

Should Intra-cerebrospinal Fluid Prophylaxis Be Part of Initial Therapy for Patients With Non-Hodgkin Lymphoma: What We Know, and How We Can Find Out More

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Central nervous system (CNS) involvement is a serious complication of non-Hodgkin lymphoma (NHL), with an extremely poor outcome. In most cases, relapse in the CNS manifests as leptomeningeal disease. The relatively short interval between the initial diagnosis of NHL and CNS involvement implies that seeding of the cerebrospinal fluid occurs early in the natural history of the disease and suggests a role for CNS prophylaxis during initial treatment. However, CNS prophylaxis in patients with aggressive NHL remains controversial because of the relatively low incidence of CNS recurrence (5%–7%) in these patients and lack of consensus on the best therapies and protocols. Risk factors for CNS relapse in patients with aggressive NHL have been identified and may help define a subpopulation of patients for whom CNS prophylaxis is justified. Because of variation in current practice and a paucity of high-quality evidence, well-designed and controlled trials are needed to assess the benefits of prophylactic treatment in such a population. This article reviews the current role of CNS prophylaxis in patients with NHL and discusses issues in the conception, design, and execution of a clinical trial to elucidate the role of CNS prophylaxis in patients with aggressive NHL.

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Central nervous system (CNS) relapse is a highly morbid and generally fatal complication of non-Hodgkin lymphoma (NHL),^{1–4} with a median survival after CNS disease diagnosis of 2.4 to 4.4 months.^{3–8} CNS involvement can occur at any time during the clinical course of NHL, and for 50% of patients, the CNS is the site of first relapse following complete remission.^{3,4,9–11} The median time from diagnosis to detection of CNS disease is less than 1 year,

suggesting that seeding of the cerebrospinal fluid (CSF) occurs early in the course of the disease and that the CSF acts as a sanctuary for surviving tumor cells.^{3,7,8,12} Further support for this hypothesis is provided by the frequent presence of malignant cells in the CSF at the time of initial diagnosis both in primary CNS lymphoma (PCNSL)¹³ and in neural NHL.^{2,9,14}

The frequency of CNS recurrence varies according to the aggressiveness of the lymphoma, being uncommon in indolent lymphomas and frequent in very aggressive lymphomas such as Burkitt lymphoma and lymphoblastic lymphoma (Table 1).^{1,4,7–9,11,15–20} In recognition of this variability in the frequency of CNS relapse, CNS prophylaxis is not administered in patients with indolent NHL, but it is almost always included as part of the primary treatment of lymphoblastic lymphoma and Burkitt lymphoma, where it has been shown to reduce relapse rates and improve survival.^{21–25} Comparable therapeutic benefits have not been conclusively demonstrated in patients with other aggressive NHL subtypes such as diffuse large B-cell lymphoma (DLBCL).^{2,10,26–28} Few published studies are available to guide the management of patients with NHL with regard to CNS prophylaxis, and most of the existing data are limited by their retrospective nature. In addition, the results of these studies are conflicting and difficult to interpret because of wide variations among

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Table 1. Frequency of Central Nervous System Involvement in Non-Hodgkin Lymphoma Subtypes

NHL Subtype	Frequency of Lymphomatous Meningitis (%)
Indolent lymphoma ^{7,15,16}	0- $<$ 5
DLBCL ^{1,4,7,8,11,15,17,18}	~5-7
Lymphoblastic and Burkitt lymphoma ^{9,19,20}	30-50

Abbreviations: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

study populations and different prophylactic regimens (Table 2).^{3-8,11,12,29-31} Furthermore, some practitioners consider the overall frequency of CNS relapse in patients with aggressive NHL to be too low (approximately 5%-7% for DLBCL) to justify including a potentially toxic CNS prophylactic regimen as part of therapy for all patients.

Although patient and disease characteristics have been identified that define high-risk subpopulations that may warrant CNS prophylaxis, there is little agree-

ment and large practice variability with regard to the composition and application of prophylactic regimens.^{3,5-7,32,33} For example, a survey conducted among clinicians in the United Kingdom who treat NHL (N = 158) revealed little consensus regarding which risk factors needed to be present to warrant CNS prophylaxis.³² The most common reasons for initiating prophylaxis in this survey were involvement of paranasal sinuses (88%), testes (85%), orbital cavities (78%), or bone marrow (65%); stage IV disease (34%); high International Prognostic Index (IPI) score (21%); involvement of more than one extranodal site (16%); and high lactate dehydrogenase (LDH) (10%).³² The majority of respondents (90%) who did use prophylaxis employed intrathecal therapy; only 4% used prophylactic systemic chemotherapy.³² Similar variations in treatment practice were evident in a survey of Canadian physicians (N = 77) that evaluated CNS surveillance, prophylaxis, and treatment of adult patients with NHL.³³ CNS prophylaxis was most commonly used in patients with NHL involving the testes (45%) or epidural space (41%).³³ A higher proportion of tertiary care physicians initiated prophylactic treatment when there was testicular (53%) or epidural (50%) involvement compared with community oncologists (32% and 26%, respectively).³³ Intrathecal therapy with methotrexate (MTX) or MTX in combination with cytarabine was used by

Table 2. Central Nervous System Relapses in Patients With Aggressive Non-Hodgkin Lymphoma (excluding lymphoblastic lymphoma and Burkitt lymphoma)

First Author, Year	N	Systemic Therapy	CNS Prophylaxis	CNS Relapse Rate (%)
van Besien, 1998 ³	605	CHOP-like	None	4.5
Bos, 1998 ¹¹	193	CHOP	None	5.0
Zinzani, 1999 ⁴	175	MACOP-B	None	5.2
Feugier, 2004 ⁸	399	CHOP v CHOP-R	None	5.0
Haioun, 2000 ⁶	974	ACVBP	IT + HD MTX	1.6
Hollender, 2002 ⁷	1220	CHOP-like	12 mg IT MTX (n = 141)	4.2
Tilly, 2003 ²⁹	635	ACVBP + GELA Cons or HDT/PBSCT v CHOP	IT + HD MTX v none	2.8 vs 8.3
Boehme, 2007 ⁵	1693	CHOP-like	Systemic etoposide	2.2
Björkholm, 2008 ³⁰	444	CNOP	12 mg IT MTX	6.5
Bernstein, 2008 ¹²	899	ProMACE-CytaBOM and m-BACOD	WBRT or 12 mg IT MTX + IT Ara-C 30 mg (n = 121)	2.8
Pfreundschuh, 2008 ³¹	1217	CHOP-14 R v CHOP-14	15 mg IT MTX	4.8

Abbreviations: CNS, central nervous system; NHL, non-Hodgkin lymphoma; CHOP, regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone; MACOP-B, regimen consisting of bleomycin, cyclophosphamide, doxorubicin, leucovorin, methotrexate, prednisone, and vincristine; ACVBP, regimen consisting of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; IT, intrathecal; MTX, methotrexate; GELA, Adult Lymphomas Study Group; Cons, consolidation; HDT/PBSCT, high-dose chemotherapy with peripheral blood stem cell transplant; HD, high-dose; CNOP, regimen consisting of cyclophosphamide, mitoxantrone, prednisone, and vincristine; ProMACE-CytaBOM, regimen consisting of cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, prednisone, and methotrexate; m-BACOD, regimen consisting of methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; WBRT, whole-brain radiotherapy.

almost three quarters (74%) of physicians.³³ Systemic prophylaxis was used by 20% of physicians but always in combination with intrathecal prophylaxis. Clearly, evidence-based data from randomized, controlled trials are needed to clarify the role of CNS prophylaxis in patients with aggressive NHL.

THE IMPACT OF INTRA-CSF THERAPY IN PATIENTS WITH AGGRESSIVE NHL

PCNSL

PCNSL represents a special case of DLBCL with a neural origin, a very aggressive course, and almost universal CNS recurrence after treatment.³⁴⁻³⁶ CNS relapse often manifests as lymphomatous meningitis (LM) or LM in association with parenchymal involvement.^{13,37} The exact frequency of LM in PCNSL remains controversial. Estimates vary according to the diagnostic strategy used, ranging from 8% when assessed by magnetic resonance imaging (MRI)³⁷ to 18% when assessed by lumbar puncture CSF cytology¹³ to 78% when assessed by ventricular CSF cytology.³⁸ There is currently no universally accepted approach to therapy or consensus on CSF prophylaxis.^{35,39}

Cranial irradiation combined with chemotherapy results in improved survival and extended time to recurrence compared with radiotherapy alone, but radiation carries a substantial risk of long-term neurotoxicity, especially in patients older than 60 years of age.⁴⁰⁻⁴⁶

Motivated by a desire to avoid the delayed toxic effects of radiation, several investigators have studied the benefits of chemotherapy alone.^{34,47-50} Because systemically administered high-dose MTX (1-8 g/m²) crosses the blood-brain barrier (BBB) and achieves therapeutic concentrations in the CSF,⁵¹ systemic chemotherapy with high-dose MTX as a single agent or in combination with other active agents (eg, corticosteroids, cytarabine, thiopeta, vincristine, cyclophosphamide, temozolomide, rituximab) has become the basis of PCNSL therapy.⁵²

McAllister et al⁴⁸ reported that among 74 patients with PCNSL treated with high-dose, MTX-based (2.5 g/m²) BBB-disruption-enhanced chemotherapy, 65% (n = 48) achieved a complete response, and the median survival time was 40.7 months. No cognitive decline occurred in patients who continued to experience a complete response after 1 year of therapy.⁴⁸ However, the role of systemic chemotherapy alone in PCNSL is still unclear. A prospective trial in which 37 patients with PCNSL received high-dose MTX (8 g/m²) was terminated due to a low complete response rate (30%).⁴⁹ The overall median survival in this study was 25 months.⁵⁰ Other investigators have reported complete response rates of 52% and 65% with similar treatment.^{34,53} Conversely, a study that combined both systemic and intra-CSF treatment reported a 79% complete response achieved in 14 immunocompetent patients

with PCNSL.⁴⁷ Patients were treated with a combination of high-dose MTX (8.4 g/m²), thiopeta, vincristine, and dexamethasone and intrathecal cytarabine (15-50 mg) and MTX (12 mg).

The multicenter Bonn Protocol, the largest prospective study to date in patients with PCNSL, was designed to assess whether targeting the CSF during initial therapy for PCNSL with an intensified chemotherapy-only regimen would result in durable tumor response while avoiding neurotoxicity.^{54,55} Frequent administration of low-dose intraventricular chemotherapy (concentration × time approach) via Ommaya reservoir, which produces a more uniform and constant drug concentration in the CSF, was employed.⁵⁶ Patients with newly diagnosed PCNSL (N = 65) were enrolled in a pilot phase II, open-label study.^{54,55} High-dose MTX- (5 g/m²) and cytarabine- (3 g/m²) based systemic therapy, also including vincristine (2 mg), ifosfamide (800 mg/m²), and dexamethasone (10 mg/m²), was combined with intraventricular MTX (3 mg), cytarabine (30 mg), and prednisolone (2.5 mg) (Table 3).⁵⁵ The median age of patients was 62 years (range, 27-75), and their median Karnofsky performance score (KPS) was 70 (range, 20-90). Follow-up was 0 to 87 months (median, 26 months). Median event-free survival (EFS), the primary study end point, was 21 months, and overall survival was 50 months. The overall response rate was 71%, with 61% of patients achieving a complete response and 10% achieving a partial response.⁵⁵ Nineteen percent of patients progressed during therapy, and 8% of patients died of treatment-related causes.

As in other trials, a markedly better clinical outcome was observed in younger patients (≤60 years of age, n = 30). Kaplan-Meier estimates for median overall survival, progression-free survival, and EFS have not yet been reached for these patients.⁵⁵ The overall response rate in the younger population was 86%, with complete responses and partial responses achieved in 76% and 10% of patients, respectively. Disease progression during treatment occurred in 7% of patients, and early death occurred in 7%. Older patients (>60 years of age, n = 35) had a median EFS of only 15 months and a median overall survival of 34 months. The 5-year survival was 75% in patients ≤60 years of age and 19% in those >60 years of age.⁵⁵ Results from this study suggest that a chemotherapy-only regimen based on high-dose and intra-CSF MTX and cytarabine is effective in younger patients with PCNSL and frequently results in long-term remission and even cure in some patients. These data compare favorably with the best results reported in combined chemotherapy and radiotherapy trials^{43,45} and other poly-chemotherapy trials.^{47,48}

No chemotherapy-related neurotoxicity was observed in patients at follow-up, and systemic toxicity was mainly hematologic (ie, leukopenia and thrombocytopenia). Infection of the Ommaya reservoir oc-

Table 3. Bonn Chemotherapy Protocol for Primary Central Nervous System Lymphoma

Chemotherapy	Day						
	1	2	3	4	5	6	7
Cycle A							
Systemic:							
Methotrexate IV (5 g/m ²)	+						
Vincristine IV (2 mg)	+						
Ifosfamide IV (800 mg/m ²)		+	+	+	+		
Dexamethasone PO (10 mg/m ²)		+	+	+	+		
Intraventricular:							
Prednisolone ICV (2.5 mg)	+	+	+	+			
Methotrexate ICV (3 mg)	+	+	+	+			
Ara-C ICV (30 mg)						+	
Cycle B							
Systemic:							
Methotrexate IV (5 g/m ²)	+						
Vincristine IV (2 mg)	+						
Cyclophosphamide IV (200 mg/m ²)		+	+	+	+		
Dexamethasone PO (10 mg/m ²)		+	+	+	+		
Intraventricular:							
Prednisolone ICV (2.5 mg)	+	+	+	+			
Methotrexate ICV (3 mg)	+	+	+	+			
Ara-C ICV (30 mg)						+	
Cycle C							
Systemic:							
Ara-C IV (3 g/m ²)	+	+					
Vindesine IV (5 mg)	+						
Dexamethasone PO (20 mg/m ²)			+	+	+	+	+
Intraventricular:							
Prednisolone ICV (2.5 mg)			+	+	+	+	
Methotrexate ICV (3 mg)			+	+	+	+	
Ara-C ICV (30 mg)							+

NOTE. Treatment consisted of six chemotherapy cycles separated by intervals of 2 weeks between each cycle. Cycle A was given on days 1–5 and 64–68, cycle B was given on days 2–26 and 85–89, and cycle C was given on days 43–49 and 106–112. The protocol was modified in the multicenter phase 2 study: no ICV therapy was given on day 1 of cycles A and B, and systemic methotrexate was reduced to 3 g/m² in patients older than 64 years of age.

Abbreviations: CNS, central nervous system; Ara-C, cytarabine; ICV, intracerebroventricular; IV, intravenous; PO, orally. Reprinted with permission.⁵⁴ Copyright © 2003 American Society of Clinical Oncology. All rights reserved.

curred in 19% of patients,⁵⁵ a rate higher than has been reported in other series.^{40,47,57,58} Although infection was managed, it resulted in treatment interruption or delay.⁵⁵ The investigators postulated that the numerous intraventricular injections required by the protocol, therapy-induced myelosuppression, and the immunocompromised status of some patients may have contributed to the high infection rate.⁵⁵ In light of this, and because other studies suggested that intrathecal MTX did not improve survival in patients with PCNSL receiving systemic high-dose MTX,^{59,60} the investigators decided to omit intraventricular treatment in subsequent cohorts of patients (modified Bonn protocol).⁶¹

Fifty patients were enrolled in the modified Bonn protocol study, of whom 35 were evaluable for re-

sponse.⁶¹ The median follow-up was 9 months (range, 1–26 months). Response rates were comparable to those obtained in the original Bonn protocol; however, omitting intraventricular therapy resulted in a significantly shorter median progression-free survival than that in the original protocol.^{61,62} Assessment of KPS, LDH levels, and CSF protein at diagnosis⁶³ indicated that study populations were balanced with regard to these prognostic factors.^{61,62} The results from these two trials strongly suggest a benefit from including intra-CSF therapy in the initial treatment of PCNSL and support the assumption that targeting the CSF is necessary to achieve sustained remission. These data also suggest that, when active therapy is completed, the CSF may act as a reservoir for surviving tumor cells that

may repopulate the CNS or extraneural loci and lead to relapse.

While the examples provided by the PCNSL studies suggest an important role for intra-CSF prophylaxis in patients with NHL, they do not provide indisputable evidence of its benefit. Trials specifically designed to elucidate the role of CNS prophylaxis in patients with NHL are needed.

LIMITATIONS AND CONSIDERATIONS FOR A CNS PROPHYLAXIS TRIAL IN PATIENTS WITH NHL

Key considerations in the design and execution of a CNS prophylaxis trial include the factors used to select patients at high risk of CNS relapse, the choice of prophylactic regimen, and the overall risks and benefits of prophylaxis in patients with NHL.

Risk Factors Determine Patient Population

Because of the relatively low incidence of CNS involvement in patients with NHL, “enriching” the trial population with patients at higher risk for developing CNS involvement is necessary to prevent overtreating the population not at risk. The two most important independent predictors of CNS disease, identified by multivariate regression analysis of large series of patients with NHL, are the presence of more than one extranodal site (relative risk [RR], 2.9–5.5) and elevated LDH [RR, 2.1–7.0]) (Table 4).^{3,5-7} van Besien and colleagues³ identified a group of patients for whom the cumulative risk of CNS relapse was 20%. Hollender and colleagues⁷ retrospectively identified three additional independent risk factors that conferred a higher risk of CNS disease among 1,220 patients: young age (<60 years) [RR, 2.8], serum albumin <3.5 g/L [RR, 2.5], and retroperitoneal lymph node involvement [RR, 1.9].⁷ Increasing the number of risk factors considerably increased the chance of CNS relapse. Patients with four or five risk factors represented 12% of the patients with NHL in this study and 54% of those with relapse (Table 5).⁷

These studies indicate that it is possible to select patients with NHL and a high risk of developing CNS disease—high enough, perhaps, to justify inclusion in a CNS prophylaxis trial. However, the higher the likelihood of developing the disease in a population, the smaller the fraction of the population one is left with, resulting in study design issues of sample size and generalizability (Table 5).⁷

Availability of Effective Therapies

The therapeutic benefit of CNS prophylaxis has been clearly demonstrated in the very aggressive NHLs (lymphoblastic lymphoma and Burkitt lymphoma).²¹⁻²⁵ However, most studies assessing the therapeutic value

Table 4. Relative Risk of Central Nervous System Relapse Associated With Prognostic Factors Identified in Multivariate Analyses

First Author, Year	Increased LDH	> 1 Extranodal Site	IPI	Age <60 Years	Albumin <3.5 g/L	Retroperitoneal Lymphadenopathy
van Besien, 1998 ³	RR, 7.0; 95% CI, 2.0–38.0; P = .0008	RR, 5.5; 95% CI, 2.1–14.9; P = .0005	—	—	—	—
Haioun, 2000 ⁶	RR, 5.0; P = .05	RR, 3.0; P = .05	RR, 7.0; P = .002	—	—	—
Boehme, 2007 ⁵	RR, 3.7; 95% CI, 1.8–7.5; P < .001	RR, 2.9; 95% CI, 1.5–5.9; P = .002	—	—	—	—
Hollender, 2002 ⁷	RR, 2.1; 95% CI, 1.0–4.4*; P = .049	RR, 3.0; 95% CI, 1.7–5.4	—	RR, 2.8; 95% CI, 1.5–5.4; P = .002	RR, 2.5; 95% CI, 1.3–4.6; P = .005	RR, 1.9; 95% CI, 1.0–3.5; P = .037

Abbreviations: CI, confidence interval; CNS, central nervous system; LDH, lactate dehydrogenase; IPI, International Prognostic Index; RR, relative risk. *LDH ≥450 U/l v <450 U/l.

Table 5. Probability of Central Nervous System Relapse According to the Number of Risk Factors Present

No. of Risk Factors	% of Population	Probability of CNS Recurrence Within 5 Years, % (95% CI)
0	13.3	1.9 (0–4.6)
1	30.5	2.0 (0.4–3.6)
2	26.7	2.8 (0.5–5.2)
3	17.3	6.2 (1.9–10.5)
4	9.8	25.3 (14.8–35.8)
5	2.5	32.7 (11.6–53.8)

Abbreviations: CNS, central nervous system; CI, confidence interval.

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of CNS prophylaxis in NHL are retrospective in nature, and the results are conflicting.

In their retrospective analysis of 1,693 patients with aggressive lymphoma, Boehme and colleagues⁵ reported a 2.2% frequency of CNS relapse. Of note, CNS prophylaxis was administered to fewer than 5% of patients.⁵ In another retrospective analysis of 68 patients with aggressive NHL in complete remission following systemic chemotherapy, significantly fewer patients who received prophylactic treatment with intra-CSF MTX and hydrocortisone experienced CNS relapse compared with patients who did not receive prophylactic treatment (0% *v* 15%; $P = .03$).⁶⁴ The absence of prophylaxis was identified by multivariate regression analysis as a significant factor for CNS relapse ($P = .01$; RR, 0.000006). Overall 5-year survival rates were 80% in the group that received prophylaxis, compared with 58% for those who did not ($P = .05$).⁶⁴ A retrospective analysis by Haioun and colleagues⁶ showed a low (1.6%) rate of isolated CNS relapse among 974 patients with aggressive NHL in complete remission following treatment with systemic chemotherapy (ACVBP regimen [doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone]) combined with intra-CSF and systemic high-dose MTX. In a prospective, randomized study, older patients (61–69 years of age) with high-risk aggressive NHL were treated with an ACVBP regimen that included CNS prophylaxis with intra-CSF MTX and two courses of systemic high-dose MTX ($n = 323$) or standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ($n = 312$).²⁹ Nine patients exhibited CNS progression in the ACVBP group, compared with 26 patients in the CHOP group [RR, 2.99; $P = .002$].²⁹ At 5 years, EFS and overall survival rates were significantly higher for those who received prophylaxis (39% and 46%) compared

with those who did not (29% [$P = .005$] and 38% [$P = .036$], respectively).²⁹ In contrast, a 20-year follow-up analysis of CNS relapse in patients with aggressive NHL retrospectively compared high-risk patients (those with large cells in their pretreatment bone marrow biopsy) who received prophylactic intra-CSF MTX and cytarabine on an m-BACOD regimen (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) or prophylactic cranial irradiation on a ProMACE (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide)-CytaBOM (cytarabine, bleomycin, vincristine, prednisone) regimen with patients on regimens that did not incorporate CNS prophylaxis.¹² This analysis found that patients who had received any form of CNS prophylaxis did not experience a significantly lower rate of CNS relapse than patients who received no prophylaxis (2.8% *v* 3.6%, respectively; $P = .74$),¹² but overall CNS relapse rates were low in this trial compared with other studies, and one of the CNS prophylaxis regimens (cranial irradiation) was not sufficient to sterilize the entire CSF space.

The use of systemic and/or intra-CSF MTX provides CNS prophylaxis that is safe, feasible, and possibly effective. Other intra-CSF therapies useful in the treatment, and perhaps in the prevention, of LM include cytarabine, liposomal cytarabine, thiotepa, and rituximab.⁶⁵ Because CNS relapse is often meningeal,^{3,7,8} further discussion of a trial investigating CNS prophylaxis will focus on leptomeningeal metastases in NHL.

Choice of Therapy and Randomization

Conventional intra-CSF therapy for the treatment of LM consists of MTX, cytarabine, liposomal cytarabine, or thiotepa administered by lumbar puncture or via an Ommaya reservoir. However, since MTX, cytarabine, and thiotepa have short half-lives within the CSF (MTX, 4.5–8 hours; cytarabine, 3.4 hours, thiotepa, 3–5 minutes),^{66–68} frequent administration is needed to maintain cytotoxic drug concentrations in the CSF. Numerous intralumbar injections may substantially compromise patients' well-being and may not be appropriate in the context of prophylaxis.

Liposomal cytarabine, a lipid-encapsulated chemotherapeutic agent, produces sustained cytotoxic concentrations of free cytarabine in both the ventricular and lumbar CSF (>14 days in most patients), decreasing the need for repeated injections.⁶⁹ Clinical trials have demonstrated that the resulting prolonged tumor exposure to cytotoxic levels of free cytarabine improves response in patients with leptomeningeal disease.⁷⁰ In a randomized, controlled trial, patients with LM were randomized to receive liposomal cytarabine 50 mg once every 2 weeks ($n = 14$) or unencapsulated cytarabine 50 mg twice a week ($n = 14$) for 1 month of induction therapy.⁷⁰ Responders received an additional

3 months of consolidation therapy followed by 4 months of maintenance therapy. Response to treatment was defined as CSF cytology conversion from positive to negative at all previously positive sites, and neurological stabilization. The response rate in patients treated with liposomal cytarabine was significantly higher compared with that in patients treated with unencapsulated cytarabine (71% *v* 15%, respectively; *P* = .006).⁶⁹ These results indicate that liposomal cytarabine may be another viable agent for investigation in a CNS prophylaxis trial.

Randomization in an LM prophylaxis trial remains complicated. A logical randomization would be between liposomal cytarabine—or another intra-CSF agent such as cytarabine or thiotepa—and no CSF treatment. The ethical basis to support a “no treatment” arm includes the wide variation in current practice together with the potential morbidity of treatment and the lack of randomized controlled trial data, providing true clinical equipoise. Since there is some, albeit disputable, evidence that prophylaxis is effective, some might argue that the only ethical randomization would be between liposomal cytarabine and another CSF-active regimen (eg, high-dose intravenous MTX, intra-CSF MTX, or cytarabine). Because of sample size constraints, only a non-inferiority randomized trial could be considered, the ethics of which would rest on the expectation that liposomal cytarabine might be more tolerable (fewer administrations) and possibly more effective. The most practical type of study, in terms of study size, would be a phase II model: a randomized phase II or single-arm trial with pre-planned historical comparisons, or a single-arm mini-max design.

Assumptions in Determining Benefits and Risks

Even with an enriched trial population based on high-risk characteristics, placing a patient with no CNS disease on potentially toxic chemotherapy remains an

important consideration. The benefit-to-risk ratio in the setting of a clinical trial (toxicity *v* efficacy) must therefore be considered. One strategy for quantifying this trade-off is to compare the number of patients needed to treat (NNT) to prevent one case of CNS relapse with the number needed to harm (NNH)—the number of patients required to receive treatment in order to result in one treatment-related adverse event. On the basis of available studies, we estimated the NNT and NNH for a potential CNS prophylaxis trial in patients with DLBCL using the following assumptions:

- The efficacy of prophylaxis will at least equal that observed in studies of treatment of actual leptomeningeal disease.
- The toxicity of prophylaxis will not be worse than in patients who are treated for overt leptomeningeal disease.
- Only grade 3 and 4 toxicities are considered.

The range of NNT and NNH calculated using these assumptions fell within the range usually considered acceptable in other disease models (Table 6).

Based on these considerations, we propose a study in patients with DLBCL with increased LDH and more than one extranodal site, or patients with DLBCL and disease at specific anatomic sites that convey a high risk of CNS relapse (eg testicular or ocular lymphoma and patients with large cell involvement of bone marrow). Patients with known brain or CSF metastases at diagnosis would be excluded. Eligible patients would be randomized to an R-CHOP-like regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) with or without intra-CSF liposomal cytarabine. Since most CNS relapses occur within 1 year of diagnosis, the 2-year CNS relapse rate would constitute a scientifically sound and logistically practical primary end point. EFS, site of disease recurrence, time to neurologic progression, and overall survival could be assessed as second-

Table 6. Potential Risk and Benefit of Central Nervous System Chemoprophylaxis in Non-Hodgkin Lymphoma

% of Population in Whom LM Develops	No. Needed to Treat	No. Needed to Harm	Odds Ratio (95% CI)
100	1.4	3.5	—
50	3.0	3.6	5.2 (1.1–25.4)
30	4.6	3.6	4.7 (1.3–16.5)
25	5.7	3.6	4.2 (1.3–14.2)
20	7.0	3.5	4.0 (1.3–11.9)
15	9.2	3.5	4.0 (1.3–12.6)
10	13.6	3.5	3.9 (1.4–11.0)
6	24.0	3.5	3.5 (1.4–8.5)

Abbreviations: LM, lymphomatous meningitis; CI, confidence interval.

ary efficacy outcomes. Alternatively, patients matching these high-risk profiles could be randomized using a phase II “pick the winner” model, to one of the two treatment arms described above, both of which would then be compared independently to a prespecified historical control arm. Table 5 in Smith and Glantz’s article elsewhere in this supplement provides sample size estimates for various response assumptions, and α and power choices for these two randomized trial models, and for a single-arm phase II model with an historical comparison.

CONCLUSION

CNS relapse, including leptomeningeal metastasis, is a generally fatal complication of NHL. Despite the relatively low frequency of relapse, the devastating effects of LM can justify treating patients at high risk of relapse prophylactically. Because CSF invasion appears to be an early event in patients with DLBCL, and because untreated CSF lymphoma may provide a reservoir of malignant cells that can reseed tumor both throughout the CNS and systemically, targeting the CSF may constitute an important part of the primary treatment regimen for patients with aggressive NHL. A number of studies have provided evidence suggesting that prophylaxis is beneficial in these patients, but due to their retrospective nature as well as variations in protocols, target patients, and therapies used, incontrovertible proof remains elusive. The availability of multiple agents that are effective in treating LM should encourage investigators to study the efficacy of these agents in prophylaxis in well-designed and well-controlled clinical trials.

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