

Role of surgical resection

PCNSL is a diffuse and often multifocal disease. In both children and adults, the role of surgery is generally restricted to biopsy for diagnostic purposes or, in rare cases, emergent debulking to relieve impending brain herniation. Surgical resection alone is generally considered ineffective as a therapeutic intervention and is associated with a median survival of 1-4 months.[11-13] Attempts at resecting PCNSL are associated with an increased risk for neurological complications without survival benefit in most reports.[14,15] In a subset analysis from 1 prospective randomized trial, there was a suggested

Conflict-of-interest disclosures: L.G.-R. and O.A. declare no competing financial interests. T.T.B. has consulted for Roche, Merck, Acerta, Foundation Medicine, Proximagen, and Oxigene.

Off-label drug use: None disclosed.

Table 1. Pediatric PCNSL cases reported from 2006 to 2016

Reference	N	Median age (range)	Percentage immunocompromised	Histology				Treatment				Outcome
				DLBCL	ALCL	BL	Other	Chemo alone	Chemo + RT	Resection before treatment	Other	Chemotherapy regimen	
Abla et al, 2006[3]	12	7.5 y (4-17 y)	33	42%	33%	8%	17%	83%	17%	8%	0	Ara-C and/or MTX based: 92% Palliative hydroxyurea: 8%	9/12 patients alive 5-y EFS 70%*
Abla et al, 2011[5]	29	14 y (2-21 y)	10	69%	17%	7%	7%	62%	31%	31%	7%	MTX-based: 93% Non-MTX based: 7%	3-y OS 82%
Yoon et al, 2012[8]	6	10 y (23 mo-13 y)	0	50%	0	33%	17%	100%	0	0	0	LMB96: 83% CCG106B: 17%	5-y OS 83%
Thorer et al, 2014[7]	17	13 y (1-17 y)	30	41%	29%	6%	24%	71%	29%	0	0	NHL-BFM90, NHL-BFM95, or B-NHL BFM04	3-y OS 63% (whole cohort) 3-y OS 92% (immune competent)
O'Suoji et al, 2016[6]	5	13 y (6-16 y)	20	40%	40%	0	20%	NR	NR	NR	NR	NR	EFS and OS 100% with median follow-up 2.1 y

*Among patients treated with chemotherapy alone.
NR, not reported.

benefit to surgical resection; however, the analysis was limited by probable selection bias.[16] The recommendation in both pediatrics and adults at this time is to restrict surgery to a diagnostic stereotactic biopsy.[1,9]

Role of whole-brain radiation therapy

Whole-brain radiation therapy (WBRT) was evaluated in a prospective trial of adult patients with PCNSL.[17] In this study, 40 Gy followed by a 20-Gy boost resulted in radiographic responses, but the responses were not durable. The median OS was 11.6 months, and the 2-year OS was 25%. A pediatric series reported similar outcomes in patients treated with WBRT alone or in combination with low-dose chemotherapy with a median OS of 17 months.[18] Subsequently, WBRT was combined with high-dose methotrexate (HD-MTX)–based chemotherapy with improved outcomes in adults.[19] To evaluate the specific contribution of WBRT, a randomized trial in adult patients was conducted evaluating HD-MTX with or without WBRT for patients who achieve a complete response after chemotherapy.[20] Results from this study suggest a trend toward improved progression-free survival (PFS) among patients treated with chemotherapy + WBRT (median PFS, 18.3 vs 11.9 months; $P = .14$), but no difference in OS. Three ongoing randomized trials in adults are assessing the role of WBRT (NCT01011920, NCT01399372, NCT00863460) for newly diagnosed patients with PCNSL. In summary, data from adult trials suggest that WBRT in combination with chemotherapy may improve PFS, but not OS, when compared with chemotherapy alone.

Although there are no randomized studies evaluating WBRT in pediatrics, there are reports of favorable outcomes among patients treated with chemotherapy alone. A retrospective series of 12 patients reported a 5-year event-free survival (EFS) of 70% among the 10 patients who received chemotherapy alone.[3] In the largest series of pediatric patients with PCNSL (29 patients), treatment with WBRT was not associated with an improved outcome, and the response rate was higher in patients who received chemotherapy alone, likely as a result of the increased dose of chemotherapy given in the absence of WBRT.[5] In 1 series, 17 pediatric patients with PCNSL were treated on the Berlin-Frankfurt-Munster (BFM) protocols in which WBRT was given only for ALCL histology (5 patients, 29%). The 3-year OS among immunocompetent patients was 92%, suggesting the majority of pediatric patients can be successfully treated without WBRT.[7] Given the potential for serious neurotoxicity that can result from WBRT in children,[21] this treatment modality should be reserved for refractory or relapsed patients.

Chemotherapeutic approaches

Systemic chemotherapy

Systemic chemotherapy is an essential component of treatment of PCNSL. Chemotherapeutic agents must be carefully selected and administered at doses that allow adequate CNS penetration. Drugs with poor penetration of the blood–brain barrier (ie, anthracyclines or cyclophosphamide), which can be quite toxic if administered at high doses, are not as effective in lymphomas of the nervous system. For example, the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone), which is highly active in systemic DLBCL in adults, demonstrates limited activity in adult PCNSL.[22] Corticosteroids are frequently used before the initiation of chemotherapy to reduce cerebral edema; however, these drugs induce only a transient response when used as monotherapy and should be avoided before histopathological diagnosis, as a biopsy specimen obtained after corticosteroid use can be nondiagnostic. In adults, HD-MTX–based

chemotherapy (≥3 g/m^2) is considered the standard of care for patients with PCNSL.[23] Prospective randomized trials in adults have demonstrated an improved response rate and PFS when HD-MTX is combined with other chemotherapeutic agents that cross the blood–brain barrier, such as high-dose cytarabine (HD-Ara-C) and thiotepa.[24,25]

In most pediatric series, patients with PCNSL have been treated with different chemotherapy regimens; however, common themes exist among these reports (Table 1). In a series of 12 children with PCNSL diagnosed from 1995 to 2003, 10 were treated with chemotherapy alone with a 5-year EFS of 70%. Nine of the 10 patients received HD-MTX and/or HD-Ara-C as part of their treatment.[6] In the largest series reported (29 patients), most patients were treated with MTX (93%), and at least 15 patients received both HD-MTX and HD-Ara-C. The most common regimen used in this cohort was the FAB/LMB 96 protocol (n = 9), which consists of multiagent chemotherapy including HD-MTX (3-8 g/m^2), HD-Ara-C (3 g/m^2), and triple intrathecal chemotherapy. There was a marginally significant relationship between higher doses of MTX and radiographic response. The 3-year OS for the entire cohort was 82%, which is similar to the outcome of patients with CNS-positive systemic NHL treated on the FAB/LMB96 protocol (4-year OS, 82%).[10] Five of 6 patients who relapsed after chemotherapy responded to second-line treatment and were in remission at the time of publication.[8] Similar outcomes were reported in a smaller series (n = 6) also treated with LMB96 or similar therapy with a 5-year OS of 83%.[8] The BFM group reported their experience treating 17 pediatric patients with PCNSL according to 3 successive BFM protocols for NHL between 1990 and 2011. Treatment consisted of 6 cycles of combination chemotherapy, which included HD-MTX, HD-Ara-C, and triple intrathecal chemotherapy. WBRT at 24 Gy was given to patients with a diagnosis of ALCL. With a median follow-up of 7.5 years, the 3-year OS in the entire cohort was 63%, and the 3-year OS among immunocompetent patients was 92%.[10] Last, the Children's Oncology Group published data from their rare NHL registry, which included 5 cases of PCNSL.[6] Outcomes in this small group of patients with PCNSL were excellent, with PFS and OS of 100% at a median follow-up of 2.1 years. In summary, although there are no prospective trials in pediatric patients with PCNSL, case reports and series demonstrate that treatment with multiagent chemotherapy including HD-MTX and HD-Ara-C is effective in the majority of patients.

Intrathecal chemotherapy

Although intrathecal chemotherapy was used in some pediatric regimens noted earlier, most chemotherapy regimens used in adults do not include intrathecal chemotherapy because of the ability to achieve micromolar concentrations in CSF after HD-MTX. Two large retrospective nonrandomized studies in adults failed to show any added benefit from intrathecal (IT) chemotherapy in the context of HD-MTX–containing regimens.[26,27] The majority of pediatric patients with parenchymal PCNSL will have negative CSF cytology (84% in a review of 43 cases).[4] The role of intrathecal chemotherapy in these cases is not clear. The outcomes of children treated with high-dose chemotherapy with and without intrathecal chemotherapy have not been compared.

Rituximab

Rituximab has been studied in adults with PCNSL and has measurable activity as a single agent, as well as in combination with HD chemotherapy. A randomized phase 2 trial showed a superior response of the combination of HD-MTX/Ara-C, thiotepa, and rituximab compared with HD-MTX/Ara-C alone, as well as HD-MTX/Ara-C and rituximab.[24]

The use of rituximab in systemic B-NHL has been studied in pediatrics in a randomized phase 3 trial.[28] In this study, patients with mature B-NHL were randomly assigned to receive LMB-based chemotherapy with or without rituximab. The randomization was terminated early by recommendation of the data monitoring committee based on a high likelihood of superiority in the rituximab group. The 1-year EFS was 94.2% vs 81.5% in the rituximab versus no rituximab groups, respectively and the hazard ratio was 0.33 (90% confidence interval, 0.16-0.69; P=.006). Rituximab has been given to a minority of pediatric patients with CD20+ PCNSL, but with insufficient numbers to draw any conclusions.

High-dose therapy/autologous stem cell transplantation

High-dose chemotherapy followed by autologous stem cell transplant (ASCT) has been used in newly diagnosed and refractory cases of PCNSL in both children and adults. It is listed as a treatment option by the National Comprehensive Cancer Network for patients either with newly diagnosed or relapsed adult PCNSL. In the largest series of pediatric PCNSL, 4 of 10 relapsed cases were treated with ASCT, with all 4 patients alive at the time of publication. ASCT was also used as consolidative therapy in in 2 of 29 newly diagnosed PCNSL cases.[8] The role of ASCT as consolidative treatment in newly diagnosed adult patients with PCNSL is currently being studied in 2 randomized trials (NCT01011920, NCT00863460).

Conclusions

Our patient has a typical presentation for PCNSL, with DLCBL histology and disease restricted to the brain parenchyma. In the absence of impending neurological deterioration, there is no role for additional surgical intervention in this case (grade 2C). Treatment with high-dose combination chemotherapy is reasonable with a regimen that includes MTX given at a minimum of 3 g/m^2 with or without HD-Ara-C (grade 2C). Because children can tolerate higher doses of MTX better than adults, it is reasonable to administer MTX at 5-8 g/m^2 as induction therapy, followed by consolidation with HD-Ara-C and HD-MTX at 3 g/m^2 or HDT/ASCT. There is insufficient evidence in pediatrics to support 1 chemotherapy regimen over another, and favorable outcomes have been reported using both the FAB/LMB96 and BFM protocols, as well as individual regimens with HD-MTX and/or HD-Ara-C. Rituximab could be considered in our patient on the basis of data suggesting a benefit in adult PCNSL, as well as pediatric systemic B-NHL (grade 2C). The use of IT chemotherapy in pediatric patients with PCNSL is unknown. In the setting of chemotherapy with HD-MTX, it would be reasonable to avoid IT chemotherapy on the basis of data from adult studies that did not show added benefit from IT chemotherapy in the context of HD-MTX[26,27] (grade 2C). Last, it would be reasonable to treat without WBRT, as the role of WBRT after chemotherapy is not established, and there is concern in pediatrics that WBRT may result in long-term neurological complications without clinical benefit (grade 2C). In summary, in the absence of prospective clinical trials, treatment decisions in pediatric PCNSL can be guided by pediatric case series and adult prospective trials. Creation of an international case registry has been proposed and would provide better insights into this rare pediatric lymphoma subtype. Last, a better understanding of the molecular biology of pediatric PCNSL, which could lead to novel targeted therapies, is an important goal for this field.

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