Cancer and Peripheral Nerve Disease

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KEYWORDS

• Neuropathy • Chemotherapy • Paraneoplastic • Radiation • Plexopathy

KEY POINTS

- Cancer-related neuropathy may be caused by direct tumor invasion or compression of nerve structures, the effects of chemotherapy or immune checkpoint inhibitors, radiation, surgery, or paraneoplastic syndromes.
- The most common presentation of chemotherapy-induced peripheral neuropathy is a symmetric, stocking-glove distribution of predominantly sensory symptoms.
- Some chemotherapy can cause symptoms of neuropathy that may progress for several months after discontinuation of treatment, a phenomenon known as coasting.
- Chemotherapy-induced neuropathy is treated symptomatically but in some cases may involve dose reduction or change of chemotherapy agent.
- Paraneoplastic syndromes necessitate prompt initiation of immunomodulatory therapy.

INTRODUCTION

As the mortality associated with many forms of cancer improves, patients with cancer face disabling complications from both the disease and its treatments. Among these, peripheral neuropathy (PN) continues to be highly prevalent among patients with cancer. PN commonly results in symptoms of pain, numbness, and weakness that can be both unpleasant and debilitating. Neuropathy can affect patients at all stages of malignancy—it can be a presenting symptom, a side effect of therapy, or a lingering malady during remission. This review presents a summary of the clinical presentations and etiologies of PN associated with malignancy as well as current treatment strategies.

BACKGROUND

Chemotherapy-induced PN is the most common type of neuropathy seen in patients with cancer, with variable reports of incidence ranging from 19% to more than 85%.[1]

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In 1 meta-analysis examining more than 4000 patients receiving chemotherapy, the prevalence of PN was 68%.[1] Of these patients, 30% continued to report chronic symptoms of PN 6 months after therapy was completed. In addition to chemotherapy-induced PN, patients with cancer also may develop neuropathy related to radiation, immune checkpoint inhibitors, direct tumor involvement of nerve structures, or paraneoplastic syndromes, causing a wide range of symptoms. The incidence of these complications is less well studied.

The disability associated with cancer-related PN cannot be overstated. PN can cause severe distal numbness and pain (often difficult to control with analgesic medications), imbalance leading to falls, vision abnormalities, and pain in the pharynx or larynx, among other symptoms. As such, PN can result in significant impairments in quality of life, mobility, social life, and occupational duties. Studies of patients with chemotherapy-induced PN have demonstrated lower scores on measures of quality of life, physical functioning, and social functioning compared with patients without PN undergoing chemotherapy.[2,3] In addition, cancer-related PN may burden patients as well as the health care system as a whole financially; a large-scale review of insurance claims records between 1999 and 2006 showed that patients with a diagnosis of PN had an average of $17,344 greater health care costs than patients without PN.[4]

CAUSES AND CLINICAL PRESENTATIONS

Ascertaining the etiology of neuropathy in a patient with cancer is essential for determining the approach to treatment. In some cases, diagnosis of neuropathy may even be the first sign that leads to an initial diagnosis of cancer.

Neuropathy Induced by Anticancer Drugs

PN is a common, debilitating side effect of many chemotherapeutic agents (**Table 1**). PN can limit the dosing of chemotherapy and may continue to burden patients for years after it is discontinued. These drugs can induce PN through a variety of neurotoxic mechanisms that ultimately result in the induction of neuroinflammation and the altered excitability of peripheral neurons.[5]

Chemotherapy-induced PN first was implicated in the vinca alkaloids, in particular vincristine. Patients receiving this chemotherapy may develop a dose-dependent, predominantly sensory neuropathy manifested by numbness and painful paresthesias in the hands and feet. Autonomic neuropathy also is common, resulting in symptoms, such as paralytic ileus, orthostatic hypotension, and urinary dysfunction. Symptoms generally improve after cessation of the drug, although in some cases neuropathic symptoms can progress or even worsen.[6] In patients with certain hereditary neuropathies (such as Charcot-Marie-Tooth disease), vincristine can result in a fulminant onset of severe weakness and numbness in all extremities.[6,7] The rapidity of this presentation can mimic Guillain-Barré syndrome, and these medications should be avoided in these patients.

Platinum-based chemotherapies, including cisplatin, carboplatin, and oxaliplatin, also can cause PN. Cisplatin and carboplatin can cause a cumulative dose-dependent PN featuring distal sensory loss, painful paresthesias, and sensory ataxia (ie, imbalance resulting from impaired proprioception). Cisplatin-induced PN can exhibit a coasting phenomenon, in which the accumulation of the drug in dorsal root ganglia may result in the new presentation or continued worsening of neuropathy symptoms for several months after the drug has been stopped.[6] Oxaliplatin is notable in that it can cause both acute and chronic forms of PN. The acute form, which occurs in up to 90% of patients to varying degrees, causes pain and discomfort in the distal

Table 1
Overview of neuropathy symptoms associated with key anticancer drugs

Anticancer Drug	Clinical Features and Complications	Treatment
Vinca alkaloids (eg, vincristine)	• Distal predominant sensory and/or motor symptoms • Autonomic involvement (ileus, orthostatic hypotension, bladder dysfunction) • Cranial neuropathies may be seen	• Prognosis is variable and depends on the specific drug—often improves but may result in chronic persistent symptoms • Pharmacologic and nonpharmacologic symptom management
Taxanes (eg, paclitaxel)	• Distal predominant sensory symptoms • Motor or autonomic symptoms may occur	• Consider chemotherapy dose modification or cessation if treatment of early or severe symptoms.
Platinum compounds (eg, cisplatin, carboplatin, oxaliplatin)	• Distal predominant sensory symptoms • May exhibit a coasting phenomenon • Oxaliplatin may cause acute sensory symptoms shortly after initiation of infusion, often aggravated by cold	• Avoid use if possible in patients with hereditary neuropathy (Charcot-Marie-Tooth disease)
Thalidomide	• May present with sensory, motor, and/or autonomic symptoms	
Bortezomib	• Distal predominant sensory symptoms • Mild weakness or autonomic symptoms may also be see	
Suramin	• Sensory and/or motor symptoms	
Ixabepilone	• Sensory, motor, and/or autonomic symptoms may occur	
Immune checkpoint inhibitors (eg, ipilimumab)	• Length dependent polyneuropathy • Demyelinating polyneuropathy • Sensory neuronopathy • Myositis • Meningoradiculitis • Myasthenia gravis • Central nervous system complications	• Consider cessation of therapy if symptoms develop • Can respond to treatment with steroids or other immunotherapy

extremities, often triggered by cold.[8,9] This typically resolves within 1 week to 2 weeks, although often incompletely.[9] In addition to the acute form of PN, oxaliplatin causes a dose-dependent chronic PN, consisting of numbness and tingling in the distal extremities that may persist even after treatment. Like cisplatin, oxaliplatin also may exhibit a coasting phenomenon.

Taxanes, including paclitaxel, docetaxel, and cabazitaxel, are a third class of chemotherapy associated with a high prevalence of PN, estimated to be between 11% and 87%, with the highest rates seen in paclitaxel.[10] Sensation to all modalities can be affected, leading to distal numbness and tingling as well as loss of proprioception and balance. In some cases, weakness from motor neuropathy or autonomic dysfunction can occur.[6] Disabling PN symptoms have been reported up to 2 years after completing taxol therapy, ranging from mild to persistently severe.[11]

Other chemotherapeutic agents implicated in chemotherapy-induced PN are suramin, thalidomide, bortezomib, and ixabepilone, among others. Combinations of these agents or high single or cumulative doses may result in more severe presentations.

PN rarely has been associated with immune checkpoint inhibitors, occurring in less than 1% of treated patients.[12] This complication most commonly has been associated with ipilimumab and less so nivolumab or pembrolizumab, and PN related to immune checkpoint inhibitors tends to be more likely acute or subacute or non–length-dependent in pattern.[13] Cases of isolated cranial neuropathies and sensory neuronopathies have been reported as well.[13,14] Immune checkpoint inhibitors can induce autoimmunity, which has been implicated in many neurologic complications of these drugs affecting the peripheral nerves, muscles, neuromuscular junction, and central nervous system.[15] Guillain-Barré syndrome has been reported at a rate of 0.1% to 0.2%, with clinical and electrophysiological features typical of cases not associated with immune checkpoint inhibitors, although both albuminocytological dissociation and pleocytosis have been reported on cerebrospinal fluid studies.[14,16] Chronic inflammatory demyelinating polyneuropathy, meningoradiculitis, myositis, and myasthenia gravis also have been reported.[12,15] Providers should be acutely aware of these potential complications in patients receiving these medications and monitor closely for any new neurologic symptoms because these symptoms may progress rapidly.

Neuropathy Related to Direct Tumor Invasion

Cancer can cause neuropathy through direct invasion of the peripheral nervous system, although this is more rare than other cancer-associated mechanisms of neuropathy. Nerve roots and nerve plexuses tend to be more vulnerable to direct invasion, although this is variable based on the type of underlying malignancy.[17] Neurolymphomatosis is one example, encompassing neuropathies caused by the spread of different forms of leukemia and non-Hodgkin lymphoma.[18] The distribution of nerve involvement is variable and can include peripheral sensory or motor nerves, spinal nerves, the brachial or lumbosacral plexuses, or cranial nerves. Therefore, the presentation of neurolymphomatosis can be highly variable in individual patients. Solid tumor involvement of peripheral nerves also can occur, albeit less commonly. For example, rectal, cervical, and prostate cancers have been shown to invade nearby nerve structures.[19,20]

In the context of a known malignancy, a new focal neurologic deficit, in particular one that is not in the distribution of a common compression neuropathy, warrants investigation for spread of neoplastic disease to nerve structures. Neuropathic symptoms, such as sensory loss, pain, or weakness in the distribution of a nerve root or plexus, even occasionally may be the first presenting symptoms of a cancer. Specific neurologic syndromes that can point toward a malignancy diagnosis have been described. For example, a lesion to the submandibular branch of the trigeminal nerve, colloquially known as the numb chin syndrome, is highly associated with an underlying malignancy and metastatic disease.[21] Patients present with anesthesia to the lip or chin that usually is unilateral, although bilateral involvement can occur. In the absence of a known alternative cause, such a presentation should prompt a work-up for metastatic disease as well as consideration of additional studies, such as lumbar puncture.

Neuropathy Related to Paraneoplastic Syndromes

Paraneoplastic syndromes can cause multiple neurologic syndromes and may present even before the diagnosis of cancer. For the diagnosis of a neurologic paraneoplastic syndrome, the 2004 diagnostic criteria from the Paraneoplastic Neurological

Syndrome-European Consortium incorporated the presence of a classical paraneoplastic neurologic syndrome, the presence of positive onconeural antibodies, the presence of a known malignancy, and response to immunotherapy.[22] Although not all criteria must be present for a diagnosis, various combinations of these criteria can lead to diagnoses of either definite or possible paraneoplastic neurologic syndromes. Recognition of classical paraneoplastic syndromes as well as a high index of suspicion in a patient with a known malignancy, therefore, will help clinicians diagnose these conditions. Although some classical syndromes are discussed in this article, the diversity and variability of paraneoplastic neurologic syndromes must be emphasized.[23]

Sensory neuronopathy is one such classical paraneoplastic syndrome. A neuronopathy (as opposed to a neuropathy) specifically involves damage to the cell body of the sensory neuron located in the dorsal root ganglion. Approximately 70% to 80% of all malignancy-associated cases of subacute sensory neuronopathy occur in the context of small cell lung cancer, most of which are associated with anti-Hu antibodies (antineuronal nuclear antibody type 1, anti-ANNA1),[24] although other malignancies and antibodies can be implicated in neuronopathies as well. Certain key clinical features can help differentiate a sensory neuronopathy from the more common axonal neuropathy. For example, symptoms often are asymmetric and can involve the upper extremities or proximal lower extremities, in contrast to the length-dependent pattern of a classic axonal PN. Proprioception often is affected, leading to prominent sensory ataxia and poor balance. The time course of a sensory neuronopathy is variable, ranging from subacute to even fulminant in some cases. Anti-Hu paraneoplastic syndromes typically are associated with sensory neuronopathies, as described previously; however, less commonly, they may present with mixed sensorimotor, pure motor, or autonomic involvement. Another example to be familiar with is paraneoplastic syndromes associated with anti-CRMP5 (CV2). These antibodies often are associated with small cell lung cancer or a thymoma and can present with neuropathy, asymmetric painful radiculopathy, and even spinal cord involvement.[25] Cases of demyelinating polyneuropathies, such as Guillain-Barré syndrome and Chronic inflammatory demyelinating polyneuropathy, however, have been described in association with Hodgkin and non-Hodgkin lymphomas. Although these may represent a possible paraneoplastic syndrome, there have not been consistently identified associated onconeural antibodies.[26]

Monoclonal gammopathies, which are present in 3% to 4% of adults over age 50, also commonly feature associated neuropathy.[27] Please refer to Yaowaree Leavell and Susan C. Shin's article, "Paraproteinemias and Peripheral Nerve Disease"; and Stephen Cox and Kelly G. Gwathmey's article, "Chronic Immune-Mediated Polyneuropathies," in this issue, for a more detailed discussion.

Neuropathy due to Iatrogenic Causes

Chemotherapy-induced PN, as described previously, is quite prevalent and disabling for certain drugs; however, other cancer treatments also may cause morbidity by damaging peripheral nerves. Cancer surgery can result in significant neuropathic pain. Neck surgeries, mastectomies, and thoracotomies all are procedures associated with a significant degree of neuropathic pain.[28] In postmastectomy pain syndrome, surgical trauma can result in injury to branches of the intercostal nerves or branches of the brachial plexus. Approximately half of respondents in 1 survey had some degree of mastectomy-related pain at a mean of 3.2 years postsurgery.[29] Patients typically present with numbness, paresthesias, or pain near the operative site, axilla, chest wall, or ipsilateral arm. Younger age, concomitant radiation or chemotherapy, and

type of procedure may be risk factors for persistent pain, although the evidence is inconsistent.[30]

Neuropathy can develop in association with radiation therapy as well, often presenting in a delayed fashion months to years after radiation is completed. Prominent among radiation nerve injuries are radiation-induced plexopathies, both of the brachial plexus and lumbosacral plexus. The risk of neuropathy is dose-dependent; radiation-induced brachial plexopathy rates have been described at 66% when associated with higher doses of radiation used in the era before modern dosing but only 1% to 2% when associated with lower doses.[31] Radiation plexopathies typically present with sensory loss and weakness in a limb near where prior radiation occurred, and there may be characteristic signs of myokymia on electrophysiologic studies. Any history of radiation therapy, even remote history, is important in diagnosis, because radiation-induced plexopathies can present as late as decades after therapy is completed.[31] Pain is not a common symptom early in the course of the disease, so presence of pain should raise suspicion for direct tumor invasion and recurrence of malignancy rather than radiation injury.

Neuropathy from Noncancer Causes

Even in patients with known malignancies, common causes of neuropathy still should be considered always. When a malignancy-related cause of neuropathy is identified (such as chemotherapy), controlling other potentially coexisting causes may help prevent worsening of neuropathic symptoms.[32] For patients who present with distal symmetric polyneuropathy, American Academy of Neurology guidelines recommend testing at a minimum for diabetes mellitus (fasting blood sugar or hemoglobin A_{1c}), vitamin B_{12}, methylmalonic acid, and serum protein immunofixation.[33] Diabetes mellitus is the most common cause of polyneuropathy in the developed world, comprising one-third of cases.[33] Vitamin deficiencies, such as vitamin B_{12}, vitamin E, thiamine, copper, and pyridoxine, may be important causes of neuropathy, particularly in cancer patients with impaired vitamin absorption due to gastrointestinal pathology or surgeries. Long-term excessive alcohol use should be elicited on taking a history, because this can cause or worsen PNs and may have a direct neurotoxic effect.[32]

GENERAL PRINCIPLES OF DIAGNOSIS

Primary care providers encounter PN (also known as polyneuropathy) frequently and it is 1 of the top 5 reasons for neurologic referral.[32] Polyneuropathies most commonly are axonal and typically occur in a length-dependent fashion. Clinical features of cancer-related PN are indistinguishable from other distal PN. Patients first may experience numbness, paresthesias, burning, or pain in the feet as well as impaired balance. Symptoms can progress further up the legs and eventually involve the arms, creating a symmetric stocking-glove distribution. Sensory symptoms usually precede motor symptoms, although in more advanced cases distal muscle weakness and atrophy can be observed. Reflexes are depressed or absent. Autonomic symptoms may be overlooked and can include postural hypotension or tachycardia, gastroparesis, urinary or bowel dysfunction, or sexual dysfunction. The time course of symptom progression is variable.

Although many PNs present with this distal axonal pattern, others follow alternate patterns that can hint at their underlying etiology. Marked sensory deficit asymmetry with proximal limb involvement can indicate a sensory neuronopathy. A mononeuritis multiplex pattern occurs when there is evidence of damage to at least 2 separate nerves occurring in a progressive, stepwise pattern. Although classically associated

with neuropathies in vasculitic and autoimmune diseases, mononeuritis multiplex may occur in direct multifocal tumor involvement, neurolymphomatosis, or certain paraneoplastic conditions.[17,24]

Diagnosis of neuropathy related to malignancy is individualized and dependent on each patient's history and examination. Careful neurologic examination helps localize the symptoms further, and a neurologic consultation should be considered if there is suspicion for peripheral nerve involvement. Common diagnostic tests that may help establish the diagnosis include nerve conduction studies and electromyography, laboratory studies, and focused imaging. Clinicians should have a low threshold to image the brain and spinal cord for patients who have cancer and neurologic symptoms, particularly if headaches, back pain, cranial nerve deficits, hyperreflexia, increased tone, or bowel or bladder symptoms are present. Cerebrospinal fluid analysis also may be helpful to evaluate for signs of inflammation and to exclude leptomeningeal metastasis. In cases of paraneoplastic syndrome suspected, testing for paraneoplastic antibodies is recommended. Because the clinical presentations of specific paraneoplastic antibodies can vary widely, testing with an antibody panel is recommended over testing single antibodies.[34] In general, neuropathy caused by chemotherapy should be considered a diagnosis of exclusion, and efforts should be made to rule out other possible causes of neuropathy when this is suspected.

Early diagnosis of peripheral nerve disorders in the setting of malignancy is important for faster initiation of treatment, prevention of further loss of function, and providing appropriate patient counseling. Delay in diagnosis of peripheral nerve complications from malignancy sometimes can occur in the setting of postsurgical immobilization, reduced activity, or sedation, all of which may obscure symptoms.[28]

HOW IS CANCER-RELATED NEUROPATHY TREATED?

The approach to treatment of cancer-related neuropathy depends on the type and cause of the neuropathy. The overall aim of treatment is to minimize symptoms, improve quality of life, and prevent loss of function.

For all patients, addressing the underlying cancer with appropriate treatment and counseling is paramount. Other general principles include both pharmacologic and nonpharmacologic treatments for neuropathic pain and providing other supportive care as appropriate. Supportive measures include physical therapy for gait training physical therapy for gait training, occupational therapy, fall prevention counseling, bracing/orthotics, behavior modifications, assistive devices such as a walker, exercise, and home safety modifications (**Box 1**).

Chemotherapy-Related Neuropathy Treatment

More specific strategies for the treatment and prevention of chemotherapy-induced PN have been studied extensively. Clinical risk factors that appear to confer an increased risk for developing neuropathy from chemotherapy include higher cumulative dose and increased number of treatments.[35] Baseline neuropathy also may portend a higher risk for developing neuropathy.[35]

In order to minimize the severity of chemotherapy-induced PN, 1 important intervention to consider is dose modification. Patients' neurologic symptoms should be recorded at baseline and then monitored closely throughout treatment. Dose reduction or even treatment discontinuation should be considered if patients develop severe symptoms or if symptoms develop early in the course of the treatment.[36] These decisions should be made carefully, however, with consideration of the effect on the underlying malignant process and in consultation with the oncology treatment team.

Box 1
Nonpharmacologic approaches to treatment of neuropathy associated with cancer

- Gait or exercise training
- Occupational therapy
- Fall prevention counseling
- Home safety evaluation
- Bracing or orthotics, as indicated
- Assistive devices, as indicated
- Foot care
- Behavior modifications

Numerous neuroprotective agents have been studied in chemotherapy-induced PN with the goal of blocking the noxious effects of chemotherapy, thereby limiting neuronal damage and promoting peripheral nerve regeneration.[37] There are some data to suggest a beneficial effect from exercise[38] but none to strongly support any medications or supplements as protective in the setting of chemotherapy-induced PN.[38,39] More research is needed to determine effective preventative measures. One challenge is that an ideal neuroprotective agent must not reduce the antineoplastic effect of the chemotherapy, promote tumor growth, or cause significant additional side effects.

Duloxetine is the only medication that has been shown to help reduce pain in patients with painful chemotherapy-induced PN in a randomized, placebo-controlled trial.[40] Empiric use of other agents used for neuropathic pain, however, is common practice and may be considered based on their use in other neuropathic pain syndromes. These agents include gabapentin, pregabalin, and tricyclic antidepressants as well as numerous nonpharmacologic approaches. For further details on therapeutic agents, see the Elizabeth J. Pedowitz and colleagues' article, "Management of Neuropathic Pain in the Geriatric Population," in this issue. Although these treatments may help with neuropathic pain in chemotherapy-induced PN, there currently are not any specific treatments available to improve symptoms of numbness.

Immune Checkpoint Inhibitor Neuropathy Treatment

Management of neuropathy caused by treatment with immune checkpoint inhibitors differs from management of neuropathy associated with other types of anti-cancer drugs. Here, management typically involves suspending treatment with the immune checkpoint inhibitor and initiating steroids as well as consideration of intravenous immunoglobulin and/or plasma exchange. Treatment duration should take into account the long half-life of immune checkpoint inhibitors and should be initiated early, because symptoms may be rapidly progressive.[41] Retrial of an immune checkpoint inhibitor after neurologic side effects may be possible in some cases; however, this requires a careful analysis of the risks versus benefits of doing so, with particular consideration of the risks of further exacerbation of the neurologic symptoms.[13,14] No clear guidelines exist on when or whether to reinitiate an immune checkpoint inhibitor in these select cases. For cases of Guillain-Barré syndrome associated with the use of immune checkpoint inhibitors, there is a potential role of the use of steroids based on limited case studies.[14,41] This is in contrast to Guillain-Barré syndrome not associated with immune checkpoint inhibitors, for which steroids are not used.

Paraneoplastic Syndrome Treatment

For a suspected paraneoplastic neuropathy, management generally consists of work-up for primary malignancy (if not already identified) and cancer treatment. Outcomes are better with earlier identification.[42] Prompt treatment should be initiated, particularly in patients who are rapidly declining.[34] Although strong evidence for the effective treatment of paraneoplastic neuropathies is scarce due to lack of data, immunomodulatory therapy may be considered both during and after cancer treatment. This may include intravenous immunoglobulin, steroids, plasma exchange, or rituximab, among others. Combinations of these treatments may also be used to improve symptoms and prevent further decline.

SUMMARY

The presentation of neuropathy related to underlying malignancy or the neurotoxic effects of cancer treatments is variable. Early recognition is important so steps can be taken to prevent progression and worsening of neurologic symptoms and disability. Currently, there are no interventions known to prevent chemotherapy or immune checkpoint inhibitor related neuropathy. Treatment depends on the type and cause of the neuropathy and typically consists of management of neuropathic pain and other supportive measures. In some circumstances, modification or discontinuation of anticancer treatment should be considered. More research is needed to determine how to best prevent these neurologic complications in patients with cancer.

CLINICS CARE POINTS

- Cancer can affect the peripheral nervous system in numerous ways; therefore, the clinical presentation may be variable. The most common pattern seen is sensory deficits in a stocking-glove distribution in the setting of chemotherapy.
- Clinicians should be aware of the neurotoxic effects of chemotherapy agents and immune checkpoint inhibitors. Patients receiving these treatments should be monitored closely because modifications in treatment or cessation of therapy may be indicated if significant symptoms develop.
- Some chemotherapy can cause symptoms of neuropathy that may progress for several months after discontinuation of treatment, a phenomenon known as coasting.
- Non–cancer-related causes of neuropathy always should be considered and investigated. Chemotherapy-induced PN is a diagnosis of exclusion.
- Paraneoplastic syndromes affecting the peripheral nervous system may include neuropathies and neuronopathies. The most common of these is associated with anti-Hu antibodies; however, a paraneoplastic antibody panel is recommended in most cases when a paraneoplastic syndrome is suspected.
- Radiation-induced plexopathy can have a delayed onset, with presentation of symptoms occurring years after the completion of treatment in some cases.
- Care for the patient with peripheral nervous system complications of cancer is multidisciplinary and may include a patient's primary care provider, oncologist, and neurologist.

DISCLOSURE

The authors have nothing to disclose.

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