Neoplastic meningitis: Keeping palliative care options open

Prognosis for patients with this complication is not good, but many still seek treatment, equating prolonged neurologic function with better quality of life.

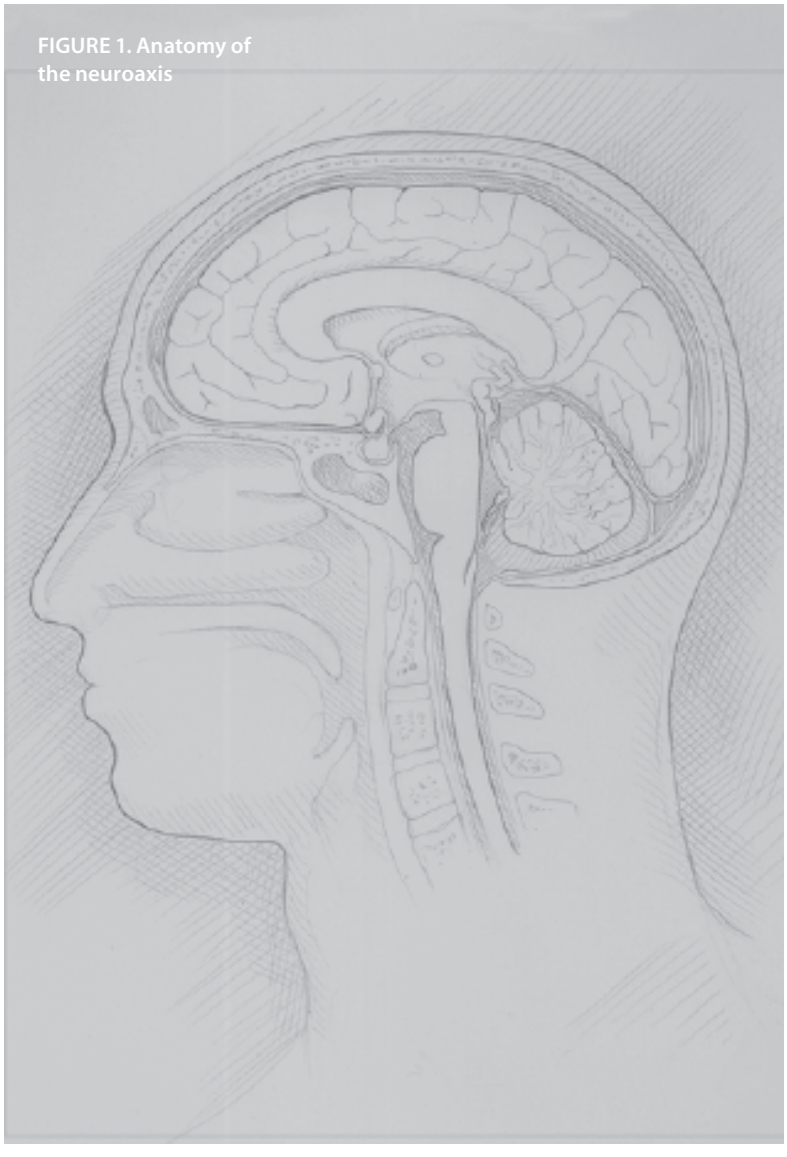

FIGURE 1. Anatomy of the neuroaxis

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Neoplastic meningitis is an increasingly frequent and devastating complication of both primary CNS and extraneural malignancies. The pathologic hallmark of neoplastic meningitis is the spread of malignant cells to the CSF.[1] Neurologic signs and symptoms frequently manifest as subtle or mild, tend to progress rapidly, and commonly result in profound morbidity and mortality. Diagnosis is often difficult, and treatment may be curative but is more often palliative as patients often have diffuse systemic disease.[2,3]

Neoplastic meningitis can occur at any level of the neuroaxis. The neuroaxis consists of the meninges (a three-layered, fibrous sheath that encloses the organs of the CNS), brain, spinal cord, and CSF (**Figure 1**). The choroid plexus produces CSF from arterial blood in the lateral and fourth ventricles of the brain at a rate of 600 to 700 mL every 24 hours.[4]

The average adult has approximately 140 mL of circulating CSF, 25 mL of which reside in the ventricle.[4] CSF functions as a cushion and lubricant for the structures of the CNS and has roles in homeostasis and nervous system metabolism.[4]

Malignant cells can gain access to the CSF and the structures of the neuroaxis through a variety of channels. Direct extension can occur from a solid tumor embedded in the brain parenchyma, or from vertebral, subdural, or epidural metastases.[5] Any metastases to the choroid plexus may allow malignant cells to shed into the CSF, or

spread may occur by retrograde invasion of peripheral or cranial nerves.[5]

The incidence of metastases to the CNS from solid tumor or hematologic malignancy has risen steadily since 1999.[6] This trend could be influenced by higher success rates of treatments that result in prolonged survival for patients with extraneural cancers and by poor access to or penetration into the CNS of chemotherapies, such as large molecule targeting agents.[1,5] Overall, 5% to 10% of all patients with cancer develop leptomeningeal metastasis.[7] True incidence data is difficult to obtain, and neoplastic meningitis in general is thought to be under-recognized, underdiagnosed, and undertreated. In addition, health care providers may be reluctant to pursue noncurative treatment in a highly morbid disease state.

THE DIAGNOSTIC TRIAD

Establishing the metastatic spread of malignant cells to the CNS is in part a process of elimination. Signs and symptoms are frequently attributable to other causes.[8] Currently, three methods are used to identify malignancy in the CNS: a thorough neurologic examination; MRI with and without gadolinium contrast; and CSF analysis, often of multiple samples.[8] The gold standard for diagnosis is positive results on cytology of the CSF; however, results for any of the above methods can stand alone as diagnostic criteria. To date, entry into a clinical trial for a treatment modality requires a positive cytology result.

A thorough, systematic **neurologic examination** can be a powerful tool for detecting the potential presence of neoplastic meningitis. Neurologic examination is designed to assess each of the three levels of the neuroaxis, and a carefully performed examination can be used to determine the functional status of the CNS. Physical examination should be combined with careful questioning of both the patient and the caregiver.

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MRI of the brain with and without contrast can demonstrate areas of suspected neoplastic disease metastasis.[9] In addition, MRI can help pinpoint lesions that may be candidates for focal radiation, especially lesions that fully or partially obstruct CSF flow or produce distressing neurological symptoms such as weakness or radicular pain.[1] MRI of the entire neuroaxis—brain and cervical, thoracic, lumbar, and sacral spine—is necessary because disease may be present in any or all of these areas regardless of observable signs or symptoms.[10]

The final component of the diagnostic triad is CSF analysis. **Lumbar puncture** is the typical method used to obtain a CSF sample and can be performed in the outpatient setting. A CSF sample can also be obtained via a ventricular access device, such as an Ommaya reservoir. The CSF is assessed for appearance (healthy fluid is clear and colorless), protein (heavy concentrations may produce a yellowish cast; normal range, 15 to 45 mg/dL), glucose (normal range, 50 to 80 mg/dL or approximately two-thirds of serum glucose), and cell count (RBC, 1,000 to 5,000/μL; WBC, 0).[11,12] Cytologic examination is performed to determine the presence of malignant cells. Sample size needed for cytology is at least 10 mL of CSF, and a 3- to 5-mL sample is needed for routine studies.[8] CSF sample should be fixed in preservative at the patient's bedside because malignant cells degrade rapidly.[8]

Clinicians should note that findings from the diagnostic triad do not always correspond. Presence of only radiographic or cytologic evidence is common, and either should be considered independently diagnostic for neoplastic disease in the CNS.[10]

TREATMENT OPTIONS

Management of patients with neoplastic meningitis is ideally multimodal. Determining the status of the underlying systemic disease is the first step in treatment planning. Identification of any extraneural sites of metastasis via positron emission tomography (PET), MRI, or other imaging studies is also necessary.[10] Treatment focuses on controlling progression of the underlying disease in patients with advanced cancer, palliating distressing symptoms, and delaying neurologic progression and the advent of new focal deficits.[2] Standard treatment approaches typically include focal radiation to lesions that are bulky, obstruct CSF flow, or produce debilitating symptoms.[1] Distressing symptoms should be treated aggressively.

Intrathecal chemotherapy agents administered directly into the CSF is another standard component of the treatment regimen for neoplastic meningitis.[1] Methotrexate, cytarabine, and cytarabine liposome are cell cycle-specific cytotoxic agents used for intrathecal chemotherapy. Trials that used other chemotherapeutic agents (rituximab, trastuzumab, and topotecan as single agents and in combination with the standard treatments) have been published.

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Intrathecal chemotherapy agents can be administered via a lumbar puncture or through an intraventricular access device. Methotrexate and cytarabine have significantly shorter durations of cytotoxic concentration compared with liposomal cytarabine; therefore, they require more frequent dosing (eg, twice a week for methotrexate and cytarabine vs once every 2 weeks for liposomal cytarabine).[2,10] Short-term use of the corticosteroid dexamethasone is always required during peritreatment with liposomal cytarabine to prevent or ameliorate chemical meningitis, also known as arachnoiditis; dexamethasone may also be required during peritreatment with methotrexate and cytarabine.[13] A patient on a chronic corticosteroid may require a stress dose, or temporary increase, that mirrors the required dose. Patients with a long-term, exogenous source of corticosteroid, such as dexamethasone, experience a shutdown of the adrenal glands, where these corticosteroids are produced endogenously. Therefore, they cannot respond to an increased need spontaneously, and the dose needs to be increased to substitute what would have been the body's natural response.

Methotrexate and cytarabine are well-established treatments. Although liposomal cytarabine may be less familiar to some clinicians, the literature suggests that its structure—cytarabine encapsulated in a lipid complex—allows the cytotoxicity of the drug to be extended and results in more efficacious clearing of malignant cells from the CSF.[14] In addition, the extended cytotoxicity of this drug is advantageous when an intralumbar route is utilized.[13,15] Lastly, some published data suggest that patients treated with the liposomal preparation have improved Karnofsky performance scores and longer neurologic stability.[8,15]

Intrathecal chemotherapy is typically administered in the outpatient setting (a clinic, the office, or an infusion center). No premedication (other than dexamethasone), hydration, or special monitoring is required. Standard lumbar puncture kits contain most of the necessary supplies, including sterile gauze pads, an alcohol swab, a 23-gauge butterfly needle, a three-way stopcock, and four 10-mL syringes; sterile gloves and betadine solution (not swabs) are also needed. As mentioned above, preserving the cytology specimen at the bedside in 10% formalin fixative (usually in a 50-mL centrifuge tube) is recommended. The importance of maintaining sterility cannot be overstated; contamination of an intraventricular device can result in bacterial meningitis, which may necessitate removal of the reservoir.[16] Standard chemotherapy precautions are necessary with all three drugs and include monitoring immediate adverse reactions and sterilizing any areas that may have come in contact with contaminants.

Patients may experience headache and fatigue while receiving intrathecal chemotherapy. Arachnoiditis, or chemical meningitis, is the most common side effect and manifests as headache, fever, stiff neck, and general malaise.[8,13,17] Patients may also have signs of mental status change or experience seizures. CSF WBC count may be elevated even in the absence of infection.[18] Patients usually respond to a marked but temporary increase in dexamethasone, followed by a slow taper as symptoms become better controlled. True infection can be ruled out with a CSF culture.[5]

The recommended treatment duration for intrathecal cytotoxic agents is not clearly delineated in the literature. The usual treatment regimen for methotrexate or cytarabine is two treatments per week for 4 weeks, and then continuing until the CSF consistently demonstrates no evidence of malignant cells or until the patient's functional status declines, precluding their candidacy for treatment.[13] Liposomal cytarabine is administered on a 5×5 regimen, which is a regimen utilized in several clinical trials. The first five doses are given at 2-week intervals and the remaining five are given at monthly intervals, again with sensitivity to the patient's condition and tolerance of the drug.[8,17] Patients should be screened at each visit for disease progression or regression via a thorough neurologic examination and CSF analysis. Close questioning of patients and caregivers, using repetitive phrasing, regarding the patient's functional status can lend valuable insight into treatment response, as the overall goal is palliation.

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TREATMENT PROGNOSIS

The prognosis for patients with neoplastic meningitis remains poor despite aggressive, multimodal treatment directed at the CNS as well as the underlying disease, where appropriate; median survival from the point of diagnosis is 2 to 6 months.[1,10,19] Although the presence and severity of any underlying or concurrent systemic disease impacts outcomes, neoplastic meningitis is resistant to treatment and significantly increases patient morbidity and mortality.

Early identification and early aggressive treatment may stabilize or slow disease progression, especially if symptoms

are limited to a single CNS domain and the patient retains normal or near-normal neurologic function.[2,14,19] If treatment is instituted after a neurologic deficit manifests, disease typically does not regress or improve but usually does stabilize. This stabilization benefits patients' quality of life and eases the burden on caregivers. Maintaining neurologic function is an important quality-of-life factor; research suggests that many patients would elect to have treatment that has no demonstrable survival advantage if functional status could be protected for a period of time.[13] Given the scope and severity of symptoms that a patient with neoplastic meningitis might experience, raising awareness about the disease would clearly benefit patients.

Nurses need to think holistically about patients with neoplastic meningitis. These patients may have endured multiple treatment regimens and often their resources—physical, emotional, and spiritual, as well as financial—are depleted. Ensuring that patients can meet the financial and transportation requirements of treatment—either twice a week or twice a month—can avoid delays and interruptions. Opening a dialogue that addresses realistic expectations of the treatment plan is critical. Patients should be encouraged to identify their goals and express their feelings about palliative-directed care (versus curative care). Signs and symptoms, especially those indicating disease progression or adverse reactions, should be discussed with patients and caregivers and reinforced at each encounter. Follow-up phone calls are also helpful.

Aggressive symptom management for all patients, even those who do not elect treatment, includes opiates for pain, including headache; anticonvulsants or tricyclic antidepressants for neuropathic pain; and corticosteroids for intracranial vasogenic edema, raised intracranial pressure, and nausea and vomiting.[20] The use of stimulant drugs, such as modafinil and methylphenidate, is controversial; however, some literature suggests that these drugs help patients with advanced cancer who have pervasive generalized fatigue. Nurses should encourage patients and caregivers to call as soon as a symptom develops or worsens to prevent the occurrence of more severe or persistent symptoms. Reporting symptoms may also provide patients with a feeling of empowerment and participation and can support or establish a rapport with and foster confidence in the health care team.

The appropriateness of an individual patient for treatment should be determined prior to making a decision regarding available treatment strategies and regimens. Again, assessing the patient's goals and expectations of treatment and its outcomes is crucial. Patients with very low Karnofsky performance status scores, significant comorbidities, poor responses, an inability to tolerate previous treatment regimens, or extensive systemic disease that will not be concurrently treated may not be candidates for palliative treatment. Patients for whom treatment is an option can be further stratified according to risk status versus potential benefit of treatment.[10] Patients with a good ratio of risk may benefit more from treatment; however, patients with poor risk status or who have particularly chemosensitive tumors (eg, small cell lung cancer, lymphoma) may still derive significant benefit from palliative treatment.[21]

NIHILISM AND PALLIATIVE CARE

Many clinicians observe a sense of hopelessness in patients with neoplastic meningitis, many of whom have end-stage disease and have undergone multiple treatments involving several body systems over an extended period of time. Patients adjust to declining functional status over time, which enhances their ability to maintain a sense of purpose and pursue treatment with undiminished hope. Clinicians, however, may not share this readiness to undertake treatment, especially if they have experience treating patients with this disease. These clinicians understand that treatment is noncurative, has physical and financial consequences, and has a success rate that is subjective and difficult to predict at the outset. However, some patients do grasp that delaying neurologic decline preserves quality of life.

Unfortunately, the oncology care provider has many opportunities to inform the patient of disease progression or poor treatment response, as well as the development of complications that can delay or disrupt treatment. The provider also experiences the anguish of coping with the inevitability of a shortened life span. A nurse who knows that cancer will ultimately prevail may have nihilistic thoughts (eg, "Why should I advocate treatment that has such modest survival benefit?"). Despite the conflicting emotions and viewpoints, a patient with neoplastic meningitis needs and can benefit from palliative care. Oncology nurses should discuss treatment options with every patient, regardless of his or her prognosis.

> Performance scores have a role in assessing quality of life, but only the patient can determine whether palliation has been achieved.

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Palliation in this disease state refers to maintaining functional status, relieving distressing symptoms, and slowing disease progression.[10] Palliation is the desired outcome; therefore, defining success is an important component of planning treatment. Clinicians should discuss what quality of life means to the patient, not as a conversation but as an ongoing dialogue, in order to assist the patient in developing realistic treatment expectations. Although cytologic clearing may be the standard measure of a positive response to therapy, the nurse should consider the patient's subjective reports of symptoms and functionality as well as input from caregivers when assessing efficacy and planning the treatment course. This is because indications of positive response to therapy also include slowing or halting disease progression, mitigating existing symptoms, and reducing the need for corticosteroids.[10] Performance scores have a role in assessing quality of life, but only the patient can say whether palliation is achieved.

Although listening to the patient is a major component of oncology care, talking about aggressive symptom management can be relegated to an as-needed conversation because the focus is on curation. In cases of neoplastic meningitis, which is an advanced and progressive disease, the patient needs to know that the clinician's commitment to palliation is equal to that of cure and that distressing symptoms will be promptly addressed. Conversely, patients should be counseled that they have a responsibility to report any symptoms they experience accurately.

The nurse should establish a rapport with the patient's caregivers in light of the high rate of cognitive and memory impairment.

Common supportive measures include administering antidepressants and anxiolytics, stimulants to counter pervasive fatigue, and prophlaxis for deep venous thrombosis; advocating for, communicating with, and coordinating home-based services and durable medical equipment; providing lists of advocacy and education organizations; providing emergency instructions and contact information; and educating patients and caregivers about infection, infection control, skin care, and nutrition. Establishing a rapport with the patient's caregivers is especially important in light of the high incidence of cognitive and memory impairment. Clinical team strategies for care of the patient with neoplastic meningitis are preventive and reactive. Treatment preparation includes education about administration methods, side effects, adverse effects, and pretreatment with corticosteroids.

CONCLUSION

Neoplastic meningitis is a devastating, late-stage disease that may develop in a patient with a hematologic, primary CNS, or solid tumor malignancy. The disease is associated with high morbidity and mortality and has a negative impact on the patient's functional status and quality of life. A high index of suspicion for the presence of malignant cells in the neuroaxis can result in an earlier diagnosis, which correlates with increased treatment options, delayed progression of neurologic sequelae, and improved quality of life. Quality of life matters to the patient regardless of the disease state, even in the absence of curative treatment. Therefore, providing palliative therapies that preserve neurologic function and maintain quality of life is an appropriate response to this challenging diagnosis. ■

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DRUGS MENTIONED

Cytarabine (Cytosar-U, generics)
Cytarabine liposome (Depocyt)
Dexamethasone
Methotrexate (Amethopterin, MTX, generics)
Methylphenidate
Modafinil (Provigil)
Rituximab (Rituxan)
Topotecan (Hycamtin)
Trastuzumab (Herceptin)

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