ABSTRACT

Meningeal metastasis from cancer has become an increasingly frequent problem as the treatment of systemic disease improves. Leukemia, lymphoma and solid tumors may all metastasize to the meninges, where the blood-brain barrier may provide a sanctuary from cytotoxic concentrations of chemotherapeutic agents. Because meningeal disease may be clinically silent or may present with unusual signs and symptoms, it is important to maintain a high index of suspicion for this problem. Diagnosis is usually made by cerebrospinal fluid cytologic testing, magnetic resonance imaging, or both. Treatment options include radiation therapy, systemic chemotherapy and intrathecal chemotherapy. Systemic therapy usually requires administration of either very high drug doses or prolonged infusions in order to overcome the poor penetration of most anticancer agents into the central nervous system. Thus, systemic toxicity is often a major drawback to this approach. Intrathecal chemotherapy results in delivery of anticancer agents directly into the cerebrospinal fluid, usually with minimal systemic toxicity. Intrathecal chemotherapy may be administered by lumbar puncture or by use of an Ommaya reservoir with the tip in the ventricle. Studies are under way to evaluate new agents for both systemic and intrathecal administration. Further research is required to overcome this difficult clinical challenge.

INTRODUCTION

Meningeal malignancy presents a difficult clinical challenge for both pediatric and adult oncologists. As improvements in systemic therapy have resulted in longer survival for patients with various malignancies, the incidence of meningeal metastasis has increased. This is probably due to the “sanctuary” effect created by the blood-brain barrier, which prevents many anticancer drugs from achieving cytotoxic concentrations in the central nervous system (CNS). In this article, advances in the treatment of meningeal disease will be presented, including both new agents and new approaches to the use of standard agents.

Meningeal malignancy results from the metastasis of intracranial or extracranial tumors to the leptomeninges (the arachnoid membrane and the pia mater). The cerebrospinal fluid (CSF), which flows in the subarachnoid space between the pia and the arachnoid, may then provide a route for metastasis along the entire neuraxis. Leukemia, brain tumors and other solid tumors may all metastasize to the meninges and spread in this fashion (Table 1).

Prior to the institution of CNS preventive therapy, meningeal leukemia occurred in more than 50% of children with acute lymphoblastic leukemia (ALL), and the CNS was the most common site of relapse in patients who achieved bone marrow remissions. The current strategies for preventive therapy have decreased the incidence of CNS leukemia to less than 10%, although relapses still occur and may be difficult to treat. Meningeal leukemia also occurs in adults: based on autopsy series, meningeal involvement may occur in 25% to 81% of cases [1, 2].

CNS involvement is common in non-Hodgkin’s lymphomas. Solid tumors also metastasize to the meninges. In adults, the tumors most commonly responsible are carcinomas of the lung, breast and gastrointestinal tract, and melanoma [3]. In children, rhabdomyosarcoma, Ewing’s sarcoma and retinoblastoma may metastasize to the CNS. Brain tumors such as gliomas, medulloblastomas, ependymoblastomas, germinomas and choroid plexus carcinomas, as well as primary CNS lymphoma, may also spread to the meninges.
**DIAGNOSIS**

Meningeal cancer may be clinically silent. Therefore, in diseases like leukemia in which meningeal spread is common, “surveillance” of the CSF with periodic lumbar punctures is often undertaken. Because of such surveillance, CNS leukemia is now usually diagnosed before it becomes symptomatic. In other cases, the clinical picture of meningeal metastasis may be nonspecific. The most common signs and symptoms of meningeal malignancy are those of increased intracranial pressure. Headache is most common, although cranial nerve and spinal cord symptoms are also frequent [4]. Unusual signs such as sudden hearing loss or complex partial seizures may also occur. Thus, it is important to keep meningeal malignancy in mind when patients with cancer present with any neurologic complaints.

The diagnosis of meningeal metastasis is usually made by examination of the CSF. For solid tumors, the presence of malignant cells in the CSF confirms the diagnosis. For leukemias, the combination of malignant blasts and an elevated cell count is usually required. The significance of leukemic blasts in the presence of a normal CSF white blood cell count is uncertain [5-7]. In some cases where meningeal malignancy is suspected, repeated lumbar punctures may be required to identify malignant cells. This is especially true for solid tumors. Even so, however, in 90% of cases the diagnosis can be confirmed by three or fewer CSF examinations [8]. The diagnostic role of tumor markers in the CSF has not yet been established.

Radiographic evaluation may sometimes be helpful in the evaluation of patients with suspected meningeal disease. Computerized tomography (CT) scanning is relatively insensitive, but magnetic resonance imaging (MRI), especially with gadolinium enhancement, may be more helpful. Many false negative and some false positive results do occur with MRI, however. In addition, 111Indium-DTPA flow studies may show abnormalities of CSF flow, although these studies are usually used as part of treatment planning prior to intrathecal therapy rather than as a diagnostic tool. A combination approach using both CSF studies and radiographic modalities is often appropriate in patients with suspected meningeal disease.

**TREATMENT**

Both chemotherapy and radiation therapy may be used in the prevention or treatment of meningeal malignancy. Cranial irradiation is part of many regimens to prevent the development of meningeal leukemia, especially in high-risk patients, and craniospinal irradiation is usually employed as part of the therapy for meningeal relapse. Radiation therapy, however, may result in both short- and long-term toxicity. Craniospinal radiotherapy often causes significant myelosuppression, which may complicate efforts to administer systemic anticancer therapy. Cranial irradiation may produce the “somnolence syndrome,” which consists of a prodrome of irritability and anorexia followed by a variable period of somnolence. Recovery is spontaneous, and the somnolence syndrome is not predictive of later complications of therapy.

Long-term complications of cranial or craniospinal irradiation may include second malignancies, short stature, growth hormone abnormalities and hypothyroidism. Cortical atrophy, IQ deficits and leukoencephalopathy may also occur. Younger children are more vulnerable to the long-term toxicities of radiation therapy than are older children [9]. The trend in leukemia therapy is toward reduced doses (e.g., 1800 cGy) of neuraxis radiation. In other childhood tumors, the minimal dose of radiation adequate for tumor control, as well as strategies for delaying radiation therapy in younger children, are under active study.

The chemotherapeutic approach to meningeal cancer can be divided into systemic (intravenous or oral) and regional (intrathecal or intraventricular) therapy; both have advantages and disadvantages. Systemic administration may produce more uniform drug distribution throughout the CNS, and prolonged intravenous infusion may produce cytotoxic CSF drug concentrations for a prolonged period. Most systemically administered agents, however, do not cross the blood-brain barrier well, and systemic toxicity limits the ability to treat meningeal disease by this route. In contrast, intrathecal drug administration may produce cytotoxic concentrations in the CSF even when small doses are used, and systemic toxicity is very rare. However, lumbar punctures may be difficult, drugs may not be delivered into the intrathecal space and drug distribution in the CSF may be uneven. The use of an Ommaya reservoir to deliver drugs directly into the ventricular CSF overcomes some of these problems, but use of this device requires special expertise as well as a neurosurgical procedure for placement. In addition, neurotoxicity may occur after direct administration of drugs into the CSF.

In the following section, specific agents used in the treatment of CNS malignancy will be discussed. Tables 2 and 3 present some typical doses and schedules for these agents, but should not be construed as recommendations for treatment of individual patients.

**METHOTREXATE**

Intrathecal methotrexate has been used in the treatment of meningeal leukemia since the 1950s. Intrathecal methotrexate either given alone or in combination with other agents can prevent the development of meningeal leukemia in 90% of children. Furthermore, intrathecal methotrexate often provides effective CNS reinduction therapy for meningeal relapse [10-12].
Because the CSF volume approaches adult size years before body surface area does, the dose for intrathecal methotrexate is based on patient age, with a constant dose administered to all patients over three years of age. This approach both reduces toxicity in older patients and improves outcome in younger patients [13, 14]. Because of these observations, most other intrathecal agents in children are also dosed based on age rather than body size.

Although methotrexate is detectable in plasma after an intrathecal administration, systemic toxicity is not usually a problem after an intrathecal dose. However, acute or delayed neurotoxicity is relatively common after intrathecal methotrexate administration. Chemical arachnoiditis, manifested by headache, back pain, meningismus, fever, vomiting and a CSF pleocytosis, may occur hours to days after methotrexate administration and is usually self-limited [15]. In severe cases, oral corticosteroids may improve symptoms. On rare occasions, transient or permanent weakness or paraplegia may occur following intralumbar administration of methotrexate. This unusual toxicity may be related to delayed clearance of methotrexate from the CSF resulting in high CSF methotrexate levels [16]. Late neurotoxicity in the form of leukoencephalopathy may also occur, usually in patients who have received intravenous methotrexate and cranial irradiation in addition to intrathecal methotrexate [17].

Inadvertent overdoses of intrathecal methotrexate can be fatal. Immediate treatment including ventriculostomy with ventriculo-lumbar perfusion, administration of systemic corticosteroids and administration of systemic leucovorin may be beneficial [18]. In addition, intrathecal administration of carboxypeptidase-G2 has been shown to rescue nonhuman primates from experimental intrathecal methotrexate overdose [19], and may play a role in the treatment of accidental intrathecal overdose in humans.

In patients with recurrent meningeal disease, intrathecal methotrexate therapy is often given through an indwelling Ommaya reservoir. Intraventricular administration through a reservoir results in a more even distribution of drug throughout the CSF and may prolong the duration of remission in CNS leukemia compared to intralumbar administration [20, 21]. In addition, the use of the Ommaya reservoir permits the administration of frequent small doses of methotrexate instead of single large doses. This “concentration times time” (C × T) therapy produces cytotoxic concentrations for a prolonged period while avoiding high peak drug levels.

Intravenous administration of methotrexate is also used in the treatment of meningeal disease. Although the CSF:plasma ratio for methotrexate is low, cytotoxic methotrexate concentrations can be attained in the CSF using very high intravenous doses. One such high-dose methotrexate regimen consisting of a 6000 mg/m^2 loading dose given over 1 h,
followed immediately by an infusion of 1200 mg/m²/h for 23 h resulted in cytotoxic steady-state CSF methotrexate concentrations and produced complete remissions in 16 of 20 children with meningeal relapse of ALL [22].

High-dose systemic methotrexate administration requires both intense hydration and alkalization of urine, and leucovorin rescue. Since methotrexate is eliminated by the renal tubule, adequate renal function should be confirmed prior to therapy, and serum creatinine and methotrexate concentrations should be monitored during therapy. If delayed clearance is encountered, intravenous hydration and leucovorin rescue should be increased. At methotrexate concentrations greater than 10⁻⁴ mol/l, however, leucovorin rescue may be ineffective [23]. In the presence of acute renal failure with severely delayed methotrexate excretion, administration of carboxypeptidase-G2 may be considered. The use of this enzyme results in a greater than 10-fold reduction of serum methotrexate concentrations within minutes of administration [24]. Information about the availability of carboxypeptidase for emergency use can be obtained from the National Cancer Institute.

Even with normal methotrexate clearance and adequate hydration and leucovorin rescue, toxicity after high-dose methotrexate is frequent. Moderate to severe mucositis and myelosuppression are common. Hepatic toxicity with elevated transaminases and bilirubin, as well as desquamating dermatitis of the hands and feet, can also occur. High-dose methotrexate, especially when given in association with cranial radiation, has also been associated with neurotoxicity [25, 26].

**Cytarabine**

Intrathecal cytarabine is used frequently in the treatment of meningeal metastasis. As with methotrexate, high CSF cytarabine concentrations with negligible systemic toxicity can be achieved by intrathecal cytarabine administration. Like methotrexate, cytarabine may be given by the intralumbar route or through a ventricular reservoir on a C x T schedule that results in cytotoxic CSF drug concentrations for a prolonged period without high peak levels [27]. In addition, cytarabine is often combined with methotrexate for intrathecal administration, especially in patients with leukemia.

Intrathecal administration of cytarabine may produce arachnoiditis or, rarely, other forms of neurotoxicity such as seizures and paraplegia [28]. Cytarabine therapy, however, has not been associated with leukoencephalopathy.

Cytarabine may also be administered systemically for the treatment of meningeal malignancy. A regimen of 3 g/m² administered every 12 h demonstrated activity in patients with meningeal leukemia [29], and 72-h continuous intravenous infusions of ≥4 g/m² also achieved cytotoxic CSF cytarabine concentrations [30]. High-dose systemic cytarabine administration is associated with significant toxicity, however. Cerebellar dysfunction requiring discontinuation of therapy may be seen in >20% of patients following multiple doses of 3 g/m² every 12 h [31]. Myelosuppression, nausea, vomiting and mucositis are also common at these doses.

**Corticosteroids**

Prednisone (the orally administered prodrug of prednisolone) and dexamethasone are widely used in the therapy of ALL. For both, the CSF concentrations are identical to the plasma concentrations of free drug. Since at equipotent doses dexamethasone is only 70% protein bound, whereas 90% of prednisolone is bound, dexamethasone penetrates much better into the CSF [32]. Patients receiving dexamethasone rather than prednisone have a significantly lower rate of CNS relapse [33].

**Thiotepa**

Thiotepa, a lipid-soluble alkylating agent, crosses the blood-brain barrier well after systemic administration. Furthermore, TEPA, an active metabolite of thiotepa, also penetrates very well into the CSF [34, 35]. Thus, systemic administration of this agent achieves high concentrations of both parent drug and active metabolite in the CSF. Systemic administration of thiotepa, however, produces profound bone marrow toxicity, especially thrombocytopenia. In contrast, intrathecal administration of thiotepa is well tolerated [36]. However, intrathecal administration of thiotepa may have some disadvantages compared to the systemic route. The active metabolite TEPA is not detected in the CSF after intrathecal administration. Furthermore, thiotepa diffuses rapidly out of the CSF space [34]. Nonetheless, intrathecal thiotepa may be useful in some settings.

**Diaziquone**

Diaziquone (AZQ) was specifically developed for its property of excellent CSF penetration after systemic administration. Unfortunately, severe myelosuppression limits the utility of this approach. Intrathecal diaziquone, however, is well tolerated at a dose of 1 mg administered twice weekly by either the intralumbar or intraventricular route and at a C x T dose of 0.5 mg every 6 h for three doses. More than 65% of patients had an objective response to this therapy, and two of four patients with meningeal spread of retinoblastoma had complete responses of three months’ duration [37].
6-MERCAPTOPURINE

6-mercaptopurine is commonly used in low oral doses as an antileukemic agent. Recent studies have shown that a 48-h intravenous infusion of 6-mercaptopurine at a dose rate of 50 mg/m²/h achieves cytotoxic concentrations in the CSF. The common toxicities include reversible hepatotoxicity, myelosuppression and mucositis [38]. Intrathecal administration of 6-mercaptopurine is also being explored. In children with refractory meningeal malignancy, a 10 mg intrathecal dose was well tolerated and produced cytotoxic concentrations in the CSF for over 12 h. Of nine patients treated at the 10 mg dose, there were four complete and three partial responses [39].

OTHER NEW AGENTS

Studies are under way with intrathecal administration of two preactivated derivatives of cyclophosphamide: mafosfamide and 4-hydroperoxycyclophosphamide (4HC). These agents have demonstrated activity in phase I trials against meningeal leukemia [40], medulloblastoma and ependymoma [41].

Topotecan, a topoisomerase I inhibitor, achieves a high degree of CSF penetration after intravenous administration [42]. A wide range of phase II studies of systemically administered topotecan in both CNS and non-CNS cancers are now under way. Intrathecally administered topotecan is also in the early stages of clinical testing.

The treatment of meningeal disease remains a difficult clinical problem. It seems likely that further improvements in the therapy of systemic cancer will continue to reveal a paradoxical increase in the frequency of meningeal metastasis. As this occurs, both the treatment of leptomeningeal cancer and CNS preventive therapy will require increased attention from researchers and clinicians alike. Although therapeutic options are expanding, much remains to be done to improve current treatment, and ultimately to prevent the development of meningeal malignancy.

REFERENCES


