Once considered the culmination of metastatic disease and a marker of the terminal end of a patient’s experience with cancer, leptomeningeal disease (LMD), also known as neoplastic meningitis and carcinomatous meningitis, has become an increasingly frequent complication of cancers (Bomgaars, Chamberlain, Poplack, & Blaney, 2002). LMD may even occur when a patient is in systemic remission. As patients live longer, leptomeningeal tissues increasingly play host to malignant cells, requiring clinicians to be alert for the signs and symptoms heralding their involvement. Research in the diagnosis and treatment of LMD is growing as prevalence rises. Although prognosis remains poor and treatment mostly is palliative, some patients are experiencing improved quality of life and length of survival with conscientious management of LMD and its symptoms.

Case Report

Ms. A is a 27-year-old woman who was diagnosed with right temporoparietal glioblastoma (GBM) in 2004. She underwent resection with placement of carmustine wafers followed by chemoradiation with concurrent temozolomide. In 2005, she had progression of her tumor and underwent a second resection with pathology consistent with GBM and radiation necrosis, followed by multiple chemotherapy regimens as the tumor continued to progress. In 2007, Ms. A was diagnosed with LMD and had an ommaya reservoir placed. She was treated with intrathecal topotecan from September 2007 to April 2008. She also received radiation to the lumbar spine for metastasis at L1 from September to October 2007. In addition, she received systemic treatment with 6-thioguanine, lomustine, capecitabine, and celecoxib from August 2007 to April 2008. Systemic therapy then was stopped because of bone marrow suppression, but she continued to receive topotecan intrathecally. In April 2008, Ms. A evidenced rising cerebral spinal fluid (CSF) protein higher than 200 mg/dl, indicating progressive disease, and topotecan was changed to methotrexate. She then experienced significant myelosuppression, so intrathecal chemotherapy was stopped on April 24, 2008. After bone marrow recovery, Ms. A was placed on protocol 2007-0931 with ANG1005, a peptide designed to cross the blood-brain barrier and release paclitaxel within the tumor (Angiochem, Inc., 2006). Protocol stopped on July 11, 2008, because of further disease progression. Ms. A began dose-dense temozolomide with sorafenib in August 2008, which she continues to date.

Prevalence

About 5% of all patients with cancer will develop LMD (Larson, Rubenstein, & McDermott, 2005). Although LMD can occur with any cancer, certain types carry a greater propensity, including breast cancer, small cell lung cancer, leukemia, non-Hodgkin lymphoma, and melanoma (Bomgaars et al., 2002; Pentheroudakis & Pavlidis, 2005). Solid tumors of the central nervous system (CNS) also may metastasize to the leptomeninges. Patients with low-grade intracranial tumors, such as pilocytic astrocytoma, are affected at a rate of 5%-10%, with higher levels related to progressive disease (Abel et al., 2006). A study by Sarker, Thirlwell, Nelson, Gazzard, and Bower (2003) examined LMD occurrence in AIDS-related non-Hodgkin lymphoma and found that 10% of patients in the study had evidence of LMD at presentation; patients with Burkitt lymphoma or disease involvement in the paraspinal and paranasal regions represented the greatest number of LMD cases.

About 25% of patients with small cell lung cancer and 5% of patients with breast cancer will develop LMD (McAllister, Ward, Schulman, & DeAngelis, 2002). Twenty-five percent of patients with metastatic melanoma also will develop LMD (Larson et al., 2005).

Pathophysiology

LMD occurs when malignant cells migrate from a primary site and infiltrate the meningeal membranes of the brain and spinal cord. Maroldi, Ambrosi, and Farina (2005) described the brain as a possible “sanctuary site” in which metastatic lesions grow and become troublesome clinically even though systemic disease may be in remission. Maroldi et al. postulated that the growth may occur because most systemic chemotherapy cannot penetrate the blood-brain barrier. Spread of malignant cells through the vascular system appears to be the most common route of infiltration. Tumor cells may seed brain parenchyma when in cerebral circulation.
Additional metastasis then may occur into the subarachnoid space, where tumor cells enter the CSF; the metastasis may result in neoplastic infiltration of the leptomeninges of the brain and spinal cord (Maroldi et al.). Patients with leukemia have a risk for extravasation of leukemic cells across capillary membranes in the brain (Lange, Brouwer, Brooimans, & Vecht, 2007). Metastasis also may occur through the bone marrow in the skull itself (Larson et al., 2005). Risk for LMD appears to be higher after surgical resection of metastatic lesions of the posterior fossa. Siomin et al. (2004) attributed the risk to “disruption of the metastatic pseudocapsule,” which may cause seeding of the tumor in the CSF as well as CSF contact with residual fragments during resection. After a tumor has metastasized to the vertebral area, spread may occur along either nerve or lymphatic routes into the subarachnoid space (Taillibert et al., 2005), where the tumor disseminates into the CSF and may seed the leptomeningeal tissues. Primary CNS tumors also may disseminate into the leptomeninges by direct contact or through CSF (Taillibert et al.).

Presentation

The most frequently occurring symptoms in patients with developing leptomeningeal involvement are altered mental status and cranial nerve involvement, with optic neuropathy occurring in 28% of patients with cranial nerve deficits (Lange et al., 2007). Subacute and progressively worsening headache presents frequently (Wheen, Anderson, Baker, Singh, & Synec, 2006). Cerebellar disease may manifest with gradually worsening balance and dysmetria (the ability to accurately gauge muscle movements). Meningeal irritation of the brain most often results in seizure activity (McAllister et al., 2002). In patients with spinal cord disease, symptoms will relate to the level of involvement. Patients often complain of radicular pain and weakness of the upper or lower extremities. Fecal or urinary incontinence or retention also may occur in lower spinal lesions.

Diagnosis

Diagnosis of LMD is difficult, frequently requiring repetitive diagnostic studies that often yield false-negative results; therefore, clinical signs and symptoms are vital in the diagnosis. Taillibert et al. (2005) noted that clinical indicators may appear to be random, with various combinations of signs and symptoms in the brain, spinal cord, cranial nerves, and spinal roots. Taillibert et al. suggested that the multifocal nature of signs, often without associated symptoms (e.g., radicular pain, headaches), is key in making a diagnosis.

Magnetic resonance imaging (MRI) of the brain and spine is standard for detecting LMD and is superior to computed tomography (CT) scanning, which may fail to visualize 58% of cases; MRI has a false-negative rate of about 30% (Sherman, Jaecelle, & Meyers, 2002) (see Figure 1). Common findings on MRI are enhancement of the leptomeninges or cranial nerves and hydrocephalus (Maroldi et al., 2005). When suspicion for LMD exists, lumbar puncture should be performed to evaluate the CSF for evidence of malignant cells. Although elevation of CSF protein (normal range = 10–45 mg/dl) is a useful marker for LMD, finding cancer cells in the CSF is diagnostic. However, CSF cytology evaluation has a high false-negative rate. Sensitivity improves with multiple lumbar punctures, rising to about 90% at the third sampling. Sample volume also is important, with a minimum of 10 cc required (Taillibert et al., 2005). In patients with hematologic cancers, such as B-cell lymphoma or Waldenstrom macroglobulinemia, flow cytometry of the CSF is helpful in diagnosing LMD. Flow cytometry may double the number of LMD cases detected over routine cytology studies (Lange et al., 2007). In a study by Hegde et al. (2005), 11 of 51 patients (22%) with newly diagnosed B-cell lymphomas were diagnosed with LMD by flow cytometry, and only one patient also had positive CSF cytology. In addition, two of nine treated patients were diagnosed with LMD by flow cytometry, with only one diagnosed by cytology (Hegde et al.).

Prognosis

Leptomeningeal metastasis generally is a late sign of advanced cancer. Prognosis is poor, with an average survival time of three to six months with treatment (Larson et al., 2005) and only four to six weeks without treatment (Mehta & Bradley, 2005). Patients with well-controlled systemic disease with good performance status often survive longer (Pentheroudakis & Pavlidis, 2005). Cognitive ability and functional status at time of diagnosis may be indicators of life expectancy. Sherman et al. (2002) predicted that patients with greater neuropsychological deficits before treatment for LMD will have a shorter life expectancy than those with higher functioning; they found that baseline cognitive performance (at the time of LMD diagnosis and before treatment) correlated positively and significantly with length of survival.

Treatment

Treatment of LMD is palliative, with the goal of improving survival time while managing symptoms and improving patients’ quality of life. Efforts to reduce tumor burden include chemotherapy, radiation, and occasionally stereotactic radiosurgery. Radiation therapy may shrink the lesions, which increases patient comfort, decreases intracranial pressure, and possibly
opens the CSF flow tracts, allowing for the administration of intrathecal chemotherapy (Mehta & Bradley, 2005). Radiation may be provided concomitantly with intrathecal or systemic chemotherapy. High-dose methotrexate administered systemically has been effective in overcoming the blood-brain barrier when used with leucovorin calcium rescue (Bomgaars et al., 2002). Cytarabine also may be given systemically but is associated with higher toxicity than methotrexate. Cytarabine may become neurotoxic in high doses, resulting in severe cerebellar dysfunction that may not resolve after treatment is stopped (Bomgaars et al.).

Intrathecal chemotherapy is administered either by lumbar puncture or via ommaya reservoir (see Figure 2). An ommaya reservoir is a port that is surgically placed under the scalp. A burr hole in the skull allows a catheter to extend from the reservoir into a lateral ventricle of the brain. Greenfield and Bilsky (2005) discussed the many advantages of ommaya reservoir versus repeated lumbar punctures, stating that chemotherapy given directly into the ventricle provides a better volume of drug distribution than when administered via lumbar puncture. In addition, hydrocephalus is managed more easily in patients with an ommaya reservoir (Aiello-Laws & Rutledge, 2008; Greenfield & Bilsky).

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Advanced Practice Nurse Interventions

Advanced practice nurses (APNs) are vital in helping patients receive adequate diagnostic studies when suspicion for LMD exists. Because APNs tend to have more frequent and longer interaction with patients and families than physicians, they often notice subtle neurologic changes in mental status, cranial nerves, or strength. The function is vital particularly in patients with cancers that have a high risk of leptomeningeal metastasis, such as those with breast cancer, small cell lung cancer, leukemia, lymphoma, and melanoma. The author’s institution operates an APN-led procedure clinic in which therapeutic and diagnostic lumbar punctures and ommaya taps are performed routinely by APNs. Intrathecal chemotherapy is often administered by APNs either through an ommaya reservoir or directly into the lumbar intrathecal sac. Because of the adverse effects of neurologic symptoms, the side effects of treatment, psychosocial and financial issues, and other stressors, frequent therapeutic contact with APNs may positively affect quality of life in patients with LMD.

Patients with LMD usually are seen on a semi- to biweekly basis for treatment, which increases the opportunity to detect treatment- or disease-related complications between physician appointments, allowing earlier intervention. Frequent contact also allows healthcare providers to teach and reinforce ways to manage chemotherapy side effects and disease-related health effects. Because patients with LMD often suffer with visual deficits, weakness, and uncertain balance, APNs should assess whether a home safety evaluation or extra assistance for caregivers is needed. A social work or case management consultation often is helpful for patients with LMD. By collaborating with physicians to provide timely interventions to decrease CSF pressure, address chemotherapy-related side effects, and decrease tumor burden by administering intrathecal chemotherapy, APNs address significant neurologic symptoms, such as intracranial pressure–related headache. The APN-led procedure clinic fosters a therapeutic relationship with patients, which can assist them in coping with their disease. By providing psychosocial support during the LMD experience, APNs may be instrumental in reducing mood disturbances in their patients (Von Ah & Kang, 2008).

Conclusion

Five years after her initial diagnosis, Ms. A continues to work and care for her seven-year-old son, despite the life-limiting nature of her disease. A social work consultation has been requested to assist her on matters related to the guardianship of her son after her death.

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