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Central Nervous System Disease in Hematological Malignancies: Historical Perspective and Practical Applications

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Abstract

Acute lymphoblastic leukemia (ALL) 5-year survival rates are approaching 90% in children and 50% in adults who are receiving contemporary risk-directed treatment protocols. Current efforts focus not only on further improving cure rate but also on patient quality of life. Hence, all protocols decrease or limit the use of cranial irradiation as central nervous system (CNS)-directed therapy, even in patients with high-risk presenting features, such as the presence of leukemia cells in the cerebrospinal fluid (even resulting from traumatic lumbar puncture), adverse genetic features, T-cell immunophenotype, and a large leukemia-cell burden. Current strategies for CNS-directed therapy involve effective systemic chemotherapy (eg, dexamethasone, high-dose methotrexate, intensive asparaginase, ifosfamide) and early intensification and optimization of intrathecal therapy. Options under investigation for the treatment of relapsed or refractory CNS leukemia in ALL patients include thiotepa and intrathecal liposomal cytarabine. CNS involvement in non-Hodgkin's lymphoma (NHL) is associated with young age, advanced stage, number of extranodal sites, elevated lactate dehydrogenase, and International Prognostic Index score. Refractory CNS lymphoma in patients with NHL carries a poor prognosis, with a median survival of 2 to 6 months; the most promising treatment, autologous stem cell transplant, can extend median survival from 10 to 26 months. CNS prophylaxis is required during the initial treatment of NHL subtypes that carry a high risk of CNS relapse, such as B-cell ALL, Burkitt's lymphoma, and lymphoblastic lymphoma. The use of CNS prophylaxis in the treatment of diffuse large B-cell lymphoma is controversial because of the low risk of CNS relapse (~5%) in this population. In this article, we review current and past practice of intrathecal therapy in ALL and NHL and the risk-models that aim to identify predictors of CNS relapse in NHL.

Keywords

acute lymphoblastic leukemia; CNS-directed therapy; liposomal cytarabine; thiotepa

INTRODUCTION

In the early 1970s, presymptomatic central nervous system (CNS) therapy changed the prognosis of pediatric acute lymphoblastic leukemia (ALL). Before then, more than half of the

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complete remissions induced by systemic chemotherapy ended in CNS relapse.[1] The contemporary use of risk-directed effective systemic chemotherapy and CNS-directed treatment (intrathecal chemotherapy with or without cranial radiation) increased 5-year event-free survival (EFS) rates for childhood ALL to 80% or more in some studies.[1,2] Still, CNS relapse remains an important cause of morbidity and mortality and can occur in up to 6% of ALL patients.[3] Recent clinical trials in ALL treatment focus on further reducing CNS relapse rates and improving long-term survival rates by providing more precise individualized therapy that avoids over- or under-treatment. Studies are also investigating ways of minimizing late complications such as secondary cancer, neurocognitive defects, and multiple endocrinopathy by eliminating or decreasing the dose of cranial irradiation. This review presents the history and current practice of CNS-directed treatments for ALL and discusses CNS-directed therapy and prophylaxis in non-Hodgkin's lymphoma (NHL). It is hoped that providing a historical perspective on the role of CNS therapy in treating ALL and NHL may serve as a paradigm for the potential benefit and techniques of CNS prophylaxis in other malignancies.

DIAGNOSING CNS DISEASE IN PATIENTS WITH ALL AND NHL

Accurate diagnosis of CNS leukemia or lymphoma is essential. Although several methods for detecting CNS leukemia are available, the standard method is light microscopic exam of cytospin preparations of cerebrospinal fluid (CSF) samples for the presence of leukemic cells. While CSF cytology is regarded as the gold standard for diagnosis, false-negatives or false-positives occur.[4] Staining for terminal deoxynucleotidyl transferase may help distinguish normal lymphocytes from leukemic cells in cases with questionable morphology. Immunocytology to detect leukemia-associated cell surface antigens has also been used to establish the diagnosis.[5]

In contrast to cytology, magnetic resonance imaging (MRI) has been reported to be highly sensitive for the presence of meningeal pathology but nonspecific for the disease entity.[6] For example, nonmalignant meningeal enhancement may be observed following diagnostic or therapeutic lumbar puncture.[7] Zeiser and colleagues[5] found that the relative sensitivity of immunocytology compared with MRI varies for different malignancies. Although MRI was more sensitive than immunocytology in the detection of solid tumor neoplastic meningitis (immunocytology: 46%, MRI: 100%), immunocytology was more sensitive than MRI for the diagnosis of B-lineage ALL (immunocytology: 89%, MRI: 44%) and B-cell NHL (immunocytology: 95%, MRI: 48%).[5]

More recent advances in detection have focused on flow cytometry and polymerase chain reaction (PCR) methods for improving sensitivity. Hegde and colleagues[8] demonstrated that multicolor flow cytometry using multiple antibody panels for light chains and B- and T-cell antigens is capable of detecting neoplastic cells that constitute as little as 0.2% of total CSF lymphocytes. In a more recent evaluation of 60 patients who had CSF malignancies, the diagnostic value of flow cytometry was found to be more than twice that of cytomorphology.[9] Because of its increased sensitivity, the National Comprehensive Cancer Network recommends the routine use of flow cytometry for the diagnosis of CNS lymphoma,[10] but strict requirements for sample processing and the lack of standardization are problematic. Because cytomorphologic examination of the CSF provides additional diagnostic value, it should still be performed in conjunction with flow cytometry.

The development of PCR as a diagnostic technique based on the detection of clonal rearrangements of the immunoglobulin or T-cell receptor genes also has potential as a sensitive test for CSF involvement from lymphoma.[11,12] In a retrospective PCR study that used two sets of consensus primers from the immunoglobulin V and J region, five of seven specimens from patients with CNS malignancy who were suspected of, but not diagnosed with, lymphoma by

conventional cytology were positive by PCR. In addition, five of 13 specimens from patients with lymphoma that showed no cytologic evidence of malignancy were positive by PCR.[11] Another study that used nested PCR of the complementary determining region III found that PCR results and CSF cytology were discordant in 10 out of 17 patients with primary CNS lymphoma.[12] However, patients in this study had already been treated, and further analysis of the CSF samples obtained immediately after diagnosis was required. Nevertheless, PCR may prove to be a useful method along with conventional cytology.

RISK FACTORS FOR CNS DISEASE RELAPSE: PATIENTS WITH ALL

Several factors associated with an increased risk of CNS relapse have been identified for pediatric patients with ALL.[3, 13] First among these is the presence of leukemic blast cells in the CSF. Traditionally, patients were considered at increased risk of CNS disease if blast cells apparent in the CSF were accompanied by a white blood cell (WBC) count that exceeded 5 cells/μL in the CSF. However, in the 1990s, it was observed that the presence of any number of blast cells in the CSF, regardless of leukocyte count, was associated with an increased risk of CNS relapse.[14,15] Therefore, a risk classification for CNS disease was proposed: CNS1, denoting the absence of identifiable leukemic cells in CSF; CNS2, denoting the presence of blast cells in a sample that contains <5 WBCs/μL; and CNS3, a sample that contains ≥5 WBC/μL with identifiable blast cells, or the presence of a cerebral mass or cranial nerve palsy with leukemic cells in CSF.[14]

The relevance of this CNS risk classification has been a subject of controversy, because a number of groups did not observe significant differences in outcome for patients categorized as CNS1 versus CNS2.[15–19] However, it is now known that the classification is relevant in the context of the treatment received.[3] Specifically, studies that did not include early CNS-directed therapy found that patients who had CSF blast cells without pleiocytosis (CNS2) had a 3.2-fold increased risk (95% confidence interval [CI]: 1.1–9.5) for CNS relapse compared with patients with no leukemic cells in their CSF (CNS1),[14] whereas studies that did feature early CNS-directed therapy or prophylactic cranial irradiation identified no differences in CNS relapse rates for CNS1 versus CNS2 patients.[16,17]

In the past decade, multiple studies have reported an increased incidence of CNS relapse associated with traumatic lumbar puncture with the presence of blast cells.[16,18,20] Several explanations for these observations have been proffered. These include iatrogenic introduction of blast cells, more advanced leukemia, unrecognized CNS2 or CNS3 cases in patients with traumatic punctures, or compromise of subsequent intrathecal treatments.[3,16] Despite this, the association between traumatic lumbar puncture and CNS relapse risk renders it imperative that diagnostic lumbar punctures be performed without trauma. Therefore, St. Jude Children's Research Hospital now routinely performs this procedure under deep sedation or general anesthesia, transfuses patients with thrombocytopenia (ie., $<100 \times 10^9$/L), and administers age-adjusted intrathecal treatment immediately after CSF collection.[3,21] In addition, only the most experienced clinicians perform the procedure, since experience is one of the most important determinants of success.[22]

Other major factors associated with an increased risk of relapse in the CNS include a large leukemia-cell burden and T-cell immunophenotype.[2,3] Recent trials at St. Jude Children's Hospital have shown that patients who have T-lineage ALL, presence of blasts in CSF, pre-B ALL with the t(1;19) have an independently higher risk of CNS relapse [Pui C-H, unpublished observation]. In this regard, it is well recognized that T-cell ALL cases, especially those with high presenting leukocyte count, are at an increased risk of CNS relapse and are candidates for cranial irradiation in many clinical trials.[3,23–25]

A number of additional high-risk genetic features have been associated with CNS relapse risk. Leukemic cell genotypes associated with an unfavorable CNS prognosis include hypodiploidy (<45 chromosomes per leukemia cell), the translocation t(4;11) with the *MLL-AF4* fusion gene, the translocation t(1;19) with *E2A-PBX1* fusion gene, and the Philadelphia chromosome, t(9;22).[2] Host pharmacogenetics can also contribute to treatment responsiveness and consequently to patient outcome. Two gene polymorphisms associated with predisposition for CNS relapse have been identified. These include the vitamin D receptor start site in high-risk ALL patients and the thymidylate synthase 3/3 genotype in low-risk patients (Fig 1).[26,27] The polymorphism of thymidylate synthase gene has been linked to increased expression of the enzyme, one of the major targets of methotrexate (MTX), and the vitamin D receptor regulates the expression of proteins that are important in the disposition of vincristine, etoposide, daunorubicin, prednisone, and dexamethasone. Examination of host genotype may thus be used to optimize therapy selection and individualize chemotherapy dosing. More recently, high expression of interleukin-15 in pediatric ALL but low expression in adult ALL in diagnostic leukemic cells was associated with CNS leukemia at diagnosis and subsequent relapse, suggesting a pathogenetic role of this cytokine in leukemic cell migration into the CNS.[28,29]

Compared with childhood ALL, relatively little is known about CNS leukemia in adults with ALL. Approximately 5% to 10% of adults with ALL have CNS involvement at presentation.[30–34] Factors associated with CNS disease at presentation include a higher WBC count, T-cell immunophenotype, and the presence of a mediastinal mass.[31] Identified risk factors for CNS relapse in adult ALL include elevated lactate dehydrogenase levels, S-phase fraction, mature B-cell phenotype, high WBC counts, and CNS leukemia at diagnosis.[35–37] Despite intensified chemotherapy and craniospinal irradiation (24 Gy cranial and 12 Gy spinal) or hematopoietic stem cell transplantation with 13.2 Gy fractionated total body irradiation in approximately half of the patients, those with CNS leukemia at diagnosis who had achieved remission had a significantly higher risk of any type of CNS relapse, combined or isolated (11.9% vs 5.6%; $P = 0.04$), and a poorer survival rate (29% vs 38% at 5 years; $P < 0.03$) compared with other patients.[31]

TREATMENT STRATEGIES FOR CNS CONTROL DURING PRIMARY ALL THERAPY

The recognition that ALL is a heterogeneous disease has led to treatment directed according to phenotype, genotype, and risk of relapse. CNS-directed therapy starts early in the clinical course and varies depending on the patient's risk of relapse and the intensity of systemic treatment. Important prophylactic strategies for CNS control include effective systemic chemotherapy and early intensification and optimization of intrathecal therapy.

Systemic Chemotherapy

Corticosteroids—Corticosteroids are an essential component of ALL treatment. Some studies have suggested potential advantages of dexamethasone over prednisone for CNS control. Two studies comparing conventional dosages of dexamethasone and prednisone reported that prednisone-treated patients had lower survival rates and experienced CNS relapse at nearly twice the rate of those treated with dexamethasone.[38,39] It was suggested that such differences in CNS relapse rates may be due to either: (1) the longer biological half-life of dexamethasone versus prednisone (>32 hours vs 4 to 6 hours, respectively)[38,40] or (2) the low-protein binding property of dexamethasone resulting in a higher CNS bioavailability.[41] However, such comparisons are difficult to make without knowledge of drug equivalent doses. Interestingly, a third study that used a 50% higher dose of prednisone (60 mg; n = 114) did not find significant differences in CNS relapse or survival rates for dexamethasone (8 mg/m^2; n = 117) compared with prednisone,[42] suggesting that when equivalent doses are matched, the two

drugs are comparable in CNS outcome. Nevertheless, the use of dexamethasone is still preferred in the clinical setting, because it is believed to have better CNS as well as systemic control.

MTX—High-dose intravenous (IV) MTX was introduced as a treatment for ALL that might be expected to prevent CNS relapse because of its ability to cross the blood-brain barrier (BBB). The question of whether this is the case in practice was addressed in a meta-analysis of eight studies that compared cranial radiation plus CSF-directed therapy with high-dose MTX plus intrathecal therapy.[43] This study found that high-dose MTX reduced hematologic relapse and improved EFS but had only a marginal effect on the control of CNS relapse (odds ratio [OR]: 0.81 [0.63–1.03]; $P = 0.08$). It should be noted that this meta-analysis included studies using a wide range of MTX doses (0.5 g/m^2 to 8 g/m^2) and dose schedules, and it is plausible that significant CNS control may be observed only with the higher MTX doses.[43] Furthermore, even a MTX dose as high as 33.6 g/m^2 would not improve outcome if the MTX treatments were given too late in the treatment course or rescued with leucovorin too early or at too high a dose.[44]

Asparaginase—Another drug used to treat ALL, asparaginase, can also provide effective CNS control. However, its efficacy for preventing CNS relapse depends on the type and dose of asparaginase used. Moghrabi and colleagues[45] demonstrated that patients treated with asparaginase derived from *Erwinia* (n = 139; 5-year CNS relapse: 6%) experienced CNS relapse at nearly six times the rate of patients treated with *Escherechia coli*-derived asparaginase (n = 147; 5-year CNS relapse rate: 1%; $P < 0.01$), when the two preparations were administered at the same dose (25,000 IU/m^2 weekly × 20 doses). However, it is well recognized that the *Erwinia* preparation had a much shorter half-life than the *E coli* preparation. Thus, one must carefully use the optimal dose depending on the type of asparaginase preparation used.

Thiopurines—Of the thiopurines, mercaptopurine has conventionally been used to treat ALL, whereas thioguanine has been used to treat acute myeloid leukemia (AML). The preference for mercaptopurine over thioguanine in ALL was historically based and had not been clinically evaluated until recently. Several recent studies have reported superior CNS control associated with thioguanine treatment of childhood ALL. One study comparing mercaptopurine (75 mg/m^2; n = 1017) and thioguanine (50–60 mg/m^2; n = 1010) for the treatment of childhood ALL found that CNS relapse rates were significantly lower ($P = 0.01$) for thioguanine-treated patients (3.5%) than for mercaptopurine-treated patients (5.5%).[46] The thioguanine group also had a higher ($P = 0.02$) 5-year EFS (85.1%) than the mercaptopurine group (77.1%).[46] A second study, which used slightly lower doses of thioguanine (40 mg), also reported a significantly lower risk (OR: 0.53; 95% CI: 0.30–0.92; $P = 0.02$) of isolated CNS relapse (2.5%; n = 748) than for mercaptopurine (4.6%; n = 744).[47] Most recently, a smaller pilot study (n = 51) reported an 8-year CNS relapse rate of zero for patients given IV-thioguanine (480 mg/m^2) during consolidation and maintenance, and oral thioguanine (60 mg/m^2/day) during maintenance.[48] However, all three studies reported high rates of liver toxicity associated with thioguanine treatment.

Stork et al.[46] reported that 20% of thioguanine-treated patients developed veno-occlusive disease (VOD) of the liver, and that 5% developed portal hypertension. In the study by Jacobs et al.[48] six patients (12%) experienced reversible VOD while receiving oral thioguanine, and the study was amended to discontinue thioguanine. Although a lower thioguanine dose (40 mg) was associated with a slightly lower occurrence of VOD (11%), associated liver toxicity renders it an unacceptable alternative to mercaptopurine. Therefore, mercaptopurine remains the thiopurine of choice for childhood ALL. Whether short courses of thioguanine could improve outcome without adding undue toxic effects is unknown.

Intensification of CSF-Directed Therapy

Triple Intrathecal Therapy Versus Intrathecal MTX—MTX has been the standard drug used for intrathecal therapy. It was thought that the addition of cytarabine and a corticosteroid (ie, triple intrathecal therapy) may have additive or synergistic benefits, and the added corticosteroid may reduce arachnoiditis associated with MTX therapy. Until recently, this had never been evaluated in a clinical trial. The Children's Cancer Group 1952 clinical trial compared intrathecal MTX (n = 1018) with triple intrathecal therapy (MTX, cytarabine, and hydrocortisone sodium succinate; n = 1009) for presymptomatic CNS treatment of childhood ALL.[49] Compared with intrathecal MTX, triple intrathecal therapy reduced the risk of CNS relapse (3.4% ± 1.0% vs 5.9% ± 1.2%, $P = 0.004$) but was linked to significantly worse overall survival (6-year survival: triple intrathecal therapy 90.3% vs intrathecal MTX 94.4%; $P = 0.01$). The reduction in overall survival was due to a significantly greater number of testicular and bone marrow relapses that have lower salvage rates than CNS relapse.[49] One explanation for this result is that a so-called isolated CNS relapse could be an early manifestation of systemic relapse, and the improved CNS control secured with triple intrathecal therapy favors overt leukemic relapse in other sites at a later time. Therefore, if triple intrathecal therapy is used, it is imperative that concurrent intense systemic treatment is also provided to prevent bone marrow and testicular relapse.

Triple Intrathecal Therapy Versus Intrathecal Cytarabine—In an ongoing multi-institutional AML trial, three of the first 33 patients who received intrathecal cytarabine had isolated CNS relapse. When triple intrathecal therapy was used instead of intrathecal cytarabine, none of the subsequent 79 patients experienced CNS relapse. These observations suggest that triple intrathecal therapy is more effective at reducing CNS relapse rates than intrathecal cytarabine alone.[50]

Optimization of CSF-Directed Therapy

Optimal drug distribution throughout the CNS is essential for effective CNS-directed therapy. Several factors associated with intrathecal administration contribute to optimal drug distribution. For example, patient body position following intralumbar dosing has important consequences for intraventricular drug perfusion. A more than 10-fold decrease in ventricular dose can occur if patients do not remain prone for 1 hour after dosing.[51] The use of atraumatic noncutting spinal needles (22 gauge or lower) can reduce the likelihood of CSF leaks and decrease the risk of postlumbar puncture headaches[3,52] and possible cerebral bleeding or thrombosis.[53] Another technique purported to improve lumbar puncture success rates involves removal of the stylet immediately after passage through the epidermal and subcutaneous tissues (early stylet removal). Baxter and colleagues[54] demonstrated that early stylet removal can significantly improve lumbar puncture success in infants <12 weeks of age (OR: 2.4; 95% CI: 1.1–5.2). The use of good technique for diagnostic and therapeutic lumbar puncture is imperative not only for ensuring treatment efficacy but also for preventing traumatic lumbar puncture at diagnosis leading to increased CNS relapse risk.[16,18,20]

Cranial Irradiation

Cranial irradiation has played a central role in the successful treatment of CNS leukemia since the 1960s. However, the use of cranial irradiation in children is complicated by a very high risk of secondary neoplasms, neurocognitive defects, and multiple endocrinopathies, including lifelong growth hormone deficiency.[55] Therefore, at St. Jude Children's Research Hospital, cranial radiation is no longer used as a preventive measure; it is used only as a salvage measure in patients who develop CNS relapse. In most collaborative groups, cranial irradiation is still recommended for 2% to 20% of patients at very high risk of CNS relapse, especially those with T-cell lineage or CNS leukemia (CNS3 status) at diagnosis.[3] Investigators participating

in the Berlin-Frankfurt-Münster trials reduced the dose of cranial irradiation to 12 Gy for high-risk patients without CNS leukemia at diagnosis. However, even with the lower dose, there was still a cumulative incidence of 1.7% (95% CI: 0.1%–3.4%) of secondary neoplasms at 15 years.[25]

The St. Jude Total Therapy Study XV was designed to determine if prophylactic CNS irradiation could be omitted totally from the treatment of childhood ALL.[21] This study adopted effective treatment components of successful clinical trials (eg, reinduction therapy, intensive asparaginase, and intensive triple intrathecal therapy) and tailored treatments according to risk and prognosis. The intensity of postremission consolidation, continuation, and reinduction therapy was based on the level of minimal residual disease at the end of induction. The dosage of MTX was targeted to achieve a steady-state concentration of 65 μM in high-risk patients and 33 μM in low-risk patients. The mercaptopurine dose was adjusted according to thiopurine methyltransferase genotype, 6-TG levels in red cells, and absolute neutrophil counts to ensure adequate drug exposure but to avoid excessive hematopoietic toxicities and to decrease the risk of therapy-related cancers.[21] Preliminary results are encouraging, with a 4-year EFS of 92 ± 4%, an overall survival rate of 96 ± 3% (n = 274),[2] and a cumulative risk of CNS relapse of approximately 3% [Pui C-H, unpublished data].

PROGNOSIS AND TREATMENT OF REFRACTORY CNS LEUKEMIA

The prognosis for patients who experience CNS relapse varies with National Cancer Institute/Rome risk criteria at diagnosis of ALL, time from diagnosis to relapse, and whether or not cranial irradiation was used during initial treatment.[3] In a study of 74 children with an isolated CNS relapse, patients who had an initial remission duration exceeding 18 months had a 4-year EFS rate of 77.7 ± 6.4%, but those with a first remission shorter than 19 months had a 4-year EFS of only 51 ± 11.3%.[56] Adult ALL patients who develop CNS recurrence have a poor prognosis. In a study of 32 patients who had CNS recurrence following complete remission, the median survival duration was 6 months; 28% of patients were alive at 1 year, 6% were alive at 4 years, and only two patients were alive and in complete remission at 10+ years.[57] In a second study, only three of 22 patients (14%) with isolated CNS relapse were alive 2 years postrelapse, and the 5-year survival rate was estimated to be zero.[58]

Currently, there are a number of treatment options for patients who have refractory CNS leukemia. Frequent early triple intrathecal therapy (ie, days 1, 3, and 5) is one option that has been used in patients with Burkitt-type (L3) leukemia.[59] Intrathecal therapy with MTX plus prednisone (days 2, 3, 4, and 5) and cytarabine (day 6) has also been used in patients with B-cell neoplasms.[60] However, neither of these has been evaluated in clinical trials that included patients with CNS disease that was refractory to conventional treatment.

Another option is intrathecal administration of liposomal cytarabine (Table 1);[13] compared with unencapsulated cytarabine, it has a longer half-life (141 hours vs 3.4 hours, respectively) and improved CSF distribution.[37,61–70] Treatment with liposomal cytarabine (25, 35, and 50 mg) was evaluated in a phase 1 trial of 18 children with overt leptomeningeal disease that was refractory to conventional treatment.[61] Of the seven leukemia (ALL or AML) patients who received liposomal cytarabine, four achieved complete remission and three had a partial remission.[61] This study also found that the maximum tolerated dose of liposomal cytarabine is lower in children (35 mg) than in adults (50 mg), and that intrathecal liposomal cytarabine must be concomitantly administered with dexamethasone to prevent chemical arachnoiditis.[61] Additional precaution should be taken with the simultaneous or closely timed administration of intrathecal liposomal cytarabine with systemic agents that penetrate the BBB (eg, high-dose MTX and high-dose cytarabine), because severe neurotoxicity can occur, as shown in a study conducted at the M.D. Anderson Cancer Center of adults with ALL.[67] In a subsequent study,

using a modified M.D. Anderson regimen in which liposomal cytarabine and high-dose chemotherapy were given 3 weeks apart, two of 14 adults with leukemia or lymphoma still developed significant neurologic events.[69] However, in a recent pediatric study, six heavily pretreated children with ALL and CNS relapse responded well to liposomal cytarabine at doses of 25 mg to 50 mg (median, 35 mg)without neurologic complications, despite concomitant systemic administration of high-dose cytarabine (2 gm/m^2) in five patients.[70] Whether the use of age-adjusted (hence reduced) dose, concomitant administration of intrathecal prednisone, or younger age contributed to this finding is uncertain. It could also simply reflect the small number of patients studied. Additional studies are needed to learn the optimal use of this highly effective agent.

A fourth option under investigation for the treatment of refractory CNS disease is the alkylating agent thiotepa, which has excellent CNS penetration.[71] Barredo and colleagues[56] demonstrated that a single systemic IV dose of thiotepa (50 mg/m^2 and 65 mg/m^2) is effective at clearing blast cells in the CSF of patients in first isolated CNS relapse (n = 19); seven of the nine patients who received the 65 mg/m^2 dose achieved partial or complete remission. However, intrathecal administration of 6.9 mg and 10 mg of thiotepa showed no additional benefit to combination therapy for the treatment of neoplastic meningitis in two children with relapsed ALL.[72]

RISK FACTORS FOR REFRACTORY CNS DISEASE IN NHL

The incidence of CNS relapse in lymphoma patients varies greatly for different NHL subtypes (Table 2).[1,30,73–81] Patients with primary CNS lymphoma and primary ocular lymphoma are at highest risk, and as many as 90% of these patients will develop refractory CNS disease.[79,82] Also at high risk are adult patients with ALL, lymphoblastic lymphoma, and Burkitt's lymphoma; up to 50% of these patients develop CNS disease.[1,30,73] At lowest risk of CNS relapse are patients with indolent NHL (<5%) and diffuse large B-cell lymphoma (~5%).[75,83,84] Several risk factors for CNS involvement in NHL have been identified. These include young age, advanced stage, bone marrow involvement, number of extranodal sites, elevated lactate dehydrogenase, B-symptoms, and poor performance status.[75,84–87]

Refractory CNS disease in lymphoma patients appears relatively early in a large majority of patients, usually occurring 5 to 12 months (range, 0 to 146 months) after initial diagnosis.[75,83,84,86–90] Intracranial disease can be parenchymal or leptomeningeal. Generally, the majority of cases of CNS lymphoma are isolated to the meninges (~65%; range, 33% to 100%), but it is not uncommon for CNS disease to be isolated to the parenchyma (~30%; range, 10% to 52%) or present in both the meninges and the parenchyma (~10%; range, 0% to 18%).[90–93] CNS disease is the sole manifestation of relapse in roughly 50% of patients and occurs in the context of progressive systemic disease in the other 50%.[93]

PROGNOSIS AND TREATMENT OF REFRACTORY CNS DISEASE IN NHL

The prognosis of patients with secondary CNS lymphoma is poor. Larger studies report a median survival of 2 to 6 months, with a 1-year survival rate of 2% to 25% with conventional treatment.[75,82,84–86] Favorable prognostic factors for survival in patients with refractory CNS lymphoma include normal lactate dehydrogenase levels at CNS disease manifestation, young age, CNS disease at first diagnosis, and high-dose chemotherapy for CNS disease.[94]

With conventional high-dose MTX and intrathecal cytarabine (+/− procarbazine), the longest median survival duration achieved is 6 months.[92] More substantial increases in survival time and survival rate have been achieved by combining high-dose chemotherapy with autologous stem cell transplant (ASCT) to treat secondary CNS lymphoma. One study of patients with CNS involvement (n = 37/750), in which 59% of patients in remission from CNS involvement received ASCT and 41% received an allogenic transplant, reported an overall 5-year survival

rate of 39% and a median overall survival of 10 months.[95] A longer median survival duration of 26 months and a 5-year overall survival rate of 41% ± 28% was observed in a smaller study that included patients with CNS involvement (n = 15/48) who received ASCT.[96] In a third study of ASCT that included 62 lymphoma patients with CNS disease, the 5-year progression-free survival was 42% if CNS disease was absent at the time of transplant and 9% in patients who had active CNS disease at the time of ASCT.[97] However, procedure-related deaths occurred in 8.9% of patients with CNS involvement who achieved CNS remission at the time of ASCT and in 29.4% of those with active CNS disease at the time of ASCT.[97] Other major procedure-related complications of ASCT included interstitial pneumonitis, fungal and viral infections, and cardiac failure.[97] Thus, although ASCT is one of the more promising treatments for refractory CNS lymphoma, the treatment itself carries a high degree of morbidity and mortality.

It is also interesting that the majority of patients who relapsed following ASCT did so in the CNS.[97] For patients with CNS disease before transplant, 13% had an isolated CNS relapse and 15% had relapse to the CNS and one other site. Not surprisingly, the CNS relapse rate was even higher in patients who had CNS involvement at the time of transplant; 35% relapsed in the CNS only, and 11% relapsed in both CNS and bone marrow.[97] These observations suggest that malignant cells in the CSF may not have been effectively cleared by pretransplant induction chemotherapy. Thus, combining more effective CNS-directed therapy with ASCT may help reduce CNS relapse rates and improve the overall prognosis of CNS lymphoma.

This approach to the treatment of CNS relapse in patients with aggressive NHL is being evaluated in the Response Adapted Therapy study (Fig 2). In this trial, all patients receive an initial treatment of MTX (4 g/m^2), ifosfamide (3 × 2 g/m^2), and liposomal cytarabine (50 mg). If patients respond well to this initial treatment (ie, complete/partial response or no change), they can continue with induction therapy for two further cycles, during which stem cells are collected. Patients who continue to have progressive disease (ie, nonresponders) following 22 days of treatment are switched to IV cytarabine (2 × 3 g/m^2), thiotepa (40 mg/m^2), and liposomal cytarabine (50 mg) and maintained on this treatment until day 43. Patients are then staged and treated with high-dose chemotherapy, including carmustine and thiotepa followed by ASCT.[98,95]

CNS Prophylaxis in Burkitt's Lymphoma and Lymphoblastic Lymphoma

Like ALL, certain subtypes of high-grade lymphoma, such as Burkitt's lymphoma and lymphoblastic lymphoma, are associated with relatively high rates of CNS relapse (Table 2).[1,30,73–81] As CNS-directed therapy for ALL has become more aggressive over the past 3 decades, CNS relapse rates and survival rates for adult ALL have greatly improved (Table 3).[30] Similarly, the adaptation of protocols from childhood B-cell ALL has greatly improved survival rates for adults with B-cell ALL.

Hoelzer and colleagues[36] adapted pediatric treatment regimens that consist of six short intensive 5-day treatment cycles. Compared with conventional ALL treatment (ALL 01/81 study; n = 9), following which all patients died, survival rates obtained with the pediatric protocols B-NHL 83 and B-NHL 86 were greatly improved (overall survival: ALL 01/81: 0%, B-NHL 83: 49% and B-NHL 86: 51%; $P = 0.001$).[36] CNS relapse rates also varied with the different combinations of CNS-directed prophylaxis used. The highest CNS relapse rate occurred with the B-NHL 83 protocol. Patients who achieved complete remission with low-dose IV MTX (0.5 g/m^2) and high-dose intrathecal MTX (12 g/m^2) were given prophylactic cranial irradiation (24 Gy), resulting in a 27% CNS relapse rate.[36] A substantially lower CNS relapse rate of 4% was observed in the B-NHL 86 study that used systemic high-dose MTX (1.5 g/m^2), triple intrathecal therapy, and subsequent cranial irradiation as prophylaxis in patients who achieved complete remission.[36] A slightly higher CNS relapse rate of 12% was

observed when cranial irradiation was omitted in the B-NHL 90 study (3 g/m^2 MTX and triple intrathecal therapy) (Thiel, unpublished data). A fourth ongoing trial, B-NHL 2002, is evaluating the effect of replacing cranial irradiation in the B-NHL 86 protocol with a consolidation therapy of 1.5 g/m^2 MTX and cytarabine (2 g/m^2 for 2 days). Although optimal CNS prophylactic regimens are still being investigated, there is universal agreement that ALL, Burkitt's lymphoma, and lymphoblastic lymphoma require CNS-directed therapy to prevent CNS relapse.[76,100]

CNS PROPHYLAXIS IN DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma is an aggressive subset of NHL. There is no clear consensus as to which patients may benefit from CNS prophylaxis, and the true rate of CNS relapse following primary treatment of diffuse large B-cell lymphoma without CNS prophylaxis is unclear. Estimates range from 4% to 27%, depending on many disease and patient variables, but most studies report an incidence of around 5%.[74–76] Although this incidence is relatively low, the outcome of those patients suffering CNS relapse is extremely poor regardless of histology,[101,102] and therefore prevention of relapse by CNS-directed therapy needs to be carefully considered.

Some studies have found that CNS prophylaxis is effective in preventing CNS relapse in diffuse large B-cell lymphoma patients. For example, CNS relapse rates were reduced to between 2% and 3% in patients who received CNS-directed prophylaxis (intrathecal MTX/high-dose MTX) following ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone).[89,91] This was about half the 5% to 8% rate observed in patients treated with standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP with rituximab who did not receive CNS prophylaxis (Table 4).[83,89–91] However, intrathecal therapy carries a high risk of complications (eg, CSF leaks from lumbar puncture, infections or surgical complications from Ommaya reservoir placement); exposing the potentially >90% of unselected diffuse large B-cell lymphoma patients who will not develop CNS disease to these risks is unacceptable. Thus, there is a need for well-defined risk models to identify patients who would benefit most from CNS prophylaxis.

Several risk factors that distinguish subgroups with a greater risk of CNS disease have been consistently identified. Clinical risk factors include advanced stage,[86,88,102] international prognostic index (IPI),[83,89] elevated lactate dehydrogenase,[75,84,87,89] involvement in more than one extranodal site,[75,84,89] young age,[75,103] low albumin,[75] B-symptoms,[88] and retroperitoneal lymph node involvement.[75] Many studies have identified specific sites of extranodal involvement as risk factors for CNS involvement, including bone marrow,[75,87,88,103] breast,[77] testes,[86,88,104] epidural space,[100,101] orbit,[104] and nasal/paranasal sinuses.[104]

There is little consensus among clinicians regarding which diffuse large B-cell lymphoma patients should receive CNS prophylaxis. A survey of practice in Canada reported that CNS prophylaxis was given to 29% to 45% of patients with lymphoma presenting in the sinuses, testes, epidural space, or orbit.[105] Less frequently, patients with advanced stage (12%) or elevated lactate dehydrogenase and extranodal disease (<10%) received CNS prophylaxis. A second 2005 British survey found slightly more aggressive practices.[106] This survey reported that 65% to 88% of clinicians used CNS prophylaxis in cases that involved sinuses, testes, orbit, and bone marrow. About one-third (34%) treated diffuse large B-cell lymphoma with stage IV disease, and fewer than 21% treated patients with a high IPI, more than one extranodal site, or raised lactate dehydrogenase.[106] That only a minority of clinicians responding to these surveys used factors such as stage IV disease, IPI score, number of extranodal sites, and elevated lactate dehydrogenase as indications for CNS prophylaxis is of concern, especially as

these factors have been identified in several large series as being the most important risk factors for CNS relapse.[75,84,89,102,107]

Still, risk-model studies suggest that these factors may not adequately define a subgroup of patients suitable for prophylactic therapy. For example, van Besien and colleagues[84] identified two factors (elevated lactate dehydrogenase [relative risk (RR): 7.0; 95% CI: 2.0–38.0] and >1 extranodal site [RR: 5.5; 95% CI: 2.1–14.9]) as independent predictors of CNS recurrence by multivariate logistic regression. Yet, if only patients with both risk factors were treated with CNS prophylaxis, 15.4% of all patients would be treated (a subgroup with a 17.4% risk of CNS recurrence), which would only capture 46% of those predicted to develop CNS disease.[84] Hollander and colleagues[75] identified five risk factors as significant in multivariate analysis: elevated lactate dehydrogenase (RR: 2.1; 95% CI: 1.0–4.4), serum albumin <35 g/L (RR: 2.5; 95% CI: 1.3–4.6), age <60 years (RR: 2.8; 95% CI: 1.5–5.4), retroperitoneal disease (RR: 1.9; 95% CI: 1.0–3.5), and >1 extranodal site (RR: 3.0; 95% CI: 1.7–5.4). If four or more of these risk factors were present, the probability of a CNS recurrence within 5 years would be at least 25% (Table 5). [75] By this model, if patients with at least four risk factors were selected for CNS prophylaxis, 12% of the overall population would be treated (a subgroup with a >25% risk of CNS relapse). However, this would result in treatment of only 54% of all patients predicted to develop CNS relapse. Thus, deciding who to treat based on known risk factors alone fails to identify about half of all patients who may benefit from prophylaxis, leaving the debate surrounding CNS prophylaxis for diffuse large B-cell lymphoma still controversial.[76,93]

CONCLUSIONS

Optimal CNS control in ALL requires effective systemic and intrathecal treatment. Isolated CNS relapse of ALL is highly curable in children who have a long initial remission (>18 months) and who have not received prior cranial irradiation, but is associated with a poor prognosis in adults. Liposomal cytarabine is effective in treating refractory CNS leukemia; however, additional studies are needed to optimize the use of this agent. CNS prophylaxis is not required in indolent NHL, but it is required for the treatment of adult B-cell ALL, Burkitt's lymphoma, and lymphoblastic lymphoma. The use of CNS prophylaxis in the treatment of diffuse large B-cell lymphoma is controversial. Improved risk-models that more accurately identify predictors of CNS relapse are needed so that prophylactic treatments can be targeted to highest-risk NHL patients. To date, the most effective treatment for CNS relapse in NHL is ASCT. The devastating effects of CNS relapse necessitate additional research, focusing on more precise risk-directed therapy to avoid over- or under-treatment, and on optimal CNS-directed treatment.

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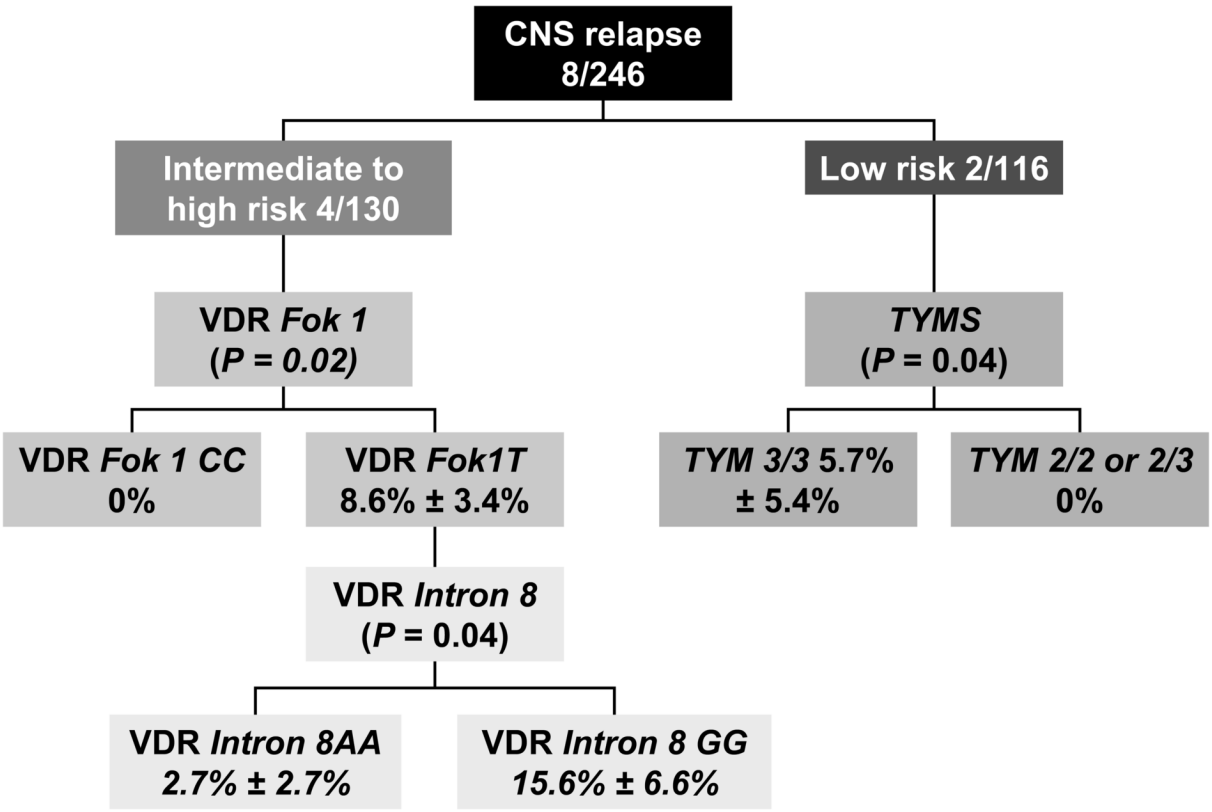

Figure 1.
Pharmacogenetic determinants of central nervous system (CNS) relapse. Reprinted with permission.[26] Abbreviations: VDR, vitamin D receptor; TYM, thymidylate; TYMS, thymidylate synthetase;

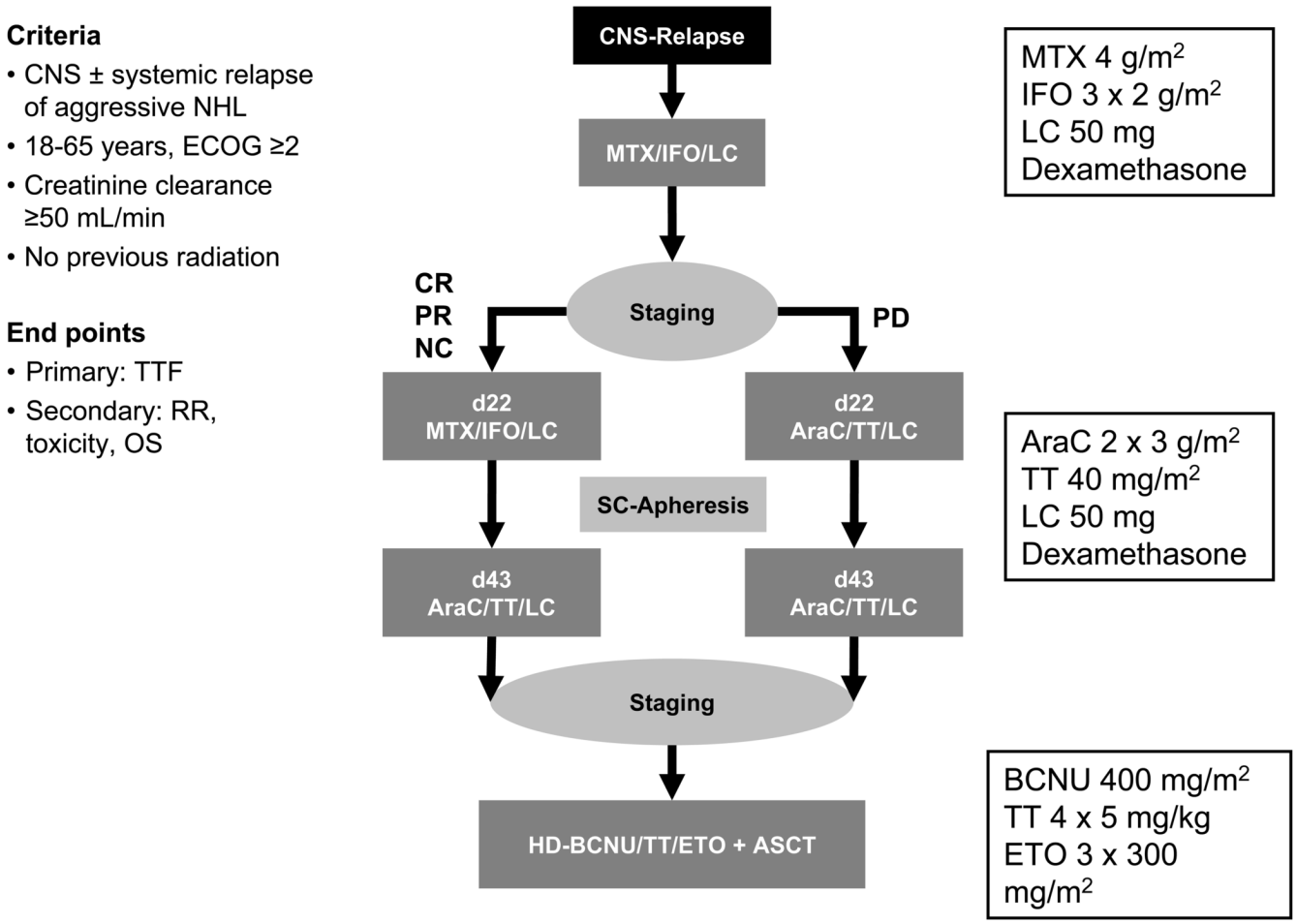

Figure 2.

Response adapted therapy study for the treatment of central nervous system (CNS) relapse of aggressive lymphoma.[98,99] Abbreviations: AraC, cytarabine; ASCT, autologous stem cell transplant; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ETO, etoposide; HD-BCNU, high-dose carmustine; IFO, ifosfamide; LC, liposomal cytarabine; NC, no change; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; OS, overall survival; PR, partial response; RR, response rate; TTF, time to treatment failure; TT, thiotepa; SC, subcutaneous.

Table 1

Summary of Studies Using Intrathecal Liposomal Cytarabine (Adapted with permission.[13] © 2008 Informa UK Ltd)

Type of study	Study (n, age)	Liposomal cytarabine dose, total doses, and frequency	Measures to prevent neurotoxicity	Concurrent cranial RT or high-dose chemotherapy	Neurotoxicity (≥ grade 3)	Proportion of patients with ≥ grade III neurotoxicity (95% CI)	Cytologic response
Phase 1	Kim (1993) (n = 12, 6 to 73 yr)[63]	12.5 to 125 mg; 47 doses; Q 2 to 3 wk	NR	Cranial RT: 2	Encephalopathy*: 3 Headache*: 2	5 of 47 cycles 10.6% (1.8% to 19.5%)	7 of 9 evaluable patients
	Chamberlain (1995) (n = 9, 23 to 67 yr)[64]	75 mg; 18 doses; Q 2 wk	DXM PO	NR	None	0 of 9 0% (0% to 28%)	6 of 8 evaluable patients
	Bomgaars[61] (2004) (n = 18, 4 to 19 yr)	25–50 mg; 78 doses; Q 2 wk x 1 mo, Q 4 wk x 2 mo, Q 8 wk x 12 mo	DXM PO/IV	None	Headache: 3	of 18 16.6% (0% to 33.9%)	8 of 14 evaluable patients
Phase 2	Glantz (1999)[65] (n = 14, 35 to 86 yr)	50 mg; 74 doses; Q 2 wk x 2 mo, Q 4 wk x 8 mo	DXM PO/IV	None	Headache*: 4 Meningismus*: 2 Confusion*: 2 Somnolence*: 2	10 of 74 cycles 13.5% (5.7% to 21.3%)	10 of 14
	Glantz (1999)[65] (n = 31, 19 to 74 yr)	50 mg; 102 doses; Q 2 wk x 2 mo, Q 4 wk x 2 mo	DXM PO/IV	Cranial or spinal RT: 4	Headache*: 4 Altered mental status*: 5 Seizures*: 1 Sensory/motor*: 1 Drug-related meningitis*: 3 CNS infection*: 3	17 of 31 54.8% (37.3% to 72.3%)	8 of 31
	Jaeckle (2001)[66] (n = 53, 28 to 74 yrs)	50 mg; 177 doses; Q 2 wk x 2 mo, Q 4 wk x 2 mo	DXM PO/IV	Cranial RT: 13	Headache: 2 Arachnoiditis: 4	6 of 177 cycles 3.4% (0.7% to 6%)	12 of 43 evaluable patients
	Jabbour (2007)[67] (n = 31, >18 yr)	50 mg on day 2 and 15 of HyperCVAD cycle, Day 10 of MA cycle	DXM PO/IV Liposomal cytarabine given >7 days after high-dose cytarabine	High-dose methotrexate and cytarabine: 31	Papilloedema and blindness: 1 Increased intracranial pressure: 2 Cauda equina syndrome: 2	5 of 31 16.1% (3.2% to 29.1%)	Prophylactic use 1 combined marrow and CNS relapse
Retrospective series	Sancho (2006)[37] (n = 6, 5 to 50 yr)	50 mg; 29 doses; Q 2 wk (25 mg in 5 yr old)	DXM PO/IV	NR	None	0 of 6 0% (0% to 39%)	2 of 3 evaluable patients

Type of study	Study (n, age)	Liposomal cytarabine dose, total doses, and frequency	Measures to prevent neurotoxicity	Concurrent cranial RT or high-dose chemotherapy	Neurotoxicity (≥ grade 3)	Proportion of patients with ≥ grade III neurotoxicity (95% CI)	Cytologic response
	Benesch (2007)[68] (n = 5, 5 to 18 yr)	15–50 mg; 33 doses Q 2 to 4 wk	DXM PO/IV	High-dose methotrexate (8 gm/m^2): 1 TBI: 1	Encephalopathy: 1 Seizures: 1	2 of 5 40% (0% to 82.9%)	3 of 5
	Sancho (2007)[37] (n = 10, 18 to 57 yr)	50 mg; 39 doses Q 2 or 4 wk (35 mg in 18 yr old)	DXM PO/IV	High-dose cytarabine: 6	Headache: 3	3 of 10 30% (1.6% to 58.4%)	9 of 9 evaluable patients
	McClune (2007)[69] (n = 14, 23 to 72 yr)	50 mg; 40 doses; Q 3 wk (25 mg if IVT)	DXM PO/IV Liposomal cytarabine Q 3 weeks	High-dose methotrexate and cytarabine: 14	Hyponatremia and somnolence: 1 Headache: 1	2 of 14 14.3% (0% to 32.6%)	Prophylactic use No CNS relapses
	Parasole (2008)[70] (n = 6, 2 to 26 yr)	35 mg (median dose); 33 doses; Q 2 wk	DXM PO/IV Intrathecal prednisone (2 patients) Age-adjusted dose	High-dose cytarabine (2 g/m^2): 5	None	0/6 0% (0% to 39%)	6 of 6

* Neurotoxic events reported per cycle of intrathecal liposomal cytarabine (not per patient).

Abbreviations: CNS, central nervous system; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; DXM, dexamethasone; IVT, intraventricular; LP, lumbar puncture; MA, maintenance; NR: not reported; RT: radiation therapy.

Table 2

Central Nervous System (CNS) Relapse Rates for Patients With Different Subtypes of Non-Hodgkin's Lymphoma (NHL) Who Have Not Received CNS Prophylaxis[1,30,73–81]

NHL subtype	CNS relapse (w/o prophylaxis)
ALL, LBL, and BL[1,30,73]	30% to 50%
DLBCL[74–76]	~ 5% (2% to 27%)
PMLCL[74]	17%
Breast NHL[77]	11% to 21%
Testicular NHL[78]	7% to 31%
Intraocular NHL[79]	50% to 90%
Indolent NHL[75]	~ 0% to 4%
Mantle cell NHL[80,81]	4% to 23%

Abbreviations: ALL, acute lymphoblastic leukemia; LBL, lymphoblastic leukemia; BL, Burkitt's lymphoma; DLBCL, diffuse large B-cell lymphoma; PMLCL, primary mediastinal thymic large B-cell lymphoma.

Table 3

Central Nervous System (CNS) Relapse Rates in Adult Acute Lymphoblastic Leukemia (ALL) With Different CNS-Directed Prophylaxis [30]

Years	Type of CNS prophylaxis	5-year CNS relapse rate (%) for overall population
1979 to 1982	None	58
1982 to 1988	High-dose Ara-C and MTX*	25
1988 to 1992	High-dose Ara-C and MTX* + IT Ara-C† after CR for high-risk patients	27
1992 to 1995	High-dose Ara-C and high- dose MTX + early IT MTX and Ara-C‡ for all patients	8¶

*Ara-C: 3 g/m^2 every 12 hours for 6 doses; MTX: 400 to 1600 mg/m^2.

†Ara-C at 100 mg weekly (22 IT doses in 12 months).

‡MTX at 12 mg on day 2 and Ara-C at 100 mg on day 8.

¶3-year CNS relapse rate.

Abbreviations: Ara-C, unencapsulated cytarabine; MTX, methotrexate; IT, intrathecal; CR, complete response.

Table 4

Central Nervous System (CNS) Relapse Rates for Studies That Did or Did Not Include CNS Prophylaxis[83,89–91]

Study	n	Chemotherapy	CNS prophylaxis	CNS relapse rate (%) *
Haioun 2000[89]	974	ACVBP	IT MTX (15 mg) High-dose MTX (3 g/m^2)	2.2
Tilly 2003[91]	635	ACVBP	IT MTX (15 mg) High-dose MTX (3 g/m^2)	2.8
		CHOP	None	8.3
Feugier 2004[83]	399	CHOP	None	4.6
		CHOP + rituximab	None	5.4
Boehme 2007[90]	1693	CHOP/ CHOEP14/21	Etoposide reduced CNS relapse rate (P = 0.017)	2.2 %

* Combined CNS relapse rate includes both isolated CNS relapses and CNS relapses that occurred concurrent with other systemic relapse.

Abbreviations: ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHOEP, CHOP + etoposide; IT, intrathecal.

Table 5

Probability for Central Nervous System (CNS) Relapse According to the Number of Risk Factors Present for Non-Hodgkin's Lymphoma Patients. (Reprinted with permission.[70] © 2002 European Society for Medical Oncology)

Number of risk factors	Number of patients	Number of patients with CNS involvement	Probability of a CNS recurrence (%) within 5 years (CI: 95%)
0	155	2	1.9 (0% to 4.6%)
1	356	6	2.0 (0.4% to 3.6 %)
2	312	6	2.8 (0.5% to 5.2%)
3	202	8	6.2 (1.9% to 10.5%)
4	115	19	25.3 (14.8% to 35.8%)
5	29	7	32.7 (11.6% to 53.8%)