Concepts on the diagnosis, prevention, and treatment of primary and secondary leukemic and lymphomatous meningitis are detailed.

### Diagnosis and Management of Leukemic and Lymphomatous Meningitis

**Hemant Murthy, MD, Claudio Anasetti, MD, and Ernesto Ayala, MD**

**Background:** Leukemic and lymphomatous meningitis is a major presentation of primary or secondary central nervous system (CNS) involvement by aggressive lymphomas or acute leukemia.

**Methods:** The medical literature and ongoing clinical trials were reviewed on the clinical presentation, diagnosis, prognosis, prevention, and treatment of leukemic and lymphomatous meningitis.

**Results:** Treatment for secondary leukemic and lymphomatous meningitis remains unsatisfactory, and efforts should be made to prevent and treat subclinical disease. Intrathecal and systemic chemotherapy remain the main therapeutic approaches for this disease. Outcomes have improved in patients with primary CNS lymphoma and meningeal involvement.

**Conclusions:** Appropriate selection of patients at high risk for leukemic and lymphomatous meningitis is important so that preventive strategies can decrease the incidence of this complication of leukemia and lymphoma. Use of chemotherapy agents that cross the blood–brain barrier and the adoption of high-dose chemotherapy with autologous hematopoietic stem cell transplantation have increased the proportion of patients whose primary disease is cured.

### Introduction

Leukemic and lymphomatous meningitis may occur in patients with primary central nervous system (CNS) lymphoma or as a secondary manifestation of systemic lymphoma or leukemia. In rare cases, leptomeningeal involvement may be the initial presentation of these diseases. Although its clinical presentation is variable, leukemic and lymphomatous meningitis from hematological malignancies tends to have a higher frequency of cranial nerve involvement than solid tumors.1

Diagnosis is based on findings after cerebrospinal fluid (CSF) examination and radiological evaluation of the neuraxis. Therapeutic options include radiotherapy, intrathecal (IT) and systemic chemotherapy, and, in select cases, high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT).

In patients with secondary leukemic and lymphomatous meningitis, treatment remains suboptimal and frequently is palliative. The most appropriate strategy is aggressive prevention. By contrast, patient outcomes have improved with the use of modern intensive approaches for leukemic and lymphomatous meningitis associated with primary CNS lymphoma (PCNSL).
Primary Central Nervous System Lymphoma

PCNSL is a form of non-Hodgkin lymphoma confined to the CNS. PCNSL includes primary ocular and leptomeningeal lymphomas, in which lymphoma is confined to the CSF alone without evidence of intracranial or spinal cord lesions. Typically, PCNSLs are aggressive, large cell subtypes of B-cell phenotypic origin. Few case reports have described PCNSLs being of T-cell origin.2

From 1970 to 1995, PCNSL was common in young adults with HIV/AIDS, but the advent of active antiretroviral therapy has been associated with a decline in the incidence of PCNSL in this population.5 By contrast, the incidence of PCNSL has continued to increase in the elderly (> 65 years of age).4,5

Despite the high rates of response to chemotherapy and radiotherapy, PCNSL remains a disease with short periods of remission and a poor long-term prognosis for numerous reasons, including the difficulty of drugs to penetrate the blood–brain barrier and treatment neurotoxicity (particularly in the elderly).6 Strategies to enhance cure rates while limiting therapy-related toxicities have helped improve its prognosis.

Clinical Presentation and Workup

Table 1 highlights the recommended workup for PCNSL at diagnosis.24 This workup also highlights the role of CSF evaluation at the time of diagnosis. If lumbar puncture can be performed, then cytological evaluation and CSF flow cytometry should be obtained. The use of biomarkers for the noninvasive diagnosis of PCNSL from CSF evaluation continues to evolve: microRNAs have shown promise. The CSF expression of microRNA 19b, 21, and 92 has shown a sensitivity rate of approximately 95% and specificity rates between 80% and 83% for the diagnosis of PCNSL.9,10 Other CSF biomarkers, such as neopterin, have also shown promise in differentiating PCNSL from other primary CNS malignancies.11 Reports have been published about the use of CSF biomarkers in monitoring disease response, although large prospective studies are needed prior to measuring the efficacy of these biomarkers.12,15

Two large studies reported on concomitant meningeal dissemination, suggesting that it occurs in 15% to 20% of patients at diagnosis and is typically asymptomatic, rather than associated with focal neurological deficits (the most common presentation of newly diagnosed PCNSL), followed by psychiatric symptoms and seizures; by contrast, the results suggest that intraocular lymphoma typically presents with visual disturbances in addition to behavioral and cognitive changes.14-17

An International Extranodal Lymphoma Study Group risk score is comprised of age, serum lactate dehydrogenase (LDH) level, performance status, elevated CSF protein level, and deep-structure involvement.18 Prognostically, meningeal dissemination is often considered a poor prognostic marker; however, this is debatable. A large phase 3 study of 415 patients with PCNSL — 65 of whom had concomitant CSF involvement — did not identify CNS involvement as impacting median progression-free survival (PFS) or overall survival (OS) rates.19 Unlike performance status and high International Extranodal Lymphoma Study Group scores, which did negatively impact PFS, CSF involvement did not impact PFS in a trial of whole-brain radiotherapy (WBRT).19 In 48 patients with primary leptomeningeal lymphoma, the median OS rate was 24 months, and performance status was the single variable with a trend toward inferior survival rates.20

Pathological diagnosis of PCNSL should be obtained and confirmed prior to initiating treatment. This is typically accomplished with either stereotactic or navigational-guided needle biopsy. When possible, corticosteroids, utilized to reduce vasogenic edema, should be withheld prior to biopsy, as doing so may complicate the pathological diagnosis due to their oncolytic effects on lymphoma cells.

Treatment

PCNSL is responsive to chemotherapy and radiotherapy, but penetration of the blood–brain barrier and therapy-related neurotoxicity — particularly among the elderly — must be considered and overcome.21

Chemotherapy: Conventional chemotherapy regimens for lymphoma (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone) are not useful

### Table 1. — Initial Workup for PCNSL

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Tissue immunohistochemical markers (CD19, CD20, Pax5, Scl6, Mum1/IRF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging/Examination</td>
<td>MRI of the brain with and without contrast</td>
</tr>
<tr>
<td></td>
<td>CT of the chest, abdomen, and pelvis or whole-body PET</td>
</tr>
<tr>
<td></td>
<td>Testicular ultrasonography (males)</td>
</tr>
<tr>
<td></td>
<td>Slit lamp/ophthalmological examination</td>
</tr>
<tr>
<td>Laboratory Testing/Procedures</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td></td>
<td>CBC</td>
</tr>
<tr>
<td></td>
<td>CSF evaluation</td>
</tr>
<tr>
<td></td>
<td>HIV serology testing</td>
</tr>
<tr>
<td></td>
<td>LDH</td>
</tr>
<tr>
<td></td>
<td>Lumbar puncture</td>
</tr>
</tbody>
</table>

9To assess for extraneural sites of lymphoma.

CBC = complete blood count, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, LDL = lactate dehydrogenase, MRI = magnetic resonance imaging, PCNSL = primary CNS lymphoma, PET = positron emission tomography.

Data from references 7 and 8.
in the treatment of PCNSL due to their lack of CNS penetration, nor is the addition of radiotherapy to regimens similar to cyclophosphamide, doxorubicin, vincristine, and prednisone.\textsuperscript{22,23} The backbone of most chemotherapy regimens for PCNSL is high-dose methotrexate (MTX). Rapid infusions of doses 3 g/m\textsuperscript{2} or more for 3 hours can achieve cytotoxic levels in the CSF.\textsuperscript{24} Single-agent, high-dose MTX was studied in a phase 2 study as monotherapy with deferred WBRT.\textsuperscript{25} A total of 25 patients were enrolled and high-dose MTX was administered at a dose of 8 g/m\textsuperscript{2} every 2 weeks until radiographical complete or partial response. The treatment was effective: 74\% of study patients achieved complete or partial response.\textsuperscript{25} No study patients experienced significant neurotoxicity, although 48\% experienced grade 3/4 toxicity.\textsuperscript{25}

Therapy with high-dose MTX combined with other chemotherapeutic agents has been shown to improve response rates, particularly among agents that can penetrate the blood–brain barrier.\textsuperscript{19,20} Results of a randomized, phase 2 trial comparing high-dose cytarabine combined with high-dose MTX and WBRT consolidation vs high-dose MTX and WBRT consolidation alone suggested a significant increase in the rate of complete remission when cytarabine was added.\textsuperscript{26} To avoid the neurotoxic effects of WBRT, Rubenstein et al\textsuperscript{19} utilized a high-dose, MTX-based induction with rituximab, temozolomide, etoposide, and high-dose cytarabine as consolidation therapy with no irradiation. They observed a median PFS rate of 2.4 years.\textsuperscript{19} PFS was similar in younger and older study patients, and no grade 3/4 neurotoxicity was reported.\textsuperscript{19}

**Rituximab:** The role of rituximab-based therapy continues to evolve. As a monoclonal antibody, rituximab is too large to freely pass through the blood–brain barrier. Animal models measuring the ability of rituximab to disrupt the blood–brain barrier showed that the prolonged CNS exposure of rituximab was lacking, but the long plasma half-life of rituximab may result in a slow leak — along with a minimally disrupted blood–brain barrier — thus resulting in improved responses and survival.\textsuperscript{27} However, based on other radiographical responses to single-agent rituximab, the drug has been added to polychemotherapy and WBRT-sparing regimens.\textsuperscript{28} The addition of rituximab to high-dose MTX resulted in complete and partial responses of 80\% and a median OS rate of 34 months.\textsuperscript{29} The rituximab-based WBRT-sparing PCNSL regimens utilized by Rubenstein et al\textsuperscript{19} demonstrated a complete response rate of more than 60\% with no reports of neurotoxicity. However, the overall benefit of systemic rituximab compared with standard therapy has yet to be confirmed and is the focus of prospective, randomized trials (NCT00072449, NCT00098774, NCT02399189).

**Intrathecal/Intraventricular Therapy:** The addition of IT or intraventricular therapy has been considered, given the proclivity of CNS lymphoma for meningeal dissemination; however, this administration is questionable, given the ability of high-dose MTX, cytarabine, etoposide, and temozolomide to penetrate the CSF in therapeutic concentrations.\textsuperscript{21} Two separate retrospective studies comparing the addition of IT to high-dose MTX failed to demonstrate any impact on survival rates, disease response rate, or rate of relapse, so it is not considered to be a standard therapeutic option for the treatment of PCNSL, regardless of CSF involvement.\textsuperscript{30,31} However, few studies have suggested a benefit of utilizing intraventricular and systemic chemotherapy; however, rates of early relapse have been reduced compared with those seen in systemic chemotherapy alone.\textsuperscript{30,31} Intraventricular rituximab may be of particular interest. A phase 1 study reported that intraventricular rituximab was tolerable.\textsuperscript{22} Overall and complete response rates were 75\% and 43\%, respectively.\textsuperscript{22} Use of intraventricular rituximab for the treatment of PCNSL is still being studied.\textsuperscript{33} As of publication, the routine use of IT or intraventricular therapy as treatment or secondary prophylaxis of PCNSL is not recommended outside of a clinical trial.

**Whole-Brain Radiotherapy:** WBRT is the standard treatment for PCNSL, and it is commonly used as consolidation therapy following high-dose chemotherapy. As a single treatment, the response to WBRT is short lived. Median survival rates are between 10 and 18 months, so WBRT is not recommended unless chemotherapy is contraindicated.\textsuperscript{34,35} The optimal dose of WBRT is controversial. For example, doses higher than 50 Gy have been associated with marked neurotoxicity.\textsuperscript{21} Standard doses of 40 to 50 Gy are commonly used. Some researchers are studying whether it is possible to reduce the dose of WBRT, whereas others are researching whether WBRT can be omitted altogether from the treatment of PCNSL.\textsuperscript{36}

**Surgery:** Surgery is not a first-line treatment modality because of its lack of efficacy. The role of surgery is limited to CSF diversion via ventriculoperitoneal shunting in patients with symptomatic hydrocephalus and the placement of subgaleal (Ommaya) reservoirs connected to intraventricular catheters for the intracSF administration of chemotherapy. Surgery can also be considered for emergent situations, particularly when it is necessary to reduce elevated intracranial pressure or relieve brain herniation.

**Secondary Disease**

Lymphomatous involvement of the CNS has been recognized since the 19th century and was well described in the mid-20th century.\textsuperscript{37} A clinical picture and the outcomes of therapy have also been detailed in small retrospective studies in the 1960s and 1970s.\textsuperscript{37} Lympho-
matous involvement of the CNS commonly presents as leptomeningeal disease, less frequently as parenchymal masses, and, rarely, simultaneously in both locations.57

Lymphomatous meningitis may occur at diagnosis, at relapse, or at any time during the treatment of the disease. The general incidence rate of CNS lymphomatous disease in patients with systemic lymphoma is approximately 5%.37,38

**Risk Factors**
Risk factors for leukemic and lymphomatous meningitis include high-grade histology, histological subtype (lymphoblastic or Burkitt lymphoma), presence and extent of extranodal disease, and an elevated LDH level.39 High-grade lymphomas (lymphoblastic and Burkitt lymphomas) are classically associated with the highest risk — comparable to acute lymphoblastic leukemia — at approximately 20% to 25% in the absence of prophylaxis.39-41 Patients with high-grade lymphoma and CMYC and BCL2 translocations or overexpression also appear to be at high risk for CNS disease at diagnosis or when the disease progresses.39-41 Subsequently, other aggressive lymphomas, such as diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and mantle cell lymphoma (blastic variant), have a rate of risk between 5% and 7%.39-41 Any CNS disease (leukemic and lymphomatous meningitis or parenchymal involvement) in low-grade histologies (eg, follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma) is rare.40 Several prospective, multicenter trials have helped to further define these risk factors, which include an elevated LDH level, more than 1 extranodal site, and high risk by International Prognostic Index (IPI; score of 4 to 5).39-41 Certain extranodal locations appear to have a much higher risk than others, particularly the testicle, breast, kidney, bone marrow, and leptomeningeal locations.40,41

**Clinical Presentation**
By contrast to PCNSL, patients with leukemic and lymphomatous meningitis initially present with a higher frequency of cranial nerve signs.1 However, the clinical picture is pleiotropic and encompasses disturbances of the cerebral hemispheres, cranial nerves, and spinal cord and its roots. Common manifestations include headache, altered mental status, confusion, and seizure. Cranial nerve involvement can manifest as double vision, hearing loss, facial numbness/paralysis, dysphagia, or loss of vision. Spinal cord and nerve-root compromise can produce weakness, numbness, and pain at different levels and dermatomes. As the disease progresses, new deficits can be observed and the initial deficits begin to worsen; coma and death can follow during the final stages of disease.37

**Diagnosis**
Once the diagnosis of leukemic and lymphomatous meningitis is clinically suspected, a useful — and typically confirmatory — test is examination of the CSF, generally obtained via lumbar puncture. In most patients, CSF findings will be abnormal regardless of the cytology report. Abnormalities frequently encountered include an elevated protein level, pleocytosis, and a decreased glucose level. Cytological findings following the examination of the CSF will initially be positive in approximately 55% to 60% of patients, and a second examination will increase the rate of positive findings on cytology in up to 80% of cases.42 Routine use of flow cytometry has significantly improved the sensitivity rate of CSF cytology for identifying leptomeningeal disease in aggressive lymphoma.37 In up to 20% of patients considered to be at high risk for CNS disease, flow cytometry will reveal lymphoma cells in the absence of diagnostic clinical findings.42 Radiologically, findings on contrast-enhanced computed tomography (CT) of the cranium will be abnormal in 25% to 55% of patients with leukemic and lymphomatous meningitis.39 Commonly encountered findings include parenchymal volume loss, subcortical enhancement, ependymal and subependymal enhancement, cisternal or sulcal obliteration, enhancing nodules, and communicating hydrocephalus. Contrast-enhanced magnetic resonance imaging (MRI) appears to have greater rates of sensitivity and specificity and may be the imaging modality of choice when leukemic and lymphomatous meningitis is suspected.37

Patients with suspected leukemic and lymphomatous meningitis should undergo CSF analysis with cytology and flow cytometry, as well as imaging studies, particularly MRI of the whole neuraxis, because leukemic and lymphomatous meningitis can simultaneously affect the CNS at different levels.37

**Prevention**
The prognosis of leukemic and lymphomatous meningitis is poor once it has spread, so prevention is key.43,44 Several studies and guidelines have addressed the prevention of CNS lymphoma in general and leukemic and lymphomatous meningitis in particular; however, no consensus exists regarding the optimal form or timing of prophylaxis.43,44

CNS prophylaxis is commonly recommended in patients considered to be at high risk for CNS lymphoma based on certain risk factors (Table 2).45 Historically, CNS prophylaxis was delivered via the IT or systemic route. Agents administered via the IT route include MTX, cytarabine (regular or sustained release), steroids (hydrocortisone and dexamethasone), and rituximab. Typically, patients receive 4 to 6 low doses (12–15 mg) of IT MTX concomitantly with ongoing systemic chemotherapy. IT MTX is not without risk, and
no randomized study has shown that IT prophylaxis is effective in preventing leukemic and lymphomatous meningitis or CNS lymphoma spread.\(^37,38,41\) Systemic chemotherapy in the form of high-dose antimetabolites (MTX, cytarabine) has been used to prevent or preemptively treat CNS lymphoma. A theoretical advantage to this therapy is its ability to treat parenchymal disease of the brain. Several large, multicenter studies have evaluated this approach and have shown a significant decrease in CNS disease.\(^46,47\) However, the optimal dose, infusion rate, number of cycles required, and need for concomitant IT MTX are unknown. In addition, high-dose MTX requires inpatient administration, clinical expertise, and rapid access to serum blood levels (to check MTX levels) to prevent toxicity. Renal impairment, mucositis, and myelosuppression are potential risks.\(^37,38\)

### Treatment

Once leukemic and lymphomatous meningitis has developed, treatment is palliative in most patients, with few surviving the disease long-term.\(^39-41\) Furthermore, in many patients leukemic and lymphomatous meningitis develops at the same time in many individuals; to compound the issue, systemic relapse makes treatment more complex.

The role of surgery is limited. The primary indication for radiotherapy is the concomitant presence of parenchymal disease of the brain. Other indications include localized disease identified on imaging or irradiation of the base of the brain in patients with symptomatic hydrocephalus to relieve the obstruction of CSF flow. The role of radiotherapy is palliative and it has no impact in survival.

Similar to the treatment of PCNSL, high-dose intravenous MTX, cytarabine, and thiopeta have been used in select cases of leukemic and lymphomatous meningitis.\(^37,57\) For patients achieving remission, high-dose chemotherapy with autologous HSCT may induce durable remissions and may be curative in some cases. Achieving complete clearance of CNS disease before autologous HSCT appears to be critical for treatment success.\(^48-50\)

Two small randomized clinical trials included 223 patients with neoplastic meningitis, 57 of them whose disease was associated with leukemia or lymphoma.\(^51,52\) In these trials, sustained-release and standard formulations of cytarabine were compared. Intention-to-treatment analysis showed a better response for sustained-release cytarabine, and treatment was associated with an improved mean change in Karnofsky performance score.\(^51,52\) In addition, more study patients treated with sustained-release cytarabine died of systemic disease, whereas more study patients treated with cytarabine died from progressive neoplastic meningitis. Sustained-release cytarabine had a higher response rate, better rates of quality of life, and better control of leukemic and lymphomatous meningitis.\(^51,52\)

Because the treatment of leukemic and lymphomatous is generally palliative, choice of therapy should be individualized. The optimal treatment remains undefined. Select patients are candidates for aggressive intervention with the goal of clearing CNS and systemic disease. If complete remission is obtained, then these patients may achieve durable disease control and cure with subsequent autologous HSCT.

### Central Nervous System Leukemia

Leukemic involvement of the CNS is rarely observed in adults, particularly when compared to children with similar diagnoses.\(^3\) The low incidence in the setting of newly diagnosed leukemia compounded with the difficulties in breaching the blood–brain barrier with antileukemic therapies raises questions regarding the identification of high-risk features for CNS involvement, as well as prophylaxis and treatment strategies for CNS leukemia.

### Acute Myeloid Leukemia

In adults, the exact incidence of CNS involvement because of acute myeloid leukemia (AML) is unknown.
Based on large retrospective studies, the incidence rate may be between 1% and 3% in all patients, regardless of age — a range less than the reported 11% incidence rate in pediatric AML.\(^5\)\(^3\)\(^-\)\(^5\)\(^6\) In fact, the incidence rate might be higher, because CNS investigations are performed only if clinically indicated, so the incidence could be higher if CNS surveillance was routinely part of the diagnostic workup.\(^5\)\(^4\)

**Risk Factors and Prophylaxis:** Risk factors for CNS involvement of AML were identified in large, retrospective series (Table 3); however, the low incidence rates of CNS involvement include all adult cases of AML.\(^5\)\(^3\)\(^,\)\(^5\)\(^4\) One such risk factor identified is young age. Two series report that an age younger than 45 or 50 years increases risk for CNS involvement.\(^5\)\(^3\)\(^,\)\(^5\)\(^4\) Hyperleukocytosis at diagnosis (white blood cell [WBC] count > 50,000 or 100,000/µL) is a risk factor for CNS involvement by AML. For promyelocytic leukemia, a WBC count above 10,000/µL is correlated with extramedullary relapse, including CNS relapse.\(^7\) Other risk factors include poor-risk cytogenetic abnormalities, elevated LDH level, or M4/5 subtype.

Clinical manifestations of CNS leukemia are indications for diagnostic imaging (MRI of the brain) and lumbar puncture; routine CSF testing is not indicated. The impact of CNS involvement has been questioned for AML. Compared with AML without CNS involvement, CNS involvement at diagnosis had no effect on 5-year OS and PFS rates.\(^5\)\(^3\) This finding may be due to the CNS penetration achieved by cytarabine, which is used in induction and consolidative regimens.\(^5\)\(^3\) Another study found similar rates of CNS involvement, regardless of intensity of cytarabine regimen used.\(^5\)\(^4\) Two other studies observed no impact of CNS involvement on outcomes following transplant.\(^5\)\(^8\)\(^,\)\(^5\)\(^9\) It is worth noting that, as reported by Bar et al,\(^5\)\(^9\) routine CSF evaluation prior to transplantation revealed cases of leukemic involvement in CNS not discovered at diagnosis. This finding led to CNS-directed treatment with IT chemotherapy and, in some cases, with craniospinal irradiation. All study patients affected achieved a complete response prior to transplant.\(^5\)\(^9\) Thus, it is plausible that this led to the outcome rates comparable with AML without CNS involvement.\(^5\)\(^9\)

Neither CSF sampling nor routine CNS prophylaxis in AML is recommended, although any patient with neurological symptoms, especially those with high-risk features, should undergo CSF evaluation and receive IT therapy if AML is detected.

**Acute Lymphoblastic Leukemia**

Leptomeningeal involvement is uncommon in adults with acute lymphoblastic leukemia (ALL), but it is more frequent in the pediatric population.\(^5\)\(^5\)\(^,\)\(^5\)\(^4\) Patients with CNS involvement may experience symptoms such as headache, cranial nerve palsy, and spinal cord abnormalities, manifested by symptoms such as pain, paresthesia, motor weakness, or bladder or bowel dysfunction. However, CNS involvement may also be asymptomatic.

Meningeal involvement has been reported in approximately 5% to 6% of adults with ALL at the time of diagnosis.\(^6\)\(^0\)\(^,\)\(^6\)\(^1\) Certain features have been identified as risk factors for CNS involvement, including B-cell phenotype, a high proliferation rate, elevated LDH level, and certain high-risk cytogenetics (Table 4).\(^6\)\(^0\)\(^,\)\(^6\)\(^2\) Patients can also be stratified according to risk for CNS recurrence based on CSF examination findings:\(^6\)\(^3\):

- **CNS1:** No leukemic blasts
- **CNS2:** < 5 WBCs/µL with blasts
- **CNS3:** > 5 WBCs/µL with blasts

A higher incidence of relapse in CNS has been described in adults, particularly with regard to the prior use of CNS prophylaxis.\(^5\)\(^3\)\(^,\)\(^5\)\(^4\) Thus, the poor prognosis associated with leukemic CNS relapse makes prevention critical to the management of ALL.

**Prophylaxis**

**Intrathecal Chemotherapy/Systemic Chemotherapy:** Except for high-dose MTX and cytarabine, systemic

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**Table 3. — Risk Factors for CNS Involvement by AML**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>&gt; 50,000/µL</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt; 2.5 × ULN</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Complex cytogenetics inv(16), 11q23 abnormalities Trisomy</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 y</td>
</tr>
<tr>
<td>FAB subtype</td>
<td>M4, M5</td>
</tr>
</tbody>
</table>

**Table 4. — Risk Factors for CNS Involvement in ALL**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cytogenetic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydratase level &gt; 600 U/L</td>
<td>Presence of Philadelphia chromosome t(9:22)</td>
</tr>
<tr>
<td>Elevated β-2 microglobulin level</td>
<td>t(8:14)</td>
</tr>
<tr>
<td>High proliferative index (&gt; 14% lymphoblasts in cell cycle [S or G2/M phase])</td>
<td>t(4:11)</td>
</tr>
<tr>
<td>Mature B-cell phenotype</td>
<td>Complex karyotype (&gt; 5 chromosomal abnormalities)</td>
</tr>
<tr>
<td>Blast expression of CD56</td>
<td>Low hypodiploidy/ near triploidy</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia, CNS = central nervous system.

Data from references 53 and 54.
chemotherapy for the prevention of CNS relapse is limited by its ability to penetrate the blood–brain barrier. IT chemotherapy produces cytotoxic concentrations in the CSF, even when small doses are used, and systemic toxicity is very rare. Commonly used agents include MTX, cytarabine, and corticosteroids. These have been used in various combinations and either as single-modality agents or in combination with systemic chemotherapy. Liposomal cytarabine is another IT therapy that can be used. A sustained-release formulation of cytarabine exists to prolong the cytotoxic drug concentrations of cytarabine in the CSF. Although it has been interchangeably used with IT cytarabine, it is generally studied only in retrospective studies or used as an investigational drug in cases granted expanded access, also known as compassionate use. Concerns exist regarding its neurotoxicity when the drug is concurrently given as prophylaxis with systemic chemotherapy, and its efficacy as a prophylaxis compared with IT cytarabine has not been studied in a prospective manner in the setting of hematological malignancies.

Pui et al demonstrated the effectiveness of intensive IT therapy, also known as triple IT therapy. Triple IT therapy consists of the simultaneous IT administration of MTX, cytarabine, and hydrocortisone. They reported that the 5-year cumulative risk of isolated CNS relapse was 1.7% and observed an isolated plus combined CNS recurrence rate of 3% to 4%. The researchers noted that these rates were comparable with those seen in cranial irradiation.

Use of escalated doses of systemic MTX and cytarabine have been tailored to increase CNS penetration, which, in combination with IT chemotherapy, represents the standard of care for the treatment of ALL in adults. Investigators compared the historical treatments of ALL, including therapy omitting IT chemotherapy (vincristine, doxorubicin, and dexamethasone; pre-VAD), chemotherapy with IT chemotherapy (modified VAD), and systemic dose–intensification with IT chemotherapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [CVAD]). The overall CNS relapse rate of pre-VAD was 31%, The overall CNS relapse rates with modified VAD and hyperfractionated CVAD were 17% and 3%, respectively, highlighting the role of intensive systemic chemotherapy and the role of IT chemotherapy in reducing CNS relapse. Combination regimen incorporating intensive systemic chemotherapy with IT chemotherapy have improved outcomes and reduced rates of CNS relapse (Table 5). Another intensive therapy utilized in the treatment of adult ALL — allogeneic stem cell transplantation — has been shown to have a beneficial effect. The risk of CNS relapse is increased in those with CNS involvement prior to allogeneic stem cell transplantation compared with those without involvement; however, 1 multicenter, retrospective study was not able to find any benefit with post-transplant IT chemotherapy prophylaxis at preventing CNS relapse.

Radiotherapy
Craniospinal radiotherapy represents one of the oldest modalities of CNS prophylaxis. It has shown to be beneficial in the pediatric population, but its role in the management of ALL in adults is limited. Lazarus et al utilized radiotherapy and IT chemotherapy for CNS prevention, reporting a CNS relapse rate of approximately 4%. This rate of relapse was similar to other radiotherapy-sparing prophylaxis strategies previously described. Because of the effects of radiotherapy, including secondary malignancies, neurocognitive deficits, and reduced quality of life, radiotherapy is not standard treatment for CNS prophylaxis in adults with ALL.

Conclusions
Leukemic and lymphomatous meningitis can arise as a sequela of various hematological malignancies, including primary central nervous system (CNS) lymphoma, secondary lymphoma, or leukemic involvement from acute myeloid leukemia or acute lymphoblastic leukemia. Identification of diseases at high risk for CNS involvement and other risk factors can be critical for the early detection of the condition, as well as for optimizing prophylaxis strategies. Leukemic and lymphomatous meningitis can be treated and, in some cases, prevented through the use of direct intrathecal therapy and systemic therapies geared toward CNS penetration. Future studies should continue to study treatment options and prevention strategies for leukemic and lymphomatous meningitis from hematological malignancies.

Table 5. — Combined Systemic and Intrathecal Regimens for ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Relapse Rate, %</th>
</tr>
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<tbody>
<tr>
<td>Chang⁵⁹</td>
<td>MTX</td>
<td>Yes</td>
<td>2.0</td>
</tr>
<tr>
<td>Kantarjian⁶⁸</td>
<td>Cytarabine MTX</td>
<td>No</td>
<td>4.0</td>
</tr>
<tr>
<td>Silverman⁶⁹</td>
<td>Cytarabine MTX Triple intrathecal therapy</td>
<td>Yes</td>
<td>3.2</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia, CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone, MTX = methotrexate.

References


