Neurologic Complications of Cancer and Cancer Therapy

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Neurologic complications that occur as a result of systemic cancer and its treatment can be more disabling for patients than their primary cancer and significantly impair functioning in varied domains. However, recognizing neurologic signs and symptoms as complications of cancer and its treatment can pose a challenge for healthcare providers. Oncology nurses must develop a high index of suspicion for neurologic complications when examining or interviewing patients who present with neurologic symptoms or deficits and have a known systemic cancer. The purpose of this article is to help oncology nurses identify the common presentations of those complications and understand the ways in which they occur, with the hope that early identification will facilitate appropriate medical intervention and slow the progression of neurologic deficits and systemic decline.

Neurologic complications can be categorized as direct or indirect, based on their underlying cause (DeAngelis & Posner, 2009). Direct complications refer to those caused by metastases or spread from the site of the primary cancer to the central nervous system (CNS) or the peripheral nervous system. In the CNS, metastasis may involve the brain or spine parenchyma or the subarachnoid space. In the peripheral nervous system, spread usually moves by infiltration of nerve roots, plexi, or muscle from neighboring malignancies. Indirect complications refer to those resulting from treatment (chemotherapy or radiation), from abnormal immune responses to cancer (e.g., paraneoplastic syndromes), or as a result of coagulation disorders causing cerebrovascular complications. The suppressive effect of cancer and its treatment on the immune system also can result in infectious complications within the nervous system, and chemotherapies may cause toxic metabolic conditions (e.g., coagulopathy, paraneoplastic syndrome, encephalopathy) that result in neurologic complications.
Direct Complications

Metastatic disease is a common direct cause of neurologic complications of cancer, affecting about 10%–40% of all patients with cancer (Kienast & Winkler, 2010). Cancers that metastasize to the CNS carry a poor overall prognosis, although the rate of median survival has been positively affected by modern therapies, better prevention and management of common complications, as well as an increased use of advanced imaging for early detection (Wadasadawala, Gupta, Bagul, & Patil, 2007).

The CNS is normally a sanctuary site, protected by the blood brain barrier (BBB), an anatomic and physiologic feature that discourages penetration of some chemical compounds and pathogens into the intracranial circulation (Van Horn & Chamberlain, 2012). The dense network of endothelial cells that comprise the BBB not only provide a physical barrier, but also express a high level of proteins that pump foreign molecules away from the brain circulation. However, this privileged area may be at risk by the very nature of its exclusion because it can prevent chemotherapy agents given for systemic disease from penetrating the neuro-axis. Alternately, the use of some systemic chemotherapy agents is believed to transiently disrupt the BBB, which may allow systemic disease to seed in the cerebrospinal fluid (CSF) (Tse & Lorenzo, 2011).

CNS metastasis occurs through a variety of mechanisms, including hematogenous spread via the complex process of metastatic cascade (Cashman, 2010; Liotta & Kohn, 2003), which is a multistep process that results in disruption of the BBB. Direct extension from a primary tumor may occur, or cells may be transported through the valveless venous plexus. Tse and Lorenzo (2011) found that the most common sources of primary tumor in patients with brain metastases are lung (21%), skin (melanoma) (40%), breast (9%), colorectal (3%), and lymphoma (mainly non-Hodgkin) (1%). Migration along the chasms carved in the extracellular matrix by nerves or vasculature or via lymphatic drainage channels may allow individual cells or cell clumps to access the CSF, or malignant cells may escape from the choroid plexus, a structure seated in the lateral ventricles and the primary site of CSF manufacture (Bartsch, Staren, & Appert, 2005). Lastly, iatrogenic seeding may take place, such as when treatments such as surgery allow the introduction or dissemination of cells within the CNS. Discovery of CNS metastases usually is concurrent with the finding of other extra-CNS metastatic sites (DeAngelis & Posner, 2009). Lung, breast, skin (melanoma), kidney (renal cell), colorectal, and genitourinary cancers have the highest rates of metastasis to the CNS (Adams, 2008; Kesari & Batchelor, 2003).

The presenting symptoms of metastatic disease to the CNS are related to their location, the tumor volume, and the metabolic activity or degree of aggressiveness of the disease. About 25% of all CNS metastases occur in the cerebellum, or the hindbrain (DeAngelis & Posner, 2009). This region of the brain receives information from sensory systems in the spinal cord as well as the vestibular system. The cerebellum is a component of the complex system that is responsible for motor movement, coordination, equilibrium, proprioception (the sense of where one is in space in relation to other objects), and muscle tone (Hansen & Koeppen, 2004). Patients may exhibit gait disorders, including a wide-based stance, circumduction (wide arc of leg when ambulating), or diminished arm swing, as well as impaired balance and dysarthria (difficulty with speech production). Dysfunction of the vestibular system may manifest as dysmetria, an inability to control a range of movement (DeAngelis & Posner, 2009). Dysmetria is related to proprioception and can be demonstrated using visuospatial tests, such as touching finger to nose, but also may be elicited with a Romberg test, tandem walking (foot to heel), rubbering heel to shin, or two-point discrimination. Neurologic symptoms, such as those originating in the cerebellum, are quite noticeable to the patient and are likely to affect functional capacity as well as cause falls and other accidents that can lead to injury and disability.

Metastases to other regions of the brain parenchyma may present with more global symptoms such as cognitive deficits, seizures, and headache (Armstrong & Gilbert, 2000; Lu-Emerson & Eichler, 2012). The most common presenting symptom is malignant headache. The hallmark of malignant headache is its time of occurrence—typically waking a patient from sleep or occurring upon awakening. The pain associated with malignant headache is related to increased intracranial pressure, most evident after a period of lying flat. Because the brain has no pain receptors, this type of headache is rarely relieved with narcotics. Steroids, because they address cerebral edema, usually do offer relief (Tsao, Khuntia, & Mehta, 2012). Other symptoms related to this type of headache that are cause for concern include accompaniment by visual changes, gait or balance disturbance, nausea and vomiting, and change in mental state.
status. These symptoms also relate to increased intracranial pressure. The headaches tend to be persistent and progressive, occurring more frequently with lengthening duration and increasing intensity (Argyriou et al., 2006; Jeyapalan & Batchelor, 2000; Yamanaka, Koga, Yamamoto, Sano, & Fukushige, 2011).

Cognitive impairment also is a common presenting symptom of direct metastasis to the brain. Patients may experience dementia, which is characterized by an impairment of memory, or delirium, which is characterized by an impairment of attention (Khasraw & Posner, 2010). These disorders share some characteristics, but in delirium the effects may be reversible, whereas dementia has a more chronic trajectory. Patients with delirium may exhibit rapid onset of confusion, disorientation, reduced attention span, and misperceptions. Conversely, delirium also may present in a hypoactive form in which the patient withdraws from social interaction and demonstrates a paucity of language (Khasraw & Posner, 2010). That type of delirium can be mistaken for depression. Of note, delirium also may have a metabolic root cause and, in general, the toxic deliriums have a better prognosis than those related to disease infiltration to the CNS (Khasraw & Posner, 2010).

Cognitive deficits or change in thought processing, memory, recall, spatial relationships, speech and language, and executive function often are noted by the patient’s family first. They will report that the patient repeats him or herself more than usual, gets lost while driving, has difficulty finding words, cannot manage the checkbook, or has lost interest in reading or other activities requiring concentration. Cognitive deficits are measurable by employing an assessment tool such as the Montreal Cognitive Assessment (Olson et al., 2011). These tools allow relatively brief, focused assessments that screen for changes or deficits in cognition. Chemotherapy-related cognitive impairment occurs in as many as 75% of patients receiving a variety of chemotherapy agents (Dietrich, Monje, Wefel, & Meyers, 2008).

Seizure is another common presentation of metastatic disease to the brain (DeAngelis & Posner, 2009). Seizures may be generalized, involving uncontrolled movement, loss of consciousness, or loss of bowel or bladder control. They also may be focal in nature, affecting a particular limb (motor) or sensory area. Seizures may result from lesions in the brain parenchyma or as a result of penetration into the CSF, as in the case of leptomeningeal disease. These also may manifest as gustatory (taste), olfactory (smell), visual, and aural (hearing) hallucinations (Gleissner & Chamberlain, 2006). These sensory seizures usually are noxious in nature (e.g., the patient smells or tastes something unpleasant). Metastatic melanoma lesions have a tendency to bleed, which often will trigger seizure activity. Other tumors associated with intracranial bleeding include thyroid and renal cell carcinomas (Tse & Lorenzo, 2011). Although 24% of patients with brain metastasis have seizures, about 67% of patients with melanoma and CNS metastases have seizures (DeAngelis & Posner, 2009). They also are more common in patients with multiple metastatic loci and with combined brain and leptomeningeal metastasis (DeAngelis & Posner, 2009).

Malignant cells may access the CSF, coat the meninges, or deposit on the cranial or peripheral nerves—referred to as neoplastic meningitis or leptomeningeal disease. Common signs of this process are cranial nerve involvement such as changes in oculomotor movement, decreased visual acuity, diplopia, facial asymmetry or weakness, difficulties with swallowing or speech production, and changes in hearing (Gleissner & Chamberlain, 2006).

Direct neurologic complications of cancer may affect the peripheral nervous system. Nerve root involvement can result in painful and disabling peripheral neuropathies. A tumor can cause a crushing injury to nerve roots or cause impingement of a nerve fiber. The nerve cell, or neuron, also can be damaged by malignant cells.

Peripheral neuropathies occurring when a spinal nerve root is involved may include paresthesia, weakness, radicular pain, or bowel and bladder dysfunction. Paresthesia may manifest as tingling, burning, or a pins-and-needles sensation. Radicular pain follows the distribution path of a nerve root and often is described as burning, shooting, electrical, or lancinating (i.e., stabbing, piercing, or cutting) pain. It may occur along the length of the nerve or at a site distal to the impingement (Kesari & Batchelor, 2003). For example, cervical nerve root impingement may result in a distinct, localized burning sensation at a point along the arm, hand, or in a finger. Bowel and bladder dysfunction most often presents as loss of tone or decrease in sensation in addition to an increased urgency to void or evacuate. That type of dysfunction may be compounded by, or mistaken for, a steroid myopathy if the patient has been maintained chronically on steroids. Steroid myopathy is characterized by proximal muscle weakness, resulting in decreased strength and tone in the large muscles close to the trunk, including the gluteals, hamstrings, and quadriceps. That weakness makes it more difficult for patients to move from standing to sitting, and this delay may result in bowel or bladder accidents that are not related to actual functional deficits of the nerve. Careful questioning around the circumstances of bowel and bladder dysfunction can assist in determining the root cause. New onset of bowel and bladder incontinence may be related to cord compression or cauda equina syndrome, so these symptoms should be evaluated immediately as they could represent a neurologic emergency.

The prognosis for patients who have direct neurologic complications of cancer is poor (DeAngelis & Posner, 2009). In part, that reflects the status of the primary disease. Patients whose systemic cancers respond to treatment have a prognostic advantage, as do those patients with Karnofsky Performance Scores greater than 70, are younger than 65 years, have responded well to steroid and chemotherapy treatments in the past, have fewer than three metastatic lesions, and whose metastatic disease is limited to the CNS (Khasraw & Posner, 2010).

**Indirect Neurologic Complications of Cancer and Cancer Treatment**

In contrast to metastatic disease or the direct causality from systemic disease, neurologic complications also can occur as a result of treatment or other physiologic responses related to the primary cancer. The modalities with the highest incidence of indirect neurologic complications are chemotherapy and radiation to the CNS. In addition, infection, coagulability disorders,
and metabolic disarray can cause neurologic deficit in the setting of systemic cancer.

**Chemotherapy**

Several classes of chemotherapy are known to be neurotoxic (see Table 1). The platinum-based agents, including cisplatin, carboplatin, and oxaliplatin, have a broad spectrum of effects against several solid tumor types. Cisplatin is a first-generation platinum agent introduced in the late 1970s for the treatment of reproductive cancers (Amptoulach & Tsavaris, 2011). Ototoxicity is a common neurologic complication of cisplatin therapy (Hartmann & Lipp, 2003). About one third of patients administered IV doses of 50 mg/m² develop tinnitus and hearing loss following their first dose. Concurrent use of other ototoxic agents (e.g., aminoglycosides) prior to treatment with cranial irradiation and preexisting inner ear damage also are risk factors for ototoxicity (Hallmark, Snyder, Juscius, & Tamimi, 1992).

Cisplatin is associated with peripheral neuropathy, occurring in about half of the patients administered the drug, when a cumulative dose of 300 mg/m² has been given. Symptoms of peripheral neuropathy caused by cisplatin include weakness, loss of vibratory sense, tingling, burning, or numbness, as well as tremor in the upper and lower extremities. Although these symptoms typically occur 3–6 months following treatment, nurses should be alert from the first dose for cisplatin-related peripheral neuropathic symptoms (Quasthoff & Hartung, 2002). Loss of taste, seizures, and leukoencephalopathy also have been reported (Bruck, Heise, & Friede, 1989; Cattaneo, Filipazzi, Piazza, Damiani, & Mancarella, 1988). Although these neurologic deficits resolve in some cases, they may be persistent or permanent (Von Schlippe, Fowler, & Harland, 2001).

In an attempt to lower the significant toxicity profile associated with this drug, the analog carboplatin was developed for use and typically is administered in conjunction with a taxane for ovarian cancer or for lung cancer with vinorelbine, gemcitabine, or paclitaxel. Overall, less than 5% of patients treated with carboplatin develop peripheral neuropathy (McWhinney, Goldberg, & McLeod, 2009). Symptoms typically are delayed from the time of administration. Concurrent therapy with other neurotoxic agents, such as taxanes, increases the risk, as does being older than 65 years or pretreated with another platinum agent (McWhinney et al., 2009).

Oxaliplatin is a third-generation platinum agent and is a standard treatment when combined with 5-fluorouracil/leucovorin (5-FU/LV) for advanced and metastatic tumors of the colon and rectum. The toxicity profile of oxaliplatin resembles that of cisplatin, with peripheral neuropathy being the most common dose-limiting toxicity (Amptoulach & Tsavaris, 2011). A high incidence (85%–95%) of acute sensory peripheral neuropathy exists during and following infusion of oxaliplatin, although 80% of these patients ultimately experience some resolution of symptoms, and about 40% have total resolution of symptoms 6–8 months following treatment. This may manifest as paresthesia and dysesthesia in the extremities and periorally, and is exacerbated by exposure to cold (Kannar...
Vinca alkaloids, including vinblastine, vincristine, and vinorelbine, are a second category of neurotoxic chemotherapeutic agents. Of those, vincristine has the highest incidence of neurotoxicity, and about 30% of patients administered this agent experience painful sensory neuropathy as well as autonomic nervous system dysfunction with symptoms such as orthostatic hypotension, dry eyes, impotence, xerostomia (dry mouth), gastroparesis, and cold hands and feet. Although symptoms typically reverse when the drug is withdrawn, recovery is prolonged, at times for months (Gutiérrez-Gutiérrez, Sereno, Miralles, Casado-Sáenz, & Gutiérrez-Rivas, 2010).

Taxanes, including paclitaxel and docetaxel, are associated with high incidences of neurotoxicity. Paresthesia, particularly numbness, as well as pain in the hands and feet, is common and may begin within 1–3 days of high dose (greater than 250 mg/m²) therapy. This so-called glove and stocking symptom distribution is related to symmetric, axonal predominately sensory distal neuropathy (Argyriou et al., 2008) and may persist for two or more years following treatment (Hershman et al., 2011; Teener & Farrar, 1998). The mechanism of nerve damage is reflected in the development of symptoms: Distal nerve endings are affected first, followed by a dying back process that proceeds in reverse (from distal to proximal), and ultimately damages the neuronal body (Argyriou et al., 2008). Therefore, symptom appearance may be delayed or worsen over time. Other chemotherapeutic agents known to cause neurologic complications include thalidomide and lenalidomide; the antiangiogenesis agents bevacizumab, sunitinib, and sorafenib; and bortezomib and eribulin mesylate.

**Radiation**

Cranial irradiation has an established relationship to neurologic complications. Factors influencing the development of neurologic complications include the total radiation dose (measured in cGy), the number of treatments (fractions), and the volume of brain tissue in the treatment field (Ballonoff & Kavanagh, 2013). Complications can be divided into three categories: those that occur acutely during or immediately after treatment, early delayed effects that present up to six months following treatment, and late effects that can occur six months to years following treatment completion. While receiving cranial irradiation, patients may experience increased intracranial pressure because of disruption of the BBB and edema of brain tissue (McQuestion & Daniels, 2010). Subacute syndromes include encephalopathy, myelopathy, and transient brachial plexopathy (Armstrong & Gilbert, 2000; Goldwein, 1987). Symptoms of late-effect neurotoxicity are more chronic and may include headache, seizure, and focal neurologic deficits; but by far the most common neurotoxic effect of cranial irradiation is cognitive deficit (DeAngelis & Posner, 2009). Neuropsychologic testing often reveals radiation-induced cognitive dysfunction—most often deficits in memory, visual motor processing, quantitative skills, and attention (Dietrich et al., 2008).

Encephalopathy is an umbrella term denoting any abnormal condition of the structure or function of the brain, typically resulting in altered mental status. In the setting of brain or leptomeningeal metastases, it typically refers to specific neurologic findings, including paralysis, sensory changes, and language disturbance with or without marked changes in cognitive functioning (Khasraw & Posner, 2010). Chemotherapy-induced encephalopathy can be acute or late onset, transient or chronic. Delayed encephalopathies are more often related to whole-brain irradiation and chemotherapy and, on radiograph, evidence of white matter changes are present (Cossaart, SantaCruz, Preston, Johnson, & Skikne, 2003). Methotrexate, vincristine, ifosfamide, cyclophosphamide, fludarabine, cytarabine, 5-FU, cisplatin, the interferons (alpha, beta), and erlotinib all are associated with the development of encephalopathy (Sioka & Kyritsis, 2009).

**Other Causes**

Nontreatment-related, indirect causes of neurologic complications include CNS infection, encephalopathy, hematologic disorders, and paraneoplastic syndromes.

**Infection:** Derangement of the BBB may allow neurotoxic, infectious agents to enter the brain, causing septic encephalopathy, a major cause of delirium (Khasraw & Posner, 2010). In addition, cases of herpes simplex virus encephalitis and CNS fungal infections including Cryptococcus and Aspergillus have been reported (Jakob et al., 2012; Pruitt, 2010). Lastly, CNS infection can be transmitted through a surgical wound or contamination of an Ommaya reservoir, an intraventricular access device used to sample CSF and deliver intrathecal chemotherapy. Immunosuppression related to chemotherapy also may contribute to the development of multifocal progressive leukoencephalopathy, caused by the John Cunningham polyomavirus (Moloney, Fernandez, & Harrington, 2012).

**Disorders of coagulability:** Cerebral infarctions in the setting of malignancy may be related to cancer-associated hypercoagulability or caused by bleeding into a metastatic tumor in the CNS. Of the solid tumors, those with the highest incidence of intratumoral hemorrhage include lung, melanoma, breast, and high-grade primary brain tumors, whereas leukemia is the most frequently associated hematologic malignancy (Velander, DeAngelis, & Navi, 2012). Chemotherapy-induced thrombocytopenia also is linked to an increased incidence of intracranial hemorrhage (Posner & Rizzolo, 2011). The monoclonal antibody bevacizumab and the tyrosine kinase inhibitor sunitinib also are associated with increased risk of bleeding and thromboembolic events (Fuloria, 2012). These agents interfere with the vascular endothelial growth factor and are considered antiangiogenic. Severe bleeding episodes have been reported with bevacizumab,
more evident when the drug is used as a second-line treatment, and a black box warning is listed on the prescribing information regarding severe bleeding complications. More minor bleeding issues, such as epistaxis, do not require discontinuation of the drug. Sunitinib has an overall lower rate of bleeding complications than bevacizumab, but bleeding incidence was significantly higher than the control groups in many randomized control trials of the drug. The pathway by which these antivascular endothelial growth factor agents induce bleeding is not completely articulated in the literature. The primary hypothesis proposes that the inhibition of vascular endothelial growth factor interrupts its function as maintaining the integrity of the vasculature and, thereby, reduces the capacity of damaged endothelial cells to repair or renew (Elice & Rodeghiero, 2012).

Conclusion

Neurologic complications of systemic cancers can negatively affect a patient’s functional status, quality of life, and outcomes, perhaps even more than the underlying malignancy. Caused directly and indirectly by a cancer or its treatment, early recognition and prompt and aggressive treatment can mitigate existing symptoms and slow progression of neurologic deficit. Awareness of the multiple causes and manifestations of these complications is an important responsibility for oncology nurses and nurse practitioners.

References
