Chapter 8

CURRENT TREATMENT OF LEPTOMENINGEAL METASTASES: SYSTEMIC CHEMOTHERAPY, INTRATHECAL CHEMOTHERAPY AND SYMPTOM MANAGEMENT

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Abstract: Treatment of leptomeningeal metastases is multifaceted and includes symptomatic therapy, intrathecal and systemic chemotherapy, and radiotherapy. As the majority of patients have widespread incurable systemic tumor, treatment is predominantly palliative; however, some patients with leukemia, lymphoma or breast cancer may have prolonged remissions and the possibility of cure.

Keywords: Intrathecal chemotherapy; systemic chemotherapy; CSF flow; breast cancer; methotrexate, cytarabine; thiotepa.

1. INTRODUCTION

Many common cancers, including leukemia, carcinomas of the lung, breast, gastrointestinal tract, and brain tumors metastasize to the leptomeninges.[1-20] Because the cerebrospinal fluid (CSF) flows between the pia mater and the arachnoid in the subarachnoid space, tumor involving one part of the leptomeninges spreads easily throughout the neuraxis.[21,22] Thus, leptomeningeal metastasis is usually considered a diffuse disease of the central nervous system (CNS) even when measurable disease appears to be limited.

The diffuse nature of leptomeningeal carcinomatosis implies that therapy must be directed to the entire CNS if tumor control is the desired outcome.[23-27] Treatment of neoplastic meningitis is therefore multimodal and encompasses the entire neuraxis including the ventricular system, base of brain cisterns and the spinal subarachnoid space[1-19] (Table 1) (Table 2) (Fig. 1).

Table 1: Leptomeningeal Metastases: Treatment Modalities

Modality	**Comments**
Corticosteroids	Temporary symptom relief in patients with bulky intraparenchymal metastasis resulting in raised intracranial pressure
Radiotherapy	Bulky lesions (symptomatic and/or seen on imaging) and sites of CSF
Limited-field	flow obstruction
Craniospinal	
Chemotherapy	Treats entire neuraxis
Regional	Pharmacokinetic advantages
Antimetabolites	
Alkylating agents	
Systemic	Improved drug distribution
High dose IV: Methotrexate, cytarabine, thio-TEPA	
Surgery	
Ommaya reservoir	
CSF diversion	
Immunotherapy	Investigational
Regional	

Table-2: Standard therapy for leptomeningeal metastasis

- Radiotherapy to sites of symptomatic and bulky disease and to sites of CSF flow obstruction
- Intra-CSF chemotherapy (one of the following; may be used sequentially in patients failing prior therapy)
  - Methotrexate
  - Cytarabine
  - Thio-TEPA
- Concurrent systemic treatment of primary tumor

Figure 1: TREATMENT ALGORITHM OF NEOPLASTIC MENINGITIS

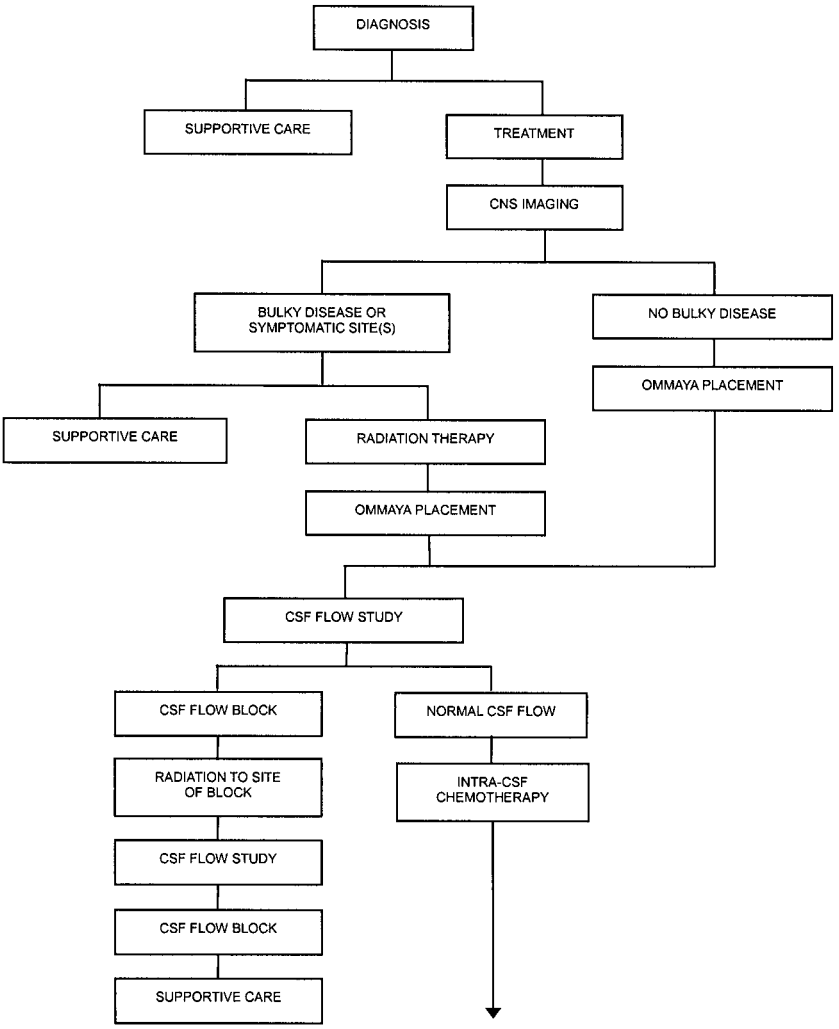
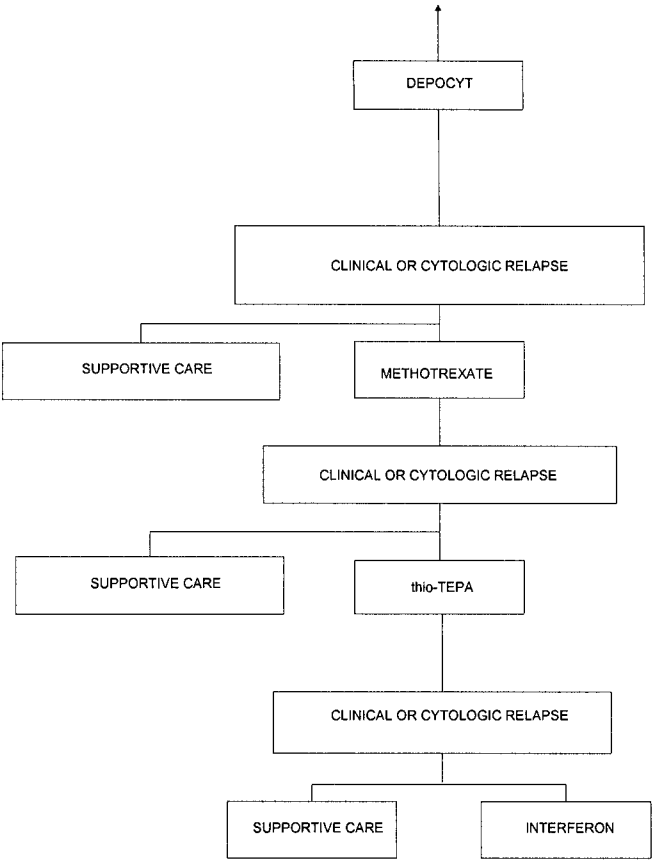


Figure 1: TREATMENT ALGORITHM OF NEOPLASTIC MENININGITIS (Continued)



Treatment often consists of involved-field radiotherapy, systemic chemotherapy and intrathecal chemotherapy. Because meningeal dissemination most often occurs in the setting of advanced systemic tumor (in approximately 70% of all patients with neoplastic meningitis), survival after a diagnosis of meningeal carcinomatosis is usually less than six months and is in part dependent upon primary tumor histology (Table 3). [23,27] Thus, treatment is usually considered palliative rather than curative.[28-33] The exception is in childhood CNS leukemia, where durable remissions may be obtained in patients who present with CNS disease at diagnosis or who have CNS relapse after initial therapy. [23-26,34] In addition, adult patients with breast

cancer or lymphoma have median survivals averaging 7-10 months, suggesting that there is a subset of patients with neoplastic meningitis who have meaningful palliation following treatment. [23,27]

Table 3: Leptomeningeal metastases: survival

	Median Survival (months)
Not treated	1.0
Treated non-responding	2.0
Primary tumor histology institutional data based on selected patients	
Melanoma	4.0
Non-small cell lung	6.0
AIDS-related lymphoma	6.0
Breast	7.5
Non-AIDS-related lymphoma	

Corticosteroids may be helpful in reducing symptoms of increased intracranial pressure although these effects are temporary. Chemotherapy may reduce symptoms when disease is treated early or if pain is the dominant symptom. Radiotherapy (Chapter 9) is useful in targeting bulky disease (subarachnoid or intraparenchymal) defined neuroradiographically, treating symptomatic regions of involvement (e.g., lumbar spine irradiation in patients with cauda equina syndrome) and treating sites of CSF flow obstruction demonstrated by either MRI or radioisotope CSF flow studies. Early recognition of neoplastic meningitis and timely treatment are important if neurologic symptoms and signs are to be reversed. In general, once neurologic deficits are established, treatment has limited impact on reversing signs resulting from neoplastic meningitis.

2. TREATMENT

Patients can present with a variety of symptoms, which may be topographically nonspecific (vomiting, headache), focal (cranial nerve palsy, paraparesis) or multifocal (encephalopathy in conjunction with cranial nerve dysfunction).[23,27] Any of these pleomorphic clinical manifestations warrant consideration of meningeal disease in patients with cancer. In general, patients present with neurologic symptoms and signs referable to three CNS domains: the cerebral hemispheres, cranial nerves or spinal cord/nerve roots.[16] Headache, nausea and vomiting, or mental status changes suggest cerebral hemisphere involvement, whereas diplopia, facial weakness, dysphagia and hearing loss are suggestive of cranial nerve involvement. Spinal cord or nerve root involvement may cause back pain only, radiculopathy, myelopathy or paraparesis.[16,23,27] Because these signs and symptoms can be vague or diffuse,

clinicians must remember to consider leptomeningeal carcinomatosis in the differential diagnosis of a wide variety of clinical presentations in the cancer patient. In addition, the diagnosis is not always evident in CSF cytology or radiographic studies. Approximately 50% of patients with pathologically proven neoplastic meningitis have consistently negative antemortem CSF cytology[35], and not all patients with leptomeningeal metastasis have neuroradiographic findings consistent with neoplastic meningitis.[23,27,36,37] Thus, there is a substantial but infrequently recognized subset of patients with neoplastic meningitis who have both negative CSF cytology and negative or uninformative neuroradiographic studies. Therefore, a diagnosis of leptomeningeal carcinomatosis may be made in three clinical contexts: (1) in patients with positive CSF cytology regardless of clinical syndrome or results of neuroimaging; (2) in patients with positive neuroimaging studies (either brain or spine) consistent with leptomeningeal metastasis regardless of clinical syndrome or CSF cytology; and (3) in patients with known cancer and a clinical syndrome consistent with neoplastic meningitis in whom CSF cytology and neuraxis neuroimaging is negative.[27]

Once a diagnosis of leptomeningeal carcinomatosis is made, deciding whom to treat is a difficult problem.[28-32] Performance status and extent of systemic cancer influence outcome in patients with neoplastic meningitis. An additional consideration is the extent of the disease in the CNS.[33,38-41] The presence of epidural spinal cord compression, parenchymal brain metastases, or bulky subarachnoid nodules may identify patients who are poor candidates for intrathecal chemotherapy. Blockage of CSF flow, as demonstrated by radionuclide ventriculography, suggests cancerous adhesions even in patients with normal neuroradiography and failure of radiotherapy to restore normal CSF flow may be a poor prognostic sign.[31,42] Based on these prognostic variables, a majority of adult patients may not be candidates for aggressive neoplastic meningitis-directed therapy.

An additional difficulty is that, because progression of systemic cancer accounts for 50-60% of deaths in patients with neoplastic meningitis and treatment-related complications for another 1-5% of deaths, it is difficult to assess response rates or duration of responses for those patients with truly progressive neoplastic meningitis.[28-31,33,43,44] When treatment is initiated, the response to treatment is primarily measured by clearing of CSF cytology and secondarily by clinical improvement of neurologic signs and symptoms.[23,27,33,45] Thus, both selection of appropriate therapy and evaluation of response to that therapy can be difficult. In the following sections we outline approaches to systemic therapy, intrathecal therapy, and other measures for symptom control.

3. SYSTEMIC THERAPY

Systemic chemotherapeutic treatment of neoplastic meningitis often fails due to poor CSF penetration of nearly all chemotherapeutic agents and the difficulty in achieving significant intra-CSF drug exposures [46-57] (Table 4). Exceptions are seen with systemic high-dose intravenous methotrexate, cytarabine and thio-TEPA, all of which produce cytotoxic CSF levels and have successfully been used to treat neoplastic meningitis. Notwithstanding the theoretical limitations of systemic chemotherapy in the treatment of patients with neoplastic meningitis, several authors contend that this approach may be sufficient and obviate the need for intra-CSF chemotherapy. A provocative study by Siegal suggests that a subset of patients with neoplastic meningitis, predominantly patients with lymphoma or breast cancer, may respond to standard dose systemic chemotherapy without the inclusion of intra-CSF therapy.[58] Similar conclusions were reached by Boogerd and Fizazi, suggesting the importance of systemic chemotherapy in treating patients with neoplastic meningitis.[59,60]

Table 4. CNS penetration of chemotherapy drugs commonly used for systemic treatment of leptomeningeal tumor

Drug	CSF: Plasma Ratio (%)
Antimetabolites	
Methotrexate	3
Mercaptopurine	25
Cytarabine	20
Alkylating Agents	
Thiotepa	>90
Antimetabolites	
Topotecan	30
Irinotecan/SN-38	14/ND
Miscellaneous	
Prednisolone	<10
Dexamethasone	15
L-Asparaginase	ND

Systemic therapy provides several potential advantages in the treatment of leptomeningeal cancer. Intravenous administration allows a uniform distribution of drugs throughout the CNS and penetration of drug into the brain parenchyma and areas of bulky tumor. Furthermore, continuous intravenous infusion permits maintenance of cytotoxic CNS drug concentrations for a relatively prolonged period. As mentioned, however, most chemotherapeutic agents penetrate poorly into the CNS, and must be used in high doses to achieve therapeutic CNS concentrations. This high dose

or prolonged infusion approach often results in severe systemic toxicity. The agents most commonly administered systemically for the treatment of meningeal disease are discussed below.

3.1 Methotrexate

Intravenously administered methotrexate is occasionally used in a prophylactic manner, particularly in strategies designed to decrease the risk of CNS relapse of leukemia (CNS prophylaxis or CNS preventive therapy) or when treating primary CNS lymphoma in patients without evidence of lymphomatous meningitis. In addition, systemic methotrexate may be effective in the treatment of overt CNS leukemia or lymphoma.[46] In one report comparing patients with recurrent primary CNS lymphoma complicated by lymphomatous meningitis, there was no difference in survival between treatment with high-dose methotrexate or intra-CSF methotrexate. Rather the differences between the groups related to toxicity (high-dose methotrexate was complicated by mucositis and renal insufficiency) and costs (high-dose methotrexate is expensive and usually requires patient hospitalization).[61]

Although the CSF:plasma ratio for methotrexate is only 3%,[48] cytotoxic methotrexate concentrations can be attained in the CSF using very high intravenous doses (3-8mg/m^2). Such high-dose methotrexate regimens must include both intense hydration and alkalinization of urine, and leucovorin rescue.[62] Because methotrexate is eliminated by the kidney, adequacy of renal function should be confirmed prior to therapy, and serum creatinine and methotrexate concentrations should be monitored during therapy. If methotrexate clearance is delayed, the intravenous fluid and leucovorin doses should be increased accordingly.[62] It is important to note, however, that leucovorin rescue may be ineffective when methotrexate concentrations exceed 10^{-4} mol/L.[62] In addition, because methotrexate is nephrotoxic, delayed methotrexate clearance may result in impaired renal function, with a further decrease in methotrexate clearance.[47] Acute renal failure with severely delayed methotrexate excretion is an emergency. In this situation, intravenous administration of carboxypeptidase-G2, an enzyme that cleaves methotrexate and results in a greater than ten-fold reduction of serum methotrexate concentrations within minutes of administration, may be considered.[63] Information about the availability of carboxypeptidase for emergency use can be obtained from the National Cancer Institute.

Toxicity after high-dose methotrexate occurs frequently even when renal function is adequate and proper hydration and leucovorin rescue are administered. Moderate to severe mucositis is common. Myelosuppression, hepatic toxicity, and desquamating dermatitis of the hands and feet can also occur. High-dose systemic methotrexate, especially when given in association

with cranial radiation, has also been linked with neurotoxicity, manifesting as either an acute encephalopathy, which is rare, or a more common late leukoencephalopathy. [64,65]

3.2 Cytarabine

The nucleoside analog cytarabine (ara-C, cytosine arabinoside) may also be useful when administered systemically for the treatment of meningeal cancer, particularly leukemic or lymphomatous meningitis. No data is available, however, regarding the utility of high-dose cytarabine in the treatment of carcinomatous meningitis. The CSF penetration of cytarabine is approximately 20%.[56,66] Several approaches for systemic cytarabine administration have been utilized. A regimen of 3 g/m^2 administered every 12 hours demonstrated activity in patients with meningeal leukemia,[49], and a 72 hour continuous intravenous infusion of doses $\geq$4 g/m^2 achieved cytotoxic CSF cytarabine concentrations.[50] High-dose systemic cytarabine administration is associated with significant toxicity, with severe myelosuppression nearly universal. In addition, cerebellar dysfunction occurs in approximately 20% of patients receiving of 3 g/m^2 of cytarabine every 12 hours, especially patients older than 60 years, and requires discontinuation of therapy.[51] Nausea, vomiting, and mucositis are also common at these high doses.

3.3 Thiotepa

Thiotepa is a lipid-soluble alkylating agent that effectively crosses the blood-brain barrier. Furthermore, TEPA, an active metabolite of thiotepa, also penetrates into the CSF. [52,53] Thus, systemic administration of this agent achieves high concentrations of both parent drug and active metabolite in the CSF. Systemic thiotepa showed some activity against medulloblastoma in a pediatric phase II trial. [53] However, thiotepa causes severe bone marrow toxicity which has limited the usefulness of this agent outside the setting of dose intensive chemotherapy with stem cell rescue and cytokine support. In children with recurrent primary brain tumors, the presence of neoplastic meningitis has increasingly been recognized as a contraindication to dose intensive chemotherapy, as observed survival in such patients has been no better with high dose than conventional dose chemotherapy.

3.4 6-Mercaptopurine

The CSF penetration of 6-mercaptopurine is approximately 25%. Prolonged infusion of this drug at dose rates of 50 mg/m^2/hr achieves cytotoxic concentrations (>1 μM) in the CSF.[67] The common toxicities include reversible hepatotoxicity, myelosuppression, and mucositis.[68] Despite

the relatively favorable pharmacokinetics, however, the overall activity of intravenous mercaptopurine against meningeal spread of solid tumors has been disappointing, and this approach is rarely used.[68]

3.5 Topoisomerase I inhibitors

Topotecan, a topoisomerase I inhibitor, achieves an $AUC_{csf}AUC_{plasma}$ ratio of 30% after intravenous administration.[69] In CNS tumors, topotecan administered as a 24-hour continuous infusion was not active.[70] Other studies of systemic topotecan in either primary brain tumors or in CNS metastasis from non-CNS primary tumors have shown modest activity at best. [71-73] The usefulness of intravenous topotecan against leptomeningeal carcinomatosis has not been confirmed to date.

3.6 Irinotecan

Irinotecan (CPT-11) is a prodrug of the active topoisomerase I inhibitor SN-38 that requires hepatic activation. Irinotecan itself penetrates reasonably well into the CSF, with an AUC_{csf}:AUC_{plasma} of about 14%. However, the active compound SN-38 is not detectable in CSF after intravenous irinotecan administration.[74] Three reports of irinotecan in adults with gliomas suggest limited activity for recurrent gliomas; however, none of these studies specifically treated patients with meningeal gliomatosis.[75-77] A phase II study of irinotecan in pediatric solid tumors, including tumors with leptomeningeal dissemination, is now underway in the Children's Oncology Group. This trial should help to define the usefulness of irinotecan in the treatment of leptomeningeal cancers.

4. CORTICOSTEROIDS

Prednisone (the orally administered prodrug of prednisolone) and dexamethasone, agents commonly used in the treatment of acute lymphoblastic leukemia, both penetrate into the CNS producing CSF concentrations that are equal to the plasma concentrations of free drug. However, dexamethasone is less protein bound than prednisone at equipotent doses. Therefore, dexamethasone can be considered to penetrate better into the CSF.[78] Patients receiving dexamethasone rather than prednisone for CNS preventive therapy of leukemia have a significantly lower rate of CNS relapse.[79] In some settings the infectious complications in patients receiving dexamethasone exceed those in patients receiving prednisone in an otherwise comparable chemotherapy regimen.[80] Thus, the substitution of dexamethasone for prednisone in leukemia therapy is not universal.

Dexamethasone is often used as a supportive care agent for the treatment

of either chemotherapy induced nausea or edema associated with intracranial tumors. In addition, oral dexamethasone is useful to mitigate the symptoms of intrathecal (IT) chemotherapy-induced chemical meningitis. Two recent trials have demonstrated that chemical meningitis is common following intrathecal chemotherapy irrespective of the agent used and is easily managed by oral dexamethasone.[28,29]

4.1 L-asparaginase

L-asparaginase is an enzyme that hydrolyzes L-asparagine, an amino acid essential for lymphoblasts but not for normal cells. L-asparaginase does not penetrate into the CSF but may still be useful in the treatment of meningeal leukemia.[81] Following systemic administration of this agent, plasma levels of L-asparagine are depleted for a prolonged period.[82,83] Although the enzyme is not detectable in CSF, CSF L-asparagine levels are also depleted for a variable amount of time following systemic administration.[84,85]

5. INTRATHECAL THERAPY

Intrathecal chemotherapy is a form of regional therapy directed specifically against leptomeningeal cancer. IT administration of relatively small drug doses produces very high CSF drug concentration usually with minimal systemic toxicity. [86] This pharmacokinetic advantage, however, is counterbalanced by limitations that must also be considered. For example, diffusion of drug from the CSF into the brain parenchyma or tumor nodules is limited to within a few millimeters of the CSF space.[87] Thus, bulky leptomeningeal nodules may not be treated effectively with intrathecally-administered agents. In addition, drug distribution throughout the CSF compartment, especially after intralumbar dosing, may be uneven because of the slow circulation of CSF and the rapid diffusion of most intrathecally administered drugs out of the CSF. For example, drug exposure in the ventricular CSF following an intralumbar dose of methotrexate is only one-tenth of that achieved after an equivalent intraventricular dose.[48] There are also technical difficulties with IT drug administration. CSF flow is sometimes abnormal as a result of blockage by tumor.[88] In this situation, there is the concern that IT drug administration may result in unexpected toxicity if drug is not distributed throughout the CSF space. In addition, intralumbar injection is inconvenient and may be painful. Furthermore, approximately 10 % of intralumbar injections are estimated be ineffective because of leakage of the drug into the epidural space or surrounding tissues.[42]

Although systemic toxicity is uncommon after IT administration of anticancer agents, neurologic toxicity is common. In addition, inadvertent IT

administration of some commonly used anticancer drugs (e.g. vincristine) is usually lethal, and IT overdose of other drugs (e.g. methotrexate) can also be fatal or life threatening.

A further disadvantage of the IT approach is the limited number of drugs that have been developed for IT use (Table 5). Methotrexate, cytarabine, hydrocortisone, and thiotepa are the only agents commonly used for direct intra-CSF administration.[23,27-31,86] A number of investigational agents are being explored including mafosfamide and 4-hydroperoxy-cyclophosphamide (derivatives of cyclophosphamide), busulfan, topotecan, diaziquinone, interferon, monoclonal antibodies, gene therapy and interleukin-2.[44,89-100] However, these agents are available only in an experimental protocol setting.

Table-5. Drugs administered by the intrathecal route

Standard agents	Investigational Agents
Methotrexate	Busulfan
Cytarabine	Mafosfamide
Hydrocortisone	Topotecan
Thiotepa	Diaziquinone
DepoCyt	4-Hydroperoxy-cyclophosphamide
	Immunotherapy
	Interferon
	Monoclonal antibody (with or without radioactive ligand)
	Interleukin-2
	Gene therapy

Some commonly used IT drug doses and schedules are listed in Tables 6 and 7. It is imperative that IT therapy only be administered by individuals familiar with the doses, schedules, and toxicities of each agent.

Table 6. Bolus intrathecal chemotherapy regimens

Drug	Induction (4 weeks)	Consolidation (4 weeks)	Maintenance
MTX[a]	10-15 mg twice weekly	10-15 mg weekly	10-15 mg monthly
Cyt	25-100 mg twice weekly	25-100 mg weekly	25-100 mg monthly
Depocyt	50 mg QOW	50 mg QOW	50 mg monthly
Thiotepa	10 mg twice weekly	10 mg weekly	10 mg monthly
Interferon	$1x10^6$ thrice weekly	$1x10^6$ weekly	$1x10^6$ monthly

QOW = every other week

Table-7. CxT intrathecal chemotherapy regimen

Drug	Induction	Consolidation	Maintenance
MTX	2 mg/day for 3-5 days, QOW x 4	2 mg/day for 3-5 days QOWx2	2 mg/day for 3-5days monthly
Cytarabine	15-25 mg/dayx3 days, weekly x 4	15-25 mg/dayx3 days QOWx2	15-25 mg/dx3days monthly
Thiotepa	10mg/dayx3days weekly x 4	10mg/dayx3 days QOWx2	10mg/dayx3days monthly

QOW = every other week
There is no CxT regimen available for Depocyt or Interferon

At present, there is no compelling data to suggest an improved response when using multiple agents versus single agent intra-CSF drug therapy. Two randomized trials in adults with carcinomatous meningitis demonstrated no survival advantage when comparing single agent (methotrexate) to polyagent (methotrexate, cytarabine and hydrocortisone) IT chemotherapy.[30,43] Furthermore, these trials suggested that polyagent IT therapy is associated with increased toxicity and less well tolerated by patients.

Because of the inconvenience and technical difficulties associated with lumbar puncture, many North American neuro-oncologists treat patients with neoplastic meningitis by the intraventricular route utilizing an intraventricular catheter and subgaleal reservoir (Ommaya reservoir). A variety of drug schedules exist and most commonly drug is administered in a bolus manner, typically twice a week.[16-19,28-31,43] Alternatively, placement of an intraventricular catheter permits the use of a concentration times time (C x T) approach based on pharmacokinetic principles.[101-107]

Few studies have compared differing intra-CSF drug schedules or drug doses in the treatment of leptomeningeal metastasis. Pharmacokinetic studies of intra-CSF drug administration in neoplastic meningitis demonstrate sustained cytotoxic lumbar and ventricular chemotherapeutic drug levels following administration by the ventricular route; however, similar studies following drug administration by the lumbar route are highly inconsistent with respect to achievement of cytotoxic ventricular chemotherapeutic drug levels.[48] Notwithstanding the pharmacokinetic advantages of intraventricular CSF drug administration as compared to intralumbar CSF drug administration, there are no studies proving that this method of administration results in improved patient survival when compared to intralumbar drug administration.

Despite the lack of conclusive evidence, many neuro-oncologists utilize a CxT method of drug delivery by the ventricular route in the hope that it will result in a lower frequency of neurotoxicity, improved tumor cell killing due to prolonged drug exposure, and better palliation and patient survival.

Whether to give intra-CSF chemotherapy concurrently with radiotherapy is problematic. The only published prospective randomized trials of neoplastic meningitis permitted both concurrent radiotherapy and intra-CSF chemotherapy, but this approach may result in an increased risk of delayed neurotoxicity as discussed below.[28,29,32]

Complications of intra-CSF drug therapy are not uncommon and may profoundly affect patients with neoplastic meningitis (Table 8).[108,109]

Table 8. Complications: intraventricular chemotherapy

	Patients	%
Meningitis	62	43
Aseptic/chemical	52	43
Bacterial (catheter infection)	9	8
Myelosuppression	21	18
Transfusion-requiring	6	5
Unidirectional catheter obstruction	5	6
Catheter misplacement	2	2
Reservoir exposure	2	2
Chemotherapy-related leukoencephalopathy	2	2
Chemotherapy-related myelopathy	1	1
1110 cycles of intraventricular chemotherapy (median 10)		
4400 Ommaya punctures (median 46)		

The placement of intraventricular catheters and subgaleal reservoirs are well known and fortunately infrequent. Misplacement of the catheter tip may be identified on post-operative plain skull films, CT or MRI and radionuclide ventriculography. Clinically significant hemorrhage is distinctly uncommon in occurrence primarily because of meticulous attention to pre-operative coagulation parameters. Infection is unfortunately a difficult problem seen at the time of intraventricular catheter placement or as a consequence of its use and occurs in up to 8% of patients. In both circumstances, skin flora, primarily *Staphylococcus epidermidis,* contaminates the system and results in iatrogenic bacterial meningitis. These infections may often be treated successfully with a combination of systemic and intraventricular antibiotics, thus preserving the intraventricular system and thereby avoiding Ommaya system removal and ultimately a re-operation. Infrequently, patients with intraventricular catheter and subgaleal reservoirs develop pressure necrosis of the skin overlying the reservoir, resulting in reservoir exposure and necessitating removal and, if clinically appropriate, replacement. Overall, serious complications requiring surgery are infrequent (6%) and most often secondary to catheter infections, Ommaya reservoir exposure or initial catheter misplacement.[108,109]

The most common complication of intraventricular catheter use relates to the toxicity of administering drugs directly into the CNS. The majority of

these complications are inflammatory and transient in nature and are best characterized as aseptic chemical meningitis with fever, headache, nausea, vomiting, meningismus, photophobia and occasionally dehydration. This complication is usually easily managed in the outpatient setting with oral antipyretics, antiemetics and steroids. Direct neurotoxicity rarely occurs as a manifestation of intra-CSF drug administration which may result in either a chemotherapy-related leukoencephalopathy or myelopathy. [65,110,111] These complications may be idiosyncratic or in some instances related to total intra-CSF drug dose and delayed drug clearance. In patients with prolonged survival, the incidence of treatment-related delayed neurotoxicity manifested primarily as a leukoencephalopathy is considerably higher and may approach 30%. This delayed neurotoxicity, defined by either neuroradiographical or clinical criteria, reflects the combined effects of both radiotherapy and intra-CSF chemotherapy and appears to be an unavoidable consequence of treatment. The majority of patients treated with partial or whole brain radiotherapy develop neuroradiographic evidence of leukoencephalopathy, which fortunately is clinically apparent in only a minority. Administering intra-CSF methotrexate prior to the application of cranial irradiation may mitigate delayed neurotoxicity. The issue of timing of radiotherapy vis-à-vis methotrexate administration is more problematic in patients with neoplastic meningitis, as radiotherapy is most often utilized initially to treat symptomatic or bulky intracranial disease.

6. STANDARD AGENTS

6.1 Methotrexate

Methotrexate has been the mainstay of IT chemotherapy for over 40 years.[16-19,23,27,29,30,32,43] It is used for CNS preventive therapy in nearly all patients with acute leukemia.[112]. In addition, it is the drug most commonly used for CNS reinduction therapy in meningeal relapse of leukemia.[112-114] Because it is successful against leukemia, and there is a large body of experience with its IT administration, methotrexate is sometimes also used as "standard" therapy for the treatment of meningeal spread of solid tumors. However, the response rate of solid tumors to methotrexate is low in this setting (approximately 20%). [29,32]

Methotrexate is detectable in plasma for relatively long periods after IT dosing, but at low concentrations.[48] Although systemic toxicity is not usually a problem after an IT dose, some protocols call for administration of a single low oral Leucovorin dose after IT methotrexate. In contrast to systemic toxicity, acute or delayed neurotoxicity is relatively common after IT methotrexate. Chemical arachnoiditis, with headache, photophobia, back pain,

meningismus, fever, nausea, vomiting, and CSF pleocytosis, often occurs (50% in a prospective study).[29,32] This transient aseptic meningitis has an onset on day 1-2, peaks by day 2-3 and resolves by day 5. Transient or permanent weakness or paraplegia may occur following intralumbar administration of methotrexate. This toxicity is fortunately rare and may be related to delayed clearance of methotrexate from the CSF.[110,111,115] Late neurotoxicity in the form of leukoencephalopathy may also occur, usually in patients who have received intravenous methotrexate and cranial irradiation in addition to IT methotrexate.[110,111,115]

IT methotrexate overdoses can be fatal. Immediate treatment includes ventriculolumbar perfusion to attempt to reduce methotrexate concentrations in the CNS, administration of systemic corticosteroids, and administration of systemic leucovorin.[116] In the nonhuman primate model, IT administration of carboxypeptidase-G2 immediately decreases CSF methotrexate concentrations very rapidly and prevents toxicity after experimental IT methotrexate overdose.[117] The role of carboxypeptidase-G2 in the treatment of IT methotrexate overdose in humans is unknown.

IT methotrexate therapy is often given through an Ommaya reservoir in patients with refractory meningeal disease. Administration through a reservoir produces more even drug distribution throughout the CSF compared with intralumbar administration and appears to prolong the duration of remission in CNS leukemia. [48,101,118]Use of the Ommaya reservoir also permits the administration of frequent small doses of methotrexate instead of single large doses. C x T therapy produces cytotoxic concentrations for a prolonged period while avoiding high peak drug levels. This combination may result in greater efficacy with less toxicity. [101] In this regimen, methotrexate may be administered as 2 mg per day for 3 - 5 consecutive days every other week for 4 treatment weeks (total 8 weeks), followed by administration at a decreased frequency in consolidation and maintenance phases.

Unlike systemically administered anticancer agents, IT drugs are usually given at a fixed dose, rather than body-surface area based dosing, in older children and adults. The reason for this is that, in contrast to body surface area, the CSF volume approaches adult size by the age of approximately three years. Therefore, the dose for IT methotrexate is based on patient age, with a constant dose administered to all patients over three years of age. For methotrexate, this dosing scheme both reduces toxicity in older patients and improves outcome in younger patients.[119] Because of these seminal observations, most other IT agents are also dosed based on age rather than body size.

6.2 Cytarabine

Like methotrexate, cytarabine can be administered intrathecally to produce high CSF cytarabine concentrations with minimal systemic toxicity. Cytarabine may be given by the intralumbar route or via an Ommaya reservoir on a C x T schedule that has the same advantages as C x T methotrexate administration.[102-107] In addition, cytarabine is often combined with methotrexate and/or hydrocortisone for IT administration in children with leukemic meningitis; this is the only standard regimen for combination IT therapy. IT administration of cytarabine, like methotrexate, may produce arachnoiditis or, rarely, other forms of neurotoxicity such as seizures and paraplegia.[120] Leukoencephalopathy and other chronic neurotoxicities, however, have not been described commonly with IT cytarabine.

6.3 Liposomal Cytarabine

A liposomal encapsulated form of cytarabine (DepoCyt™) has been shown to be an active agent with potential advantages compared to free cytarabine or methotrexate.[28,29,32,122] These advantages include once every two-week drug administration whether the intraventricular or intralumbar route is used. Two randomized trials in adults compared liposomal cytarabine to methotrexate (in patients with carcinomatous meningitis) or free cytarabine (in patients with lymphomatous meningitis).[28,29] In both trials, the response rate was better, the time to neurologic disease progression was delayed, and death due to neoplastic meningitis was reduced in the liposomal cytarabine cohort. No difference in survival between the treatment arms was seen in either trial, but quality of life was improved in the liposomal cytarabine cohort. Because of the convenience of once every two weeks administration in addition to the modest merits mentioned above, liposomal cytarabine is increasingly being considered as first-line therapy for either carcinomatous or lymphomatous meningitis. Insufficient data exists regarding liposomal cytarabine's effectiveness for leukemic meningitis, though an on-going Phase 1 trial in pediatric neoplastic meningitis may generate some conclusions. Importantly, because of a high incidence of chemical meningitis when this agent is administered without corticosteroids, oral dexamethasone at a dose of 2 – 4 mg by mouth twice per day for 5 days should be utilized whenever liposomal cytarabine is administered regardless of delivery route.

6.4 Thiotepa

IT administration of thiotepa, in contrast to systemic administration of the same agent, is well tolerated although it may be associated with myelosuppression.[31] The active metabolite TEPA, however, is not detected in CSF after IT administration. In addition, because the drug is highly lipid soluble unlike most other intrathecally administered agents, thiotepa diffuses

rapidly out of the CSF.[121] Thus, the usual pharmacokinetic advantages of IT drug administration may be less prominent for thiotepa than for some other drugs. Nonetheless, IT thiotepa has been shown in one of four randomized trials in adults with neoplastic meningitis to be as effective as methotrexate. Thiotepa may also be administered on a C x T schedule. No survival benefit has been demonstrated when comparing thiotepa to methotrexate in the treatment of neoplastic meningitis in adult carcinomatous meningitis.[31]

7. INVESTIGATIONAL AGENTS

7.1 Mafosfamide

Mafosfamide is a preactivated derivative of cyclophosphamide that does not require hepatic metabolism to have antitumor activity. This agent has demonstrated activity in phase I trials against meningeal leukemia and leptomeningeal dissemination of brain tumors. [92,99] It is currently undergoing further study in an adult Phase 1 trial and in the Pediatric Brain Tumor Consortium to determine its efficacy in adult carcinomatous meningitis and in preventing leptomeningeal recurrence of primary brain tumors in infants, respectively.[93]

7.2 Topotecan

IT administration of the topoisomerase I poison topotecan was studied in a recent phase I trial in children.[123] Arachnoiditis was the dose-limiting toxicity, and the maximum tolerated dose was 0.4 mg. Several patients with leptomeningeal spread of solid tumors demonstrated responses or prolonged stable disease. A phase II trial of IT topotecan in children with neoplastic meningitis is in progress in the Children's Oncology Group as is a Phase 1 trial in adults with carcinomatous meningitis.

7.3 Monoclonal antibodies

Monoclonal antibody therapy directed at meningeal metastasis is a relatively new approach that theoretically has the advantage of selectively targeting malignant cells that express specific antigens while sparing normal tissues that do not share these epitopes. Most studies have utilized ^{131}I linked to an antibody of interest (so- called radioimmunoconjugates) in the particular tumor being studied. Toxicity, particularly systemic myelosuppression, and the need to have an appropriate antibody limit this approach at present although it remains under exploration.[91,94-98,100]

8. SYMPTOMATIC THERAPY

A variety of medical therapies are utilized in the care of patients with leptomeningeal metastasis irrespective of whether the patient is offered aggressive neoplastic meningitis-directed therapy. A minority of patients will manifest seizures as a consequence of neoplastic meningitis and the use of non-sedating anticonvulsant drugs is appropriate for this group of patients. Patients with difficult to control pain may be managed with narcotics or, in the instance of neuropathic pain, either anticonvulsant drug or tricyclic antidepressant drug therapy. Depression is a very common symptom in patients with cancer and is often neglected or not recognized. Early recognition and initiation of antidepressants in symptomatic patients is recognized to improve quality of life and benefit both patients and families. In addition, antidepressants, especially tricyclic agents, are also useful for chronic insomnia. Corticosteroids are most useful to control vasogenic edema secondary to parenchymal brain or epidural metastases but have very limited use in the management of neoplastic meningitis-related neurologic symptoms. Steroids may be useful in patients with raised intracranial pressure or in patients with chronic nausea or vomiting. Similarly, nausea or vomiting may be managed by anti-emetics. Concurrent steroids, megestrol acetate or cannabinols may mitigate weight loss and cancer-related anorexia. Finally, decreased attention and somnolence, common side effects of whole brain irradiation and chemotherapy, may be improved modestly by the use of psychostimulants such as dextroamphetamine or modafinil.

9. CONCLUSIONS

Neoplastic meningitis is a complicated disease for a variety of reasons. Not all patients necessarily warrant aggressive CNS-directed therapy, yet few guidelines exist permitting appropriate choice of therapy. In general, only pain-related neurologic symptoms improve with treatment. Neurologic signs such as confusion, cranial nerve deficit(s), ataxia and segmental weakness minimally improve or stabilize with successful treatment. The majority of patients die due to progressive systemic disease occurring either in isolation or in combination with progressive neoplastic meningitis. Notwithstanding aggressive treatment, survival ranges only from 2-10 months depending upon tumor histology, and in adult neoplastic meningitis, therapy is considered palliative rather than curative. However, specific tumor histologies may have different responses to therapy. For example, the consensus is that breast cancer is inherently more chemosensitive than non-small cell lung cancer or melanoma, and therefore, survival following chemotherapy is likely to be

better. This observation has been substantiated in patients with systemic metastases though comparable data regarding CNS metastases, and in particular neoplastic meningitis, is meager.[32,59,60]

Supportive comfort care (radiotherapy to symptomatic disease, antiemetics, and narcotics) rather than aggressive therapy may reasonably be offered to a majority of adults with neoplastic meningitis. Palliative therapy of neoplastic meningitis often affords the patient protection from further neurological deterioration and consequently an improved neurologic quality of life. No studies to date have attempted an economic assessment of the treatment of neoplastic meningitis and therefore no information is available regarding a cost-benefit analysis as has been performed for other cancer directed therapies.

A number of challenges remain in the treatment of neoplastic meningitis. Treatment failure may result from (1) *de novo* or acquired drug resistance; (2) incomplete distribution of drug within CSF spaces; (3) inability to achieve adequate CSF drug levels; (4) failure to control primary non-CNS tumor; (5) toxicity, both neurologic and systemic toxicity of regional chemotherapy; (6) concurrent CNS metastatic disease (parenchymal brain, dural and epidural spinal cord metastases); and (7) inability of patients to tolerate treatment.[28,29,32,38-41,48,124] Each of these challenges must be overcome to make substantial improvements in the therapy of leptomeningeal carcinomatosis.

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