Leukemias and Lymphomas: Treatment and Prophylaxis of the Central Nervous System

*Janet L. Franklin, MD, MPH**
Jonathan Finlay, MB, ChB

Address
*Children's Hospital Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027, USA.
E-mail: jfranklin@chla.usc.edu

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Opinion statement

Central nervous system (CNS)–directed therapy is required for many acute leukemia patients and for nearly all aggressive or high-grade non-Hodgkin's lymphoma patients as part of an overall chemotherapy plan for disease eradication. The CNS therapy decisions differ for overt disease treatment versus prophylactic treatment and take into consideration the type of leukemia or lymphoma, the age of the patient, and other prognostic factors. A variety of CNS-directed therapies are used for prevention or treatment of CNS disease in acute leukemias or aggressive lymphomas: intrathecal medications (cytosine arabinoside, methotrexate, or both in combination with hydrocortisone) with or without cranial or craniospinal irradiation, intrathecal medication only with intensive systemic chemotherapy, or high-dose chemotherapy specifically chosen for CNS penetrance. Any type of CNS-directed therapy, whether intrathecal chemotherapy, high-dose systemic chemotherapy, or irradiation, may cause acute or delayed (late) toxicity. Ongoing clinical trial research aims to reduce the risk of toxicity from CNS-directed therapy while preserving or improving treatment efficacy.

Introduction

Overt involvement of the central nervous system (CNS) is evident at the time acute leukemia is diagnosed in 5% to 10% of all patients [1,2, Class II] and to a similar extent in advanced-stage non-Hodgkin's lymphoma (NHL) [3,4, Class II], most commonly in high-grade NHL. Acute leukemia and high-grade NHL patients without evidence of CNS involvement at diagnosis are still at risk for disease spread to the CNS. Therefore, CNS-directed therapy is an integral part of treatment decisions for these patients. Our understanding of the need to effectively treat the CNS is balanced with the knowledge that these treatments may create unfortunate and irreversible side effects in a subgroup of patients [5•,6,7; 8, Class I], especially younger children.

The CNS is now well described as an extramedullary site of disease extension and as a potential tumor sanctuary site in a select group of aggressive leukemias and lymphomas [9,10]. These hematologic malignancies, which occur in children and adults, include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and several subtypes of aggressive or high-grade NHL—Burkitt's lymphoma (BL), lymphoblastic lymphoma (LL), and large cell lymphoma (LCL). CNS involvement is distinctly uncommon in less aggressive (intermediate and indolent) subtypes of NHL and Hodgkin's lymphoma [11]. Other hematologic malignancies that occur in adults exclusively, such as multiple myeloma and plasma cell leukemia, have only anecdotal reports of CNS disease occurrences in the medical literature [12].

The biologic basis for CNS metastases in these diseases is unclear. CNS dissemination is thought to occur from hematogenous spread of circulating tumor cells or by direct extension from involved cranial bone marrow. Hematogenous dissemination occurs with petechial hemorrhages or with cell migration through venous endothelium. Understanding exactly how these tumor cells in the

Table 1. Definitions of CNS disease

	CSF findings	Other
CNS-3	≥ 5 leukocytes and detection of blasts	CNS mass, cranial nerve palsy, meningeal or optic nerve infiltration
CNS-2	< 5 leukocytes and detection of blasts	
CNS-1	< 5 leukocytes and no blasts	

CNS—central nervous system; CSF—cerebrospinal fluid.

CNS evade anticancer therapy remains a mystery, although it is thought that the blood-brain barrier and "hideaway" sites such as the subarachnoid veins diminish the systemic chemotherapy exposure these cells receive compared with other sites in the body.

Many of the general principles that we apply to our current CNS prophylactic and CNS-directed treatment strategies for all at-risk hematologic malignancies were first learned in the context of childhood ALL. In the early treatment era during the 1960s and early 1970s, the full importance of CNS prophylactic or CNS-directed therapy was not appreciated. The CNS site was the most common area of initial relapse when improved systemic therapy permitted longer survival in ALL patients [13]. CNS relapses strongly correlated with the subsequent development of bone marrow relapses that were virtually incurable. The early improvements in prognosis for ALL patients occurred only when CNS prophylactic therapy was added to the systemic treatment plan [14]. Similar inclusion of CNS prophylactic therapy for childhood AML and for aggressive NHL yielded clinical improvements in event-free survival (EFS).

Since that time, many leukemia and lymphoma clinical trials have studied a variety of strategies for CNS prophylaxis to prevent disease spread and CNS treatment for overt disease detected at initial diagnosis or at relapse. Current therapy modalities include intrathecal chemotherapy (single or multidrug regimens), intensive systemic chemotherapy, cranial irradiation, and craniospinal irradiation. The risk-benefit analysis of each type of treatment modality is assessed in the context of the type of hematologic malignancy, the age of the patient, and the patient-specific prognostic features. In general, the use of radiation therapy has become more selective over the past 20 years, such that only a small percentage of patients (all stratified as very high risk) receive cranial irradiation for CNS prophylaxis and at much lower doses than previously: 1200 cGy to 1800 cGy, compared with 2400 cGy or more historically. CNS disease warrants cranial or craniospinal irradiation in ALL patients, best studied in children. AML patients may receive irradiation in selected circumstances, whereas NHL patients vary in the need for irradiation as a part of CNS disease control.

Central nervous system disease in ALL [15, Class I] and AML [16, Class I] is classically defined as equal to or greater than five leukocytes per high-powered field and the presence of blasts (so-called CNS-3 disease) on examination of a cytocentrifuged cerebrospinal fluid (CSF) specimen. Other manifestations of CNS disease include the presence of cranial nerve palsy, optic nerve infiltration, meningeal infiltration, an intraparenchymal mass, or any combination of these findings with or without CSF involvement. CT scans and MRI are performed on the basis of physical examination or a clinical history suggesting CNS disease, and not on a routine basis. Certain leukemia treatment approaches add the more stringent disease definition of any blasts in the CSF irrespective of leukocyte numbers seen, also known as CNS-2 disease. For NHL, the presence of any tumor cells detected on CSF examination is considered evidence of CNS disease and triggers a detailed CNS evaluation by CT scan or MRI, if not already being done for diagnostic staging (Table 1).

Treatment

Acute lymphoblastic leukemia

Childhood

- The aims of CNS-directed therapy for childhood ALL are primarily for prophylaxis of this disease sanctuary site, because 5% or fewer patients present with overt CNS disease at the time of their bone marrow disease diagnosis. As proven historically, adequate CNS-directed therapy increases EFS rates in ALL. Currently, standard-risk ALL patients have an EFS of approximately 80% [17] in the context of intensive systemic chemotherapy and CNS-directed therapy. Systemic therapy regimens for standard-risk and high-risk patients include asparaginase and dexamethasone, both shown to decrease the number of CNS relapses when included in a multiagent chemotherapy

plan [18,19••,20, Class I]. For current approaches, intrathecal chemotherapy and/or high-dose methotrexate (at least 5 g/m^2) are the mainstay CNS-directed therapy component of a comprehensive treatment plan.

- The use of radiation therapy as CNS prophylaxis in children has been greatly reduced on the basis of several clinical research trials. The Children's Cancer Group (CCG) demonstrated that 2400 cGy craniospinal radiation could be replaced with 2400 cGy cranial irradiation plus six doses of intrathecal methotrexate [14], and subsequently, that 2400 cGy cranial irradiation could be replaced by 1800 cGy without an increase in CNS relapses [21, Class I]. Elimination of cranial irradiation prophylaxis by use of maintenance intrathecal methotrexate was demonstrated first in low-risk patients [22, Class I] and later in average-risk patients [23, Class I] receiving an intensified chemotherapy regimen.
- High-risk ALL patients have a 65% to 75% EFS on current treatment strategies and rely on a more intensive systemic chemotherapy than do standard-risk patients. Even certain high-risk ALL patients, such as those with a rapid response to a multiagent Berlin-Frankfurt-Munster (BFM)–based chemotherapy regimen, can also avoid CNS irradiation [24, Class I]. In very high-risk ALL patients, such as infants or those with Philadelphia (Ph) chromosome–positive ALL, outcomes still remain at 40% or lower. Most infant treatment protocols substitute high-dose methotrexate and/or triple intrathecal medications for CNS irradiation, whereas Ph chromosome–positive ALL may warrant irradiation in patients demonstrating a slow response to systemic therapy.
- In general, the highest therapy-associated risks are accepted for the poorer outcome subgroups. When irradiation is used for prophylaxis, only cranial irradiation is given to avoid the growth retardation caused by spinal irradiation in children. In the small percentage of patients who present with CNS leukemia, cranial irradiation at 1800 cGy is given.

Adults

- Similar to pediatric ALL, CNS-directed therapy is incorporated into the total treatment plan for adult-onset ALL. A series of studies have established that intrathecal chemotherapy and systemic intensive chemotherapy [25,26, Class I] give adequate CNS prophylaxis. As a result, CNS irradiation is usually not part of the comprehensive treatment plan in patients who do not have CNS disease. Cranial irradiation at 2400 to 3000 cGY is given for CNS disease such as cranial nerve root involvement. A CNS disease presentation in adult ALL occurs only in 5% to 10% of cases.

Acute myeloid leukemia

Childhood

- Childhood AML presents with CNS leukemia in only 5% of patients, whereas CNS chloromas occur in an even smaller percentage of patients [27]. The diagnostic work-up for all newly diagnosed or relapsed AML patients includes CSF examination by lumbar puncture for CNS involvement. Selected patients may have CT or MRI of the head based on presenting symptoms or, less rarely, on the basis of their AML histological subtypes (M5 subtype). The North American CCG, now known as the Children's Oncology Group (COG), and the United Kingdom Medical Research Council trials do not require cranial irradiation as CNS prophylaxis [28,29, Class I]. The key components of CNS-directed therapy are intrathecal cytosine arabinoside or intrathecal "triple" therapy, and intensive systemic cytosine arabinoside. Trials carried out by the BFM group traditionally have

included the use of CNS prophylactic irradiation [30]. All treatment regimens have a common theme of intensive chemotherapy. There is no one standard regarding the use of irradiation with CNS disease, at original diagnosis or at relapse. CNS involvement in newly diagnosed patients does not have an adverse prognostic significance [31,32]. Emergency radiation therapy may be used for any CNS chloroma (granulocytic sarcoma) with an anatomical location that portends an impending neurologic deficit.

Adults

- CNS involvement in adult AML cases is a much rarer occurrence than in pediatric AML. At diagnosis, CSF examination may be considered for monocytic or monoblastic AML subtypes, because CNS disease has a higher incidence in this group [33]. In general, adult AML protocols do not include intrathecal medications or cranial irradiation for CNS prophylaxis as a component of the total treatment plan. However, higher doses of cytosine arabinoside, which can penetrate the CNS, are usually an integral part of systemic therapy [34,35]. CNS disease in adults is usually symptomatic; disease is treated with intrathecal cytosine arabinoside or methotrexate, often with the addition of 2400 cGy irradiation [36].

Non-Hodgkin's lymphoma

- Central nervous system involvement in NHL varies in incidence by histological subtype. It is most common in Burkitt's or Burkitt's type lymphoma, also known as small non-cleaved cell lymphoma, followed in incidence by LL and then LCL. CNS involvement is defined similarly to that of acute leukemia—evidence of tumor cells in the CSF, cranial nerve palsy, or intraparenchymal mass. Current era treatment approaches for BL are short in duration, very intensive, and have shown that the presence of CNS involvement is no longer the independent poor prognostic factor that it was once considered for these patients [37–39, Class I]. CNS-negative patients do not require CNS irradiation for good disease outcomes [40, Class I]. The common chemotherapy agents in all protocols are the use of high-dose methotrexate and intrathecal methotrexate, with the occasional use of intrathecal cytosine arabinoside. Adults and children with this disease can be successfully treated with similar strategies.
- Lymphoblastic lymphoma is effectively treated with strategies that mirror ALL protocols. Intrathecal chemotherapy for CNS prophylaxis is a mainstay for effective disease treatment protocols; most protocols use high-dose systemic methotrexate. In the BFM cooperative group trials, the elimination of cranial irradiation for advanced-stage CNS-negative LL patients produced outcome not inferior to that achieved in trials that included cranial irradiation [41]. Recent COG trials have reserved cranial irradiation for CNS-positive LL patients [42]. The roles of radiation therapy and optimal drug treatment for adults with LL have yet to be answered but are unlikely to differ from that used in children.
- Large cell lymphoma is unique in this group of NHL patients at risk for CNS involvement because the incidence is very low; a recent review of the CCG experience found the incidence of CNS involvement to be as low as 2% [43, Class I]. Low rates of CNS disease make it difficult to assess its independent prognostic significance. CNS irradiation of 1800 cGy is frequently incorporated in addition to intrathecal medications for CNS disease [43,44] but is not used for CNS prophylaxis. The role of CNS prophylaxis for CNS-negative LCL patients is unresolved.

- Primary CNS lymphoma is an entity that is usually associated with immunodeficiency (acquired or congenital) but can be seen in an immunocompetent individual. Treatment approaches are nonuniform.

Diet and lifestyle

- Patients should be cautioned that herbal medicines and vitamins taken to "boost" the appetite or the immune system should be screened by the treating physician. Many herbal or alternative medicine treatments have drug interactions with the common chemotherapeutic agents used to treat these hematologic malignancies. Such drug interactions may result in less efficacy of the conventional drugs and/or increased toxicity.

Pharmacologic treatment

Central nervous system prophylaxis by use of chemotherapy

Intrathecal methotrexate

Standard dosage	Age adjusted: 8 mg for 1–1.99 years, 10 mg for 2–2.99 years, 12 mg for 3–8.99 years, and 15 mg for age ≥ 9 years. When intrathecal medications are delivered by an Ommaya reservoir instead of by lumbar puncture, the medication doses are reduced by 50%. Some adult protocols cap the methotrexate dose at 12 mg.
Contraindications	Prior severe neurologic reactions such as transverse myelitis, known hypersensitivity to methotrexate or any component, severe renal or hepatic impairment, and for high-dose administration, profound bone marrow suppression.
Main drug interactions	Several drug interactions are known. Salicylates may delay clearance. Sulfonamides and phenytoin may displace methotrexate from its protein-binding sites. Drugs such as probenecid, penicillin, and rofecoxib may decrease renal elimination. Nonsteroidal anti-inflammatory drugs may increase toxicity.
Main side effects	Potential side effects that occur occasionally include headache, CSF pleocytosis, and learning disability. Rare side effects include vomiting, meningismus, paresis, somnolence, leukoencephalopathy, seizures, transverse myelitis, and progressive neurocognitive deterioration.
Special points	Dose adjustment is not needed for renal impairment. A single dose of leucovorin (folinic acid) 10 mg administered orally 24 hours after lumbar puncture administration may be used in patients with a history of mucositis caused by intrathecal methotrexate.
Cost/cost effectiveness	The medication cost for each intrathecal dose is $3.70.

Intrathecal cytosine arabinoside

Standard dosage	Age adjusted: 20 mg for ≤ 12 months, 30 mg for 13–24 months, 50 mg for 25–35 months, and 70 mg for ≥ 36 months. When intrathecal medications are delivered by an Ommaya reservoir instead of by lumbar puncture, the medication doses are reduced by 50%. Some adult protocols cap the dose of cytosine arabinoside at 50 mg.
Contraindications	Prior severe neurotoxicity from cytosine arabinoside and hypersensitivity to cytosine arabinoside or any component.
Main drug interactions	Digoxin reduces absorption.
Main side effects	Potential common side effects are nausea, vomiting, fever, and headaches. Occasionally, arachnoiditis may occur. Rare side effects are seizures, paresis, somnolence, ataxia, myelosuppresion, necrotizing leukoencephalopathy, paraplegia, and blindness.
Special points	Dose adjustment is not needed for renal impairment. Dose reductions are indicated for severe hepatic impairment and severe bone marrow suppression.
Cost/cost effectiveness	The medicine cost for each intrathecal dose is $3.14.

Table 2. Standard dosage for intrathecal "triples"

Age	Methotrexate	Hydrocortisone	Cytosine arabinoside
> 6 months to ≤ 1 year	7.5 mg	7.5 mg	15 mg
> 1 to < 2 years	8 mg	8 mg	16 mg
2 to < 3 years	10 mg	10 mg	20 mg
3–8 years	12 mg	12 mg	24 mg
≥ 9 years	15 mg	15 mg	30 mg

Intrathecal "triples" (methotrexate, cytosine arabinoside, and hydrocortisone)

Standard dosage See Table 2. When intrathecal medications are delivered by an Ommaya reservoir instead of by lumbar puncture, the medication doses are reduced by 50%.

Contraindications In addition to the earlier-mentioned listing for methotrexate and cytosine arabinoside, hypersensitivity to hydrocortisone and serious infections.

Main drug interactions In addition to the earlier-mentioned listing for methotrexate and cytosine arabinoside, live viral vaccines are contraindicated.

Main side effects No appreciable side effects other than those listed for methotrexate and cytosine arabinoside.

Special points No special points other than those listed for methotrexate and cytosine arabinoside.

Cost/cost effectiveness The medicine cost for each intrathecal dose is $7.74.

High-dose methotrexate

Standard dosage The range for high-dose methotrexate is quite varied amongst protocols, from 3–33 g/m^2. The dose is administered by an initial intravenous bolus to quickly achieve serum and CSF levels to steady state and is followed by a 24- to 36-hour intravenous continuous infusion at a lower dose per hour.

Contraindications Prior severe neurologic reaction such as transverse myelitis, known hypersensitivity to methotrexate or any component, severe renal or hepatic impairment, and for high-dose administration, profound bone marrow suppression.

Main drug interactions Several drug interactions are known. Salicylates may delay clearance. Sulfonamides and phenytoin may displace methotrexate from its protein-binding sites. Drugs such as probenecid, penicillin, and rofecoxib may decrease renal elimination. Nonsteroidal anti-inflammatory drugs may increase toxicity.

Main side effects Potential side effects that occur occasionally include headache, CSF pleocytosis, and learning disability. Rare side effects include vomiting, meningismus, paresis, somnolence, leukoencephalopathy, seizures, transverse myelitis, and progressive neurocognitive deterioration.

Special points High-dose methotrexate requires adequate renal function; impaired renal function, ie, a creatinine clearance < 60 mL/minute, dictates that the dose should be withheld. Hydration and alkalinization are required for doses > 1 g/m^2. Leucovorin rescue is an integral part of a high-dose methotrexate administration regimen.

Cost/cost effectiveness The medication cost varies by g/m^2 dose. A dose of 5 g/m^2 with a maximum of 10 g per course costs $500. Additional costs to consider are the inpatient hospital stay and additional pharmacy fees for handling and disposal of the drug administration materials.

High-dose cytosine arabinoside

Standard dosage There is a varied range of doses used for high-dose cytosine arabinoside. A common dose used for 3-hour intravenous infusions is 3 g/m^2. Longer continuous intravenous infusions run for up to 24–72 hours and begin with a bolus dose to quickly achieve steady state blood levels. The continuous-infusion regimens deliver up to 8 g cytosine arabinoside per dose.

Contraindications Prior severe neurotoxicity from cytosine arabinoside and hypersensitivity to cytosine arabinoside or any component.

Table 3. Standard dosage for CNS radiation therapy

Disease	CNS prophylaxis	CNS disease therapy
ALL: Children	Selected at-risk cases only 1200 or 1800 cGy; protocol dependent	1800 cGy
ALL: Adults	Usually not given	2400–3000 cGy
AML: Children	Usually not given	Usually not given
AML: Adults	Usually not given	Usually not given
NHL: Children	Not indicated	1800 cGy in lymphoblastic lymphoma
NHL: Adults	Not indicated	Variable

ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; CNS—central nervous system; NHL—non-Hodgkin's lymphoma.

Main drug interactions Digoxin reduces absorption.

Main side effects Potential common side effects are nausea, vomiting, fever, chemical conjunctivitis, and headaches. "Cytosine arabinoside syndrome" is a term that encompasses the symptoms of fever, myalgia, bone pain, rash, conjunctivitis, and malaise and occurs 6–12 hours after administration. Occasionally, arachnoiditis or pulmonary edema may occur. Rare side effects are seizures, paresis, somnolence, ataxia, myelosuppression, necrotizing leukoencephalopathy, paraplegia, and blindness.

Special points Dose reductions are indicated for severe hepatic impairment and history of prior cytosine arabinoside–associated severe bone marrow suppression. Dexamethasone eye drops are commonly given as prophylaxis for avoiding chemical conjunctivitis.

Cost/cost effectiveness The medication cost varies by g/m^2 dose. 1 g of cytosine arabinoside costs $8.86. One example of cost per regimen: a 3-hour intravenous cytosine arabinoside dose of 3 g/m^2 with a maximum of 24 g per course (6 g per dose for a 2-m^2 person for four doses) costs $215. Additional costs to consider are the inpatient hospital stay and additional pharmacy fees for handling and disposal of the drug administration materials.

Nonpharmacologic treatment

Central nervous system radiation therapy for prophylaxis or for disease treatment

Standard dosage See Table 3.

Contraindications Each patient is evaluated before the start of radiation therapy for suitability.

Main drug interactions The combined exposure to intrathecal chemotherapy and CNS irradiation may add to the risk for neurocognitive changes in a patient, especially children.

Main side effects Possible side effects from cranial or craniospinal radiation include nausea, vomiting, cataracts, poor growth in children, decreased thyroid hormone production, fatigue, temporary loss of hair, diminished intelligence, seizures, leukoencephalopathy, somnolence, and secondary cancers.

Special points There are target volume conventions routinely used by radiation oncologists to ensure that the entire brain and meninges are treated reproducibly. Included in the treatment fields are the frontal lobe and posterior halves of globes of the eyes, with optic disk and nerve superior to the vertex and posterior to the occiput. The caudal border of the treatment field is below the skull at the C2 vertebral level.

Cost/cost effectiveness A representative cost for cranial irradiation administration (hospital and physician) is 1) craniospinal (2400 cGy head, 6000 cGy spine, 12 fractions) = $2120; 2) cranial (2400 cGy head, 12 fractions) = $1994; 3) cranial (1800 cGy head, 10 fractions) = $1835; and 4) cranial (1200 cGy head, eight fractions) = $1734.

Surgery

- Surgical interventions for leukemia and lymphoma patients are generally limited to biopsy of CNS masses, when deemed surgically feasible and clinically necessary, and the placement of an Ommaya reservoir for the rare

patient who has a recalcitrant course of CNS involvement requiring multiple courses of intrathecal therapy. In special circumstances, neurosurgical intervention may be required for increased intracranial pressure caused by an intraparenchymal mass or a CNS hemorrhagic event.

Emerging therapies

- Although CNS relapses of acute leukemia and high-grade NHL have become more infrequent, there is still an ongoing need to explore new chemotherapeutic agents [45, Class II] or novel delivery methods of standard chemotherapy drugs for the treatment of resistant CNS disease. CNS relapses that occur less than 18 months from diagnosis have a particularly unfavorable outcome [46]. Several antineoplastic drugs for intrathecal delivery or intensive systemic delivery have been tested with mixed clinical results in a variety of hematologic malignancies and other malignancies with leptomeningeal disease, including mafosfamide, topotecan, diaziquone, thiotepa, etoposide, rituximab, and liposomal cytarabine (Depocyt; SkyePharma, New York, NY). Drug development for some of these agents is hampered by their specialized use in a relatively small population of cancer patients.
- Mafosfamide is a chemically stable thioethane sulfonic acid salt of a widely used cancer drug, cyclophosphamide. Unlike the parent compound, this drug does not require hepatic activation to produce an antitumor effect and therefore can be administered through the intrathecal route. This treatment strategy has been studied in limited-dose escalation studies [47, Class II] for adult and pediatric refractory meningeal malignancies and in limited pilot studies for pediatric brain tumors with meningeal dissemination [48,49, Class II]. Antitumor activity was demonstrated against meningeal leukemia and possibly brain tumors that involve the meninges.
- Topotecan has activity against a variety of tumors when administered systemically. The intrathecal administration of this drug in a phase 1 study [50] greatly exceeded the CNS exposure that occurs from systemic administration, prompting further study in a phase 2 clinical trial.
- Diaziquone demonstrated an advantage for its delivery as an intrathecal antineoplastic agent because it achieved a greater drug exposure throughout the neuroaxis, and it avoided the severe myelosuppression that occurs after systemic drug delivery. Antitumor responses were demonstrated [45,51, Class II].
- Thiotepa and etoposide have been administered in high doses as part of an intensive systemic chemotherapy regimen before autologous bone marrow transplant in high-risk CNS tumors such as primary CNS lymphomas and malignant brain tumors [52–54]. These drugs achieved good CNS penetrance and are thought to enhance the antitumor activity of such multiagent regimens. Intrathecal etoposide has also been administered in limited experience [49, Class II].
- Rituximab, a novel humanized anti-CD20 monoclonal antibody that is active in CD20-positive tumors such as mature B-cell lymphoma, has been administered through the intrathecal route in limited case reports of adult primary CNS lymphoma [55–57]. These early experiences indicate that intrathecal delivery is safe and feasible. Additional study is required to demonstrate efficacy.
- Liposomal cytosine arabinoside (Depocyt) is one the newest CNS-directed agents that has been successfully tested in adult and pediatric clinical research trials [58] and recently licensed for intrathecal use. It has a longer half-life than standard cytosine arabinoside because of its sustained-release formulation. Clinical benefit in the treatment of neoplastic meningitis caused by lymphoma [59••, Class I] and other solid tumors has been demonstrated.

- The concentration times time treatment strategy for intraventricular methotrexate and cytosine arabinoside produces more uniform drug distribution and allows for a more flexible drug administration schedule when treating recurrent meningeal leukemia and lymphoma [60]. An Ommaya reservoir is required. This regimen is a well-tolerated palliative treatment.

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