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REVIEW

Neoplastic meningitis: diagnosis and treatment considerations

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Neoplastic meningitis is an increasingly recognized complication of advanced metastatic cancer and, if left undiagnosed or untreated, is characterized by rapid neurologic deterioration and death. Thus, the diagnosis and treatment of neoplastic meningitis present challenges for the clinical oncologist. The diagnosis of neoplastic meningitis is based on clinical signs and symptoms, laboratory analysis of cerebrospinal fluid to determine cell count and cytology, and analysis of neuroimaging studies for evidence of leptomeningeal or cranial nerve enhancement. Once diagnosed, conventional treatment regimens may include radiotherapy combined with systemic or intrathecal chemotherapy, often with the antimetabolites cytarabine and/or methotrexate. However, the prognosis for neoplastic meningitis secondary to an underlying solid tumor or recurrent leukemia is poor with conventional treatment regimens. Therefore, novel agents for intrathecal administration, including DepoCyt™, mafosfamide, and topotecan, or novel therapeutic approaches, including conjugated monoclonal antibodies and immunotoxins or gene therapy, are currently under investigation. Such new agents and therapeutic approaches will facilitate the development of effective treatment strategies and will ultimately improve the outcome for patients with this devastating disease. This article provides an overview of the approaches to the diagnosis, evaluation, and treatment of neoplastic meningitis. *Medical Oncology* (2000) **17,** 151–162.

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Introduction

The leptomeninges, consisting of the arachnoid membrane and the pia mater, are a unique site of metastatic spread for certain intracranial and extracranial tumors. Neoplastic meningitis (NM), otherwise known as leptomeningeal metastasis, is a general term that describes the dissemination of a multitude of different tumor

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types to the leptomeninges, including carcinomas (carcinomatous meningitis), leukemias (leukemic meningitis or leukemia of the central nervous system [CNS]), lymphomas (lymphomatous meningitis or CNS lymphoma), and gliomas (leptomeningeal gliomatosis). In patients with solid tumors, NM most commonly occurs when advanced systemic disease is present at the time of initial diagnosis or with recurrence of the primary tumor. In patients with leukemia and lymphoma, leptomeningeal disease may be present at the time of initial diagnosis or may occur as a site of isolated disease recurrence. Less commonly, NM heralds the presence of malignancy.[1–6] Although the signs and symptoms of NM may be focal at the time of initial diagnosis, the circulation of cerebrospinal fluid (CSF) between the arachnoid and the pia mater provides a pathway for the spread of malignant cells throughout the neuraxis (brain and spinal cord). Therefore, the entire neuraxis must be considered in the evaluation and treatment of this diffuse CNS disease.

The reported incidence of NM varies widely, and the dissemination of cancer to the leptomeninges probably occurs more frequently than is clinically recognized. The observation that the CNS is a sanctuary site, protected from the therapeutic and toxic effects of most systemically administered agents, was made in the early 1970s following the institution of effective combination systemic chemotherapy for acute lymphoblastic leukemia (ALL). The complete remission rate and survival of children with ALL improved dramatically, but the meninges subsequently emerged as the most frequent site of relapse, occurring in 50–75% of patients.[7,8] Thus, improvements in systemic treatment with resultant longer durations of survival were accompanied by an increase in the incidence of leptomeningeal relapse.[9–12] A similar pattern has been observed in some nonhematologic cancers such as breast, ovarian, and small-cell lung cancer.

In adults, the tumors that most commonly metastasize to the leptomeninges are melanoma and carcinomas of the breast, lung, and gastrointestinal tract.[13–17] As evidence that NM occurs more frequently than is usually recognized, results from autopsy series indicate that the incidence of NM ranges from 5–52% in adults with solid tumors and from 25–81% in adults with leukemia.[9] In children with solid tumors, dissemination to the leptomeninges may occur from rhabdomyosarcoma,[18] retinoblastoma,[19] and Ewing's sarcoma.[18,20,21] Tumors of the CNS that have a propensity for leptomeningeal dissemination include gliomas,[19,22–24] medulloblastomas, ependymomas, germinomas, and carcinomas of the choroid plexus.[20,25–29]

Diagnosis of neoplastic meningitis

The diagnosis of NM is based on correlation of data from multiple sources, including clinical evaluation of the patient, laboratory findings, and neuroimaging studies. In the past, the presence of malignant cells in the CSF was required for the diagnosis of leptomeningeal disease. However, discrepancies may exist between clinical signs and symptoms and results of CSF cell counts and cytology. Improvements in neuroimaging technology, especially the widespread availability of magnetic resonance imaging (MRI), have increased the feasibility of establishing a diagnosis of NM using imaging techniques. Thus, in some instances the presence of typical clinical features coupled with appropriate neuroimaging abnormalities is adequate for the diagnosis of NM.[30] Nevertheless, establishing a diagnosis of NM is still usually based on confirmation between clinical signs and symptoms, laboratory analysis of CSF, and neuroimaging.

Clinical presentation of neoplastic meningitis

The signs and symptoms of NM are highly variable. In patients with leukemia, it is not uncommon for the initial evidence of leptomeningeal dissemination to occur following a surveillance lumbar puncture in an asymptomatic patient. In contrast, leptomeningeal dissemination associated with solid tumors most often occurs in association with a known advanced systemic cancer and is frequently accompanied by a wide spectrum of signs and symptoms. Although NM eventually affects the entire neuraxis, it may preferentially involve one of three CNS regions: (1) the cerebral hemispheres, (2) the cranial nerves, or (3) the spinal cord and associated nerve roots. Thus, the signs and symptoms associated with NM are dependent on the primary site of involvement within the CNS (Table 1).[31] However, as NM is a diffuse process, in some instances there may be simultaneous disturbances of neurologic function at multiple levels of the neuraxis.[1,31–36]

The most common signs and symptoms of meningeal disease are those resulting from increased intracranial

Table 1 Signs and symptoms of neoplastic meningitis by site and decreasing order of frequency[31]

Region affected	*Signs*	*Symptoms*
Cerebral hemisphere	Mental status change	Headache
	Seizure	Mental status change
	Papilledema	Difficulty walking
	Diabetes insipidus	Nausea/vomiting
	Hemiparesis	Unconsciousness
		Dysphasia
		Dizziness
Cranial nerves	Ocular muscle paresis (III, IV, VI)	Diplopia
	Facial weakness (VII)	Hearing loss
	Decreased hearing (VIII)	Visual loss
	Optic neuropathy (II)	Facial numbness
	Trigeminal neuropathy (V)	Decreased taste
	Hypoglossal neuropathy (XII)	Tinnitus
	Blindness	Hoarseness
	Diminished gag (IX, X)	Dysphagia
		Vertigo
Spinal cord and roots	Reflex asymmetry	Lower motor neuron weakness
	Weakness	Paresthesias
	Sensory loss	Radicular pain
	Pain on straight leg raising	Back/neck pain
	Decreased rectal tone	Bowel/bladder dysfunction
	Nuchal rigidity	

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pressure, including headache, nausea, and vomiting. Cranial nerve findings, spinal cord symptoms, and mental status changes are also frequently observed. Relatively unusual signs and symptoms of NM include sudden hearing loss,[37,38] subacute polyradiculopathy,[39] subarachnoid hemorrhage,[40] or complex partial seizures.[41] A high index of suspicion is critical in malignancies from which leptomeningeal dissemination is possible.

Laboratory evaluation

Laboratory evaluation of CSF samples remains the single most important diagnostic tool in a patient with suspected NM. Essential elements of the laboratory evaluation of CSF include cell count, cytology, and protein and glucose concentrations. In patients with primary solid tumors, the finding of malignant cells in the CSF is unequivocal evidence of NM. In some cases serial CSF sampling via lumbar puncture or CSF sampling from alternate sites (eg cisternal or ventricular) is required to detect malignant cells. In a series of 90 patients with NM secondary to solid tumors, Wasserstrom *et al* found positive cytology results in only 55% of CSF samples from the initial lumbar puncture. The incidence of positive cytology increased to 80% after a second lumbar puncture, but increased by only 2% with each subsequent lumbar puncture. An additional 5% of patients had positive cytology results in CSF from cisternal or ventricular sites, while 10% of patients had persistently negative CSF cytology results.[31] In a separate series of 63 patients with NM secondary to either solid tumors or leukemias/lymphomas, Kaplan *et al* found that 71% of patients had positive cytology results from the initial lumbar puncture, and 92% of patients had positive results from a second lumbar puncture. The CSF cell count was normal in approximately one third of the cases with positive cytology results.[42] Thus, a diagnosis of NM cannot be ruled out based on the absence of positive cytology in the CSF, but must be substantiated with additional evidence.

The traditional definition of leptomeningeal leukemia requires the presence of at least 5 leukocytes/μL of CSF and the unequivocal presence of leukemic blast cells in a centrifuged specimen. However, this definition has recently undergone scrutiny because of findings in several retrospective studies. An analysis of 351 children with newly diagnosed ALL treated at St Jude Children's Research Hospital (Memphis, TN)

demonstrated that patients with 5 leukocytes/μL and with blast cells present in the CSF were at higher risk for subsequent leptomeningeal relapse.[43] Similarly, investigators from the Pediatric Oncology Group found that there was approximately a twofold-greater risk of CNS relapse in patients testing positive for lymphoblasts in the CSF than in patients testing negative for such lymphoblasts.[44] These results indicate that, in the absence of positive cytology, the presence of lymphoblasts in the CSF may be a risk factor for the subsequent development of leptomeningial leukemia. As a result, many investigators have elected to administer more intensive initial intrathecal chemotherapy to the small subset of patients with leukemia who exhibit 5 leukocytes/μL and positive CSF cytology. However, the results in the literature are contradictory. In a retrospective analysis of more than 1400 patients with intermediate-risk ALL treated on Children's Cancer Group protocols, the presence of 5 leukocytes/μL in the CSF was not found to be of prognostic significance.[45]

Other nonspecific abnormalities often found in the CSF of NM patients include an elevated CSF opening pressure, an increase in protein concentration, an increase in white blood cell count, and a decrease in glucose concentration (Table 2).[31] Specific immunohistochemical studies or biochemical markers (eg carcinoembryonic antigen, alpha fetoprotein, or β_1-human chorionic gonadotropin) may be helpful in selected cases of NM, but their diagnostic utility is largely dependent on the underlying malignancy. The value of these indicators in screening patients for NM is questionable; however, these markers may serve as useful adjuncts in monitoring an individual patient's response to therapy. Flow cytometry and chromosomal analysis of malignant cells in the CSF may also provide additional information in select cases of leptomeningeal leukemia or lymphoma; however, there is no role for these markers in screening patients for leptomeningeal dissemination.

Table 2 Laboratory evaluation of CSF in patients with neoplastic meningitis secondary to solid tumors[31]

Variable	*Initial (n=90)*	*Subsequent (n=90)*
CSF pressure > 160 mm Hg	45 (50%)	64 (71%)
Cells > 5/mm^3	51 (57%)	65 (72%)
Protein > 50 mg/dL	73 (81%)	80 (89%)
Glucose < 40 mg/dL	28 (31%)	37 (41%)
Positive cytology	49 (54%)	82 (91%)
Normal	3 (3%)	1 (1%)

CSF = Cerebrospinal fluid; mm Hg = Millimeters of mercury.
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Neuroimaging

For patients with suspected or documented NM, various neuroimaging studies may be useful in establishing a diagnosis, defining the extent of NM, identifying areas of bulky disease, and assessing CSF flow dynamics. Contrast-enhanced computed tomography (CT) scans of the head may show abnormalities; however, these scans are relatively insensitive compared with gadolinium Gd-enhanced MRI.[46,47] Chamberlain *et al* reported that all abnormalities detected with contrast-enhanced CT scans were also observed with Gd-enhanced MRI, and that MRI revealed additional lesions not observed on CT scans.[47] Despite the greater sensitivity of Gd-enhanced MRI, abnormal meningeal enhancement is still observed with CT in approximately two thirds of patients with positive CSF cytology.[48,49]

Neuroimaging findings suggestive of NM include leptomeningeal, subependymal, dural, or cranial nerve enhancement, superficial cerebral lesions, and communicating hydrocephalus.[30] In patients with negative CSF cytology, MRI findings must be closely correlated with the clinical evaluation because findings of nonspecific leptomeningeal enhancement may lead to 'false positive' interpretations of the MRI scans.

Spinal cord imaging is another important component of the diagnostic evaluation of nonleukemic NM patients, as approximately 20% of adults and 50–70% of children so afflicted will exhibit spinal cord imaging abnormalities.[50] Gadolinium-enhanced MRI of the spinal cord has been shown to be qualitatively similar to CT myelography in defining the extent of involvement of the spinal cord in leptomeningeal disease.[50] Thus, the comparable diagnostic effectiveness of MRI and CT myelography, coupled with the greater patient acceptance and lower procedure-related morbidity of MRI, indicates that MRI is the preferable tool for imaging the spinal cord. Imaging studies of the spinal cord should be considered for all NM patients, but are obligatory in patients who demonstrate signs or symptoms consistent with spinal cord dysfunction.

Cerebrospinal fluid flow studies, using either indium in 111-diethylenetriamine pentaacetic acid (DTPA) or technetium Tc 99-DTPA,[51] are also an invaluable tool in the diagnosis and treatment of patients with NM. These studies are superior to both CT and MRI scanning in detecting abnormalities in CSF flow.[47,52] Clinicians should realize, however, that alterations in CSF flow are not limited to patients with bulky leptomeningeal disease. In fact, radionuclide imaging studies have shown that up to 70% of patients with NM have ventricular outlet obstruction, abnormal flow in the spinal canal, or impaired flow over the cerebral convexities.[51] It is important to identify patients with CSF flow abnormalities prospectively, as flow disturbances can affect the distribution of intrathecal chemotherapy, leading to decreased efficacy or severe toxicity. If a spinal subarachnoid block is documented in the radionuclide-aided CSF flow study of a patient whose spinal cord has not been recently evaluated, additional imaging studies of the spinal cord, such as MRI or CT myelography, should be performed.[47] Abnormalities in CSF flow sometimes can be corrected with positional or directed radiotherapy.[52]

Treatment of neoplastic meningitis

The varied manifestations of NM preclude recommendations for a single treatment approach. The primary treatment modalities for either presymptomatic or overt NM include radiotherapy, intrathecal chemotherapy, and high-dose systemic chemotherapy. Factors to consider in making specific treatment recommendations include the primary malignancy, the age of the patient, history of prior CNS-directed therapy, the extent of systemic disease at initial diagnosis, and the presence or absence of abnormal CSF flow.

Presymptomatic or 'preventative' CNS-directed therapy is a standard component of the front-line treatment for the majority of patients who have leukemia or lymphoma. In addition, some patients who have solid tumors with a predisposition for dissemination to the neuraxis (eg childhood medulloblastoma) may also receive presymptomatic treatment for NM.[53] For patients with overt NM it may be difficult to accurately assess the durability of response to treatment, especially in patients with solid tumors, as therapy for NM is often ineffective against the primary malignancy.[47,52] Although treatment of overt NM in this setting may not be curative, in many instances it is palliative.[2,31,54,55]

Radiotherapy

Radiotherapy has been shown to be beneficial in both the prevention and treatment of highly radiosensitive tumors such as leptomeningeal leukemia or lymphoma. Thus, cranial irradiation has been utilized in some treatment regimens to prevent the development of leptomeningeal leukemia in patients who are at high risk for developing CNS relapse.[56] Patients who exhibit overt CNS leukemia may receive cranial irradiation plus intrathecal chemotherapy or craniospinal irradiation.[56] Craniospinal irradiation may also be beneficial in the prevention of neuraxis dissemination in childhood medulloblastoma and in the treatment of overt leptomeningeal spread of medulloblastomas and ependymomas.[53]

For tumors that are relatively insensitive to radiation treatment, radiotherapy is usually reserved for sites of symptomatic or bulky disease. Although not curative, such directed radiotherapy often is palliative, providing local control of tumor growth and a potential for associated reduction in neurologic deficits. Furthermore, in some cases directed radiotherapy may reduce or eliminate abnormalities in CSF flow. Restoration of CSF flow is a prerequisite for the safe administration of intrathecal chemotherapy.

Radiotherapy may be associated with both acute and long-term sequelae, although these effects are sometimes difficult to differentiate from the effects of other aspects of therapy or from manifestations of the disease itself. Craniospinal irradiation may cause significant myelosuppression, as a substantial portion of active bone marrow is irradiated.[57] Cranial irradiation may result in the 'somnolence syndrome,' which consists of a prodrome of anorexia and irritability followed by a variable period of somnolence from which recovery is spontaneous.[58] Long-term complications of cranial or craniospinal irradiation include secondary malignancies,[59] neuroendocrine sequelae such as hypothyroidism[60,61] and disturbances in the secretion of growth hormone,[62] and neuropsychological sequelae such as decreases in intellect and mild-to-severe leukoencephalopathy.[63–65] Because of the potential for severe long-term complications from radiotherapy, the

Table 3 Central nervous system penetration of commonly used antineoplastic agents.

Agent	*CSF : plasma ratio (%)*
Alkylating agents	
Cyclophosphamide	50 : 15[a]
Ifosfamide	30 : 15[a]
Thiotepa	> 95
Carmustine	> 90
Cisplatin	40 : < 5[b]
Carboplatin	30 : < 5
Antimetabolites	
Methotrexate	3
6-Mercaptopurine	25
Cytarabine	15
5-Fluorouracil	50 : 15[c]
Antitumor antibiotics	
Anthracyclines	ND[d]
Dactinomycin	ND
Plant alkaloids	
Vinca alkaloids	5
Epipodophyllotoxins	< 10
Miscellaneous	
Prednisolone	< 10
Dexamethasone	15
L-Asparaginase	ND[e]

[a] Includes parent compound/active metabolite.
[b] Includes free platinum/total platinum.
[c] Includes bolus dose/infusion.
[d] ND=not detectable in CSF.
[e] Although drug is ND in CSF, CSF L-asparagine is depleted by systemic administration of L-asparaginase.
ND=Not detectable; CSF=Cerebrospinal fluid.
Adapted with permission from Balis and Poplack.[66]

identification and application of effective but less-toxic treatment strategies are high priorities.

Chemotherapy

As measured by the ratio of CSF concentration to plasma drug concentration, the penetration of most systemically administered (ie intravenous) chemotherapeutic agents into the CSF is limited (Table 3).[66] Consequently, the blood–brain barrier creates a pharmacologic sanctuary, isolating the CSF from the cytotoxic effects of systemically administered chemotherapy. To circumvent the limitations of systemic delivery of chemotherapy imposed by the blood–brain barrier, two general pharmacologic approaches for the prevention and treatment of NM have been employed: (1) high-dose systemic administration of chemotherapy to achieve cytotoxic concentrations of drug within the CSF, and (2) direct administration of drugs into the CSF via either lumbar puncture or a ventricular access device (eg Ommaya reservoir). There are advantages and limitations to both approaches.

High-dose systemic chemotherapy

The pharmacokinetics and pharmacodynamics of high-dose systemic chemotherapy have been extensively reviewed.[67] One advantage of high-dose systemic chemotherapy is that drug distribution within the CNS may be more uniform compared with intrathecal administration. Furthermore, therapeutic drug concentrations in the CSF may be maintained for longer periods of time with prolonged intravenous infusions, and there may be better penetration of the drug into the brain tissue and deep perivascular spaces.[68] A limitation to this approach is that the physiochemical properties of the various agents define their CSF penetration. Theoretically, even for an agent that penetrates the blood–brain barrier poorly, therapeutic concentrations in the CSF could be achieved if a high enough systemic dose of the drug could be administered. The obvious disadvantage to this strategy is the potential for severe systemic toxicity. Toxicity, in fact, often limits the effectiveness of systemic cytotoxic agents, even when CSF penetration is not a goal. To overcome some of the limitations of systemic chemotherapy, direct intrathecal administration of chemotherapy is often used.

Intrathecal chemotherapy

Intrathecal chemotherapy, which may be administered via the intralumbar or intraventricular route, is a regional form of therapy in which high concentrations of drug are delivered directly into the CSF. Because of the small volume of distribution and the relatively slow clearance of many drugs after intrathecal administration, cytotoxic concentrations may be attained in the CSF at a fraction of the dose that would have to be administered systemically to achieve the same concentration.[69] Therefore, systemic toxicity is rare when chemotherapy is delivered intrathecally. Factors that can limit the effectiveness of intrathecal chemotherapy include (1) the pain and inconvenience of repeated lumbar punctures, (2) injection or leakage of drug into the subdural or epidural space,[70] (3) rapid metabolism and/or elimination of drug from the intrathecal space, and (4) the compromised ventricular

concentration of drug caused by the need for the drug to ascend the spinal subarachnoid space against the downward CSF flow following intralumbar drug administration. There are other factors that may affect drug distribution throughout the neuraxis, including CSF volume, patient position immediately after drug administration,[71] the presence of leptomeningeal disease itself,[72] or the presence of obstructive hydrocephalus.

The antimetabolites methotrexate and cytarabine, either alone or in combination with hydrocortisone (triple intrathecal chemotherapy), are the most commonly used agents for intrathecal (intraventricular or intralumbar) administration. Early studies with intrathecal methotrexate revealed that one important factor in drug distribution in the CNS after an intrathecal injection is CSF volume. In the growth of a child, CSF volume increases much more rapidly than body surface area. Indeed, the CSF volume of a child at 3 years of age is essentially equivalent to that of an adult. Using age, rather than body surface area, to determine appropriate dosing of intrathecal methotrexate resulted in reduced neurotoxicity and a lower incidence of CNS relapse.[73,74] Thus, because CSF volume increases much more rapidly than body surface area, dosages for all agents administered intrathecally should be based on patient age (unlike in systemic administration of chemotherapy).

Intraventricular drug administration via an indwelling subcutaneously implanted ventricular access device such as an Ommaya reservoir may circumvent some of the problems associated with intralumbar drug administration and is associated with more uniform drug distribution throughout the neuraxis.[75] Ventricular access devices also facilitate drug administration via various dosing schedules, such as the concentration×time (C×T) schedule.[76] Repeated intraventricular administration of low-dose chemotherapy over a relatively short period of time increases the duration of CSF exposure to cytotoxic drug concentrations, an important determinant of cytotoxicity for cell-cycle-specific agents such as methotrexate and cytarabine. In addition, the C×T approach may potentially reduce neurotoxicity by avoiding excessively high peak drug concentrations and reducing the total dose of administered drug.[77] Because the insertion of a ventricular access device requires a neurosurgical procedure, however, it is generally reserved for the treatment of patients with overt meningeal disease.

New agents and approaches

Preclinical and clinical investigations of several promising new intrathecal agents and therapeutic strategies for the treatment of NM are outlined.

DepoCyt™

Because of the limited number of agents available for intrathecal administration, one approach to the treatment of NM is to enhance the antitumor activity of known agents by administering them in a pharmacokinetically advantageous way. For example, the cytotoxicity observed following treatment with cell-cycle-specific agents such as cytarabine and methotrexate is increased after continuous exposure to a therapeutic concentration of the drug. Based on this pharmacokinetic principle, Kim *et al* developed a depot form of cytarabine for intrathecal administration.[78]

Preclinical studies in a nonhuman primate model demonstrated that the cytarabine sustained-release liposomal injection DepoCyt (DTC 101; a licensed trademark of CHIRON Therapeutics, Emeryville, CA, and SkyePharma plc, London, UK) had a distinct pharmacokinetic advantage compared with unencapsulated cytarabine.[78] The pharmacokinetic advantage of DepoCyt was confirmed in a phase I study. Following a single intrathecal dose of DepoCyt, the terminal half-life of free cytarabine was increased more than 40-fold, from 3.4 to 141 h.[78] After a single intraventricular injection, lumbar cytarabine concentrations were equal to ventricular cytarabine concentrations within 6 h of injection,[79] and cytotoxic concentrations of cytarabine in the lumbar CSF were maintained for an average of 9 d. After intralumbar injection, the peak ventricular cytarabine concentration was observed within 1 d, and therapeutic cytarabine concentrations were maintained for several days. The toxicities observed with intrathecal DepoCyt were similar to the toxicities observed with unencapsulated (free) cytarabine and included fever, headache, back pain, nausea, and encephalopathy. The incidence of toxicities was reduced with concomitant administration of oral dexamethasone.[79]

In a randomized, multicenter, controlled trial of patients with lymphomatous meningitis (ie NM) secondary to lymphoma, 10 of 14 (71%) patients treated with intrathecal DepoCyt had a complete response (ie negative CSF cytology and no neurologic worsening)

compared with 2 of 13 (15%) patients treated with intrathecal free cytarabine ($P = 0.006$).[80] Median time to neurologic progression (78.5 versus 42 d) and median survival (99.5 versus 63 d) tended to be improved in patients treated with intrathecal DepoCyt.[81] Finally, Karnofsky performance status scores following the induction period were better in patients treated with DepoCyt ($P = 0.04$ versus free cytarabine). Based on these encouraging results, DepoCyt has received US regulatory approval for the intrathecal treatment of lymphomatous meningitis.

In the same trial involving a separate group of patients with NM secondary to solid tumors, intrathecal DepoCyt was at least as effective as standard chemotherapy (ie intrathecal methotrexate) with respect to complete response (8/31 [26%] versus 6/30 [20%], $P = 0.76$) and median survival (105 versus 78 d; log-rank, $P = 0.15$).[82] A similar benefit in time to clinical progression was observed in patients treated with intrathecal DepoCyt (median 58 d) versus intrathecal methotrexate (median 30 d; log-rank, $P = 0.007$). Finally, NM-specific median survival was prolonged in the DepoCyt arm compared with the methotrexate arm of the study (343 versus 98 d, respectively; log-rank, $P = 0.07$).[82] Further studies are required to determine the clinical significance of this novel drug delivery system. A phase IV study of DepoCyt in adult patients with leptomeningeal metastases is in progress.

Mafosfamide

Mafosfamide is a preactivated cyclophosphamide derivative that, unlike cyclophosphamide, does not require activation by hepatic microsomal enzymes to express an antitumor effect. *In vitro* cytotoxic target concentrations have been defined for mafosfamide. Preclinical pharmacokinetic studies in a nonhuman primate model demonstrated that following intrathecal administration, ventricular CSF concentrations in excess of *in vitro* cytocidal levels could be attained at doses that were not associated with systemic or neurologic toxicity (Arndt *et al*, unpublished data).[83] Various trials of mafosfamide are ongoing, and preliminary results show activity against leptomeningeal cancers.[84,85]

Topotecan

Based on the promising antitumor activity of topotecan, its novel mechanism of action, and the lack of neurologic toxicity following systemic administration, preclinical pharmacokinetic and toxicity studies were performed in a nonhuman primate model to determine the feasibility of intrathecal topotecan administration. These studies revealed that intraventricular topotecan administration was safe and was not associated with either systemic or neurologic toxicity. Following administration of a 0.1 mg intraventricular dose, the ventricular CSF drug exposure to the parent drug was 450-fold greater than following intravenous administration of a 40-fold higher dose (10 mg/m^2). In addition, peak lumbar levels approached 1 μM. Plasma levels of both the lactone and open-ring form were not measurable. Thus, compared with systemic topotecan administration, intrathecal administration resulted in a dramatic pharmacokinetic advantage in terms of CSF drug exposure. Furthermore, there were no significant systemic or neurologic toxicities associated with intrathecal topotecan administration in nonhuman primates.[86] Various studies of intrathecal topotecan are in progress.

Monoclonal antibodies

Monoclonal antibody therapy directed at leptomeningeal metastases has the theoretic advantage of selectively targeting malignant cells that express specific antigens while sparing normal tissues that do not share these epitopes. Several preliminary studies have been performed in which tumor-specific monoclonal antibodies were conjugated to iodine I 131 and administered via lumbar puncture or an Ommaya reservoir. Several transient responses have been reported.[87] Acute toxicities following intrathecal administration of monoclonal antibodies include aseptic meningitis and myelosuppression.[87,88] Additional studies are needed to demonstrate the safety and efficacy of this approach.

Immunotoxins

A xenograft model for human CNS leukemia using NALM-6 leukemia cells in severe combined immunodeficient mice was recently developed to study the therapeutic efficacy and toxicity of intrathecal B43 (anti-CD19)-pokeweed antiviral protein.[89] Following intrathecal administration of this anti-B-lineage ALL immunotoxin directed against the pan-B-cell antigen

CD19/Bp95 there was improved survival of the severe combined immunodeficient mice relative to methotrexate-treated and control animals.[89] Neurotoxicity following administration of a single large intrathecal dose or following multiple weekly doses was observed.[89] Further preclinical studies assessing the efficacy and toxicity of this approach are required.

Gene therapy

Gene therapy studies have demonstrated encouraging results in tumor regression and subsequent challenge protection in a variety of animal models. The effectiveness of adenoviral vectors in transducing hematopoietic cells has also been demonstrated in B- and T-cell lines and in bone marrow lymphoblasts.[90,91] The feasibility of adenoviral gene transfer into the intrathecal space was recently demonstrated in Fisher 344 rats with meningeal tumors.[92] Preclinical studies to assess the feasibility and distribution of an adenoviral vector in nonhuman primates are in progress. This novel therapeutic approach may have potential application in the treatment of patients with leptomeningeal metastases; however, extensive preclinical and clinical studies are still required.

Conclusions and future directions

Neoplastic metastasis remains a significant diagnostic and treatment challenge for clinical oncologists. There has been considerable progress over the past several decades in the treatment and prevention of leptomeningeal leukemias and lymphomas; however, for a variety of reasons, the long-term outcome for most patients with leptomeningeal metastases from an underlying solid tumor is poor. Continued investigations are required to improve the long-term outcome of patients with leptomeningeal metastases and to minimize the potential toxicities of treatment. Ongoing and future research efforts must be directed toward more efficient methods of delivering currently available agents, the identification of new agents and drug combinations for intrathecal administration, the identification of agents that significantly penetrate into the CSF after systemic administration, and the development of novel therapeutic strategies for the treatment of leptomeningeal metastases.

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