

Neurologic Complications of Cancer Therapies

By Eudocia C. Quant, MD, and Patrick Y. Wen, MD

Overview: Patients with cancer are living longer because of earlier diagnoses and improvements in treatments. Unfortunately, neurologic complications from cancer therapies are an increasing source of morbidity and may play a role in limiting potential treatments. Acute, subacute, and chronic syndromes may affect the central or peripheral nervous system. Although cytotoxic chemotherapy and radiation remain

NEUROLOGIC COMPLICATIONS of cancer therapies are an important source of morbidity in oncology. Cytotoxic chemotherapy, radiation, and novel therapies have all been associated with side effects on the central nervous system (CNS) and/or the peripheral nervous system (PNS). In addition, the combination of neurotoxic treatments increases the risk of neurologic complications. The severity of these manifestations range from reversible, self-limited conditions to severe, life-threatening disorders. Some neurologic complications occur during treatment, but others—such as cognitive dysfunction—do not become apparent for months to years after completion of therapy. As patients live longer, the incidence of these delayed complications will continue to rise. Neurotoxicities may also lead to reduction of dosages or cessation of therapy, thus limiting potential therapies. Treatment regimens must be optimized to eradicate disease without excessive injury of normal neural structures, especially when the nervous system is directly affected by cancer. Because neural tissue repair is limited, prevention and early recognition are keys to avoiding permanent neurologic damage. Several compounds have been proposed as neuroprotectants, but few have demonstrated activity in clinical trials. Neurotoxicity from cancer therapy should also be differentiated from other etiologies, such as compression or infiltration by tumor, metastatic disease, metabolic factors, nutritional deficiencies, infections, and paraneoplastic disorders.

Neurologic Complications of Cytotoxic Chemotherapy

Cytotoxic chemotherapy may adversely affect both the CNS and PNS (Table 1). Peripheral neuropathy is the most common neurologic complication of cancer therapy, with vincristine, cisplatin, paclitaxel, oxaliplatin, and thalidomide as the most neurotoxic. CNS manifestations include encephalopathy, cerebellar dysfunction, and cerebrovascular accidents. The main causes of central neurotoxicity are methotrexate, cytarabine, and ifosfamide. Research into chemotherapy-induced cognitive impairment has gained momentum recently, but this area is still poorly understood.

PNS Disorders

Chemotherapy-induced peripheral neuropathy (CIPN) is typically dose-dependent and appears after several courses.¹ Many agents have been linked to neuropathy, including vinca alkaloids, taxanes, platinum analogs, and thalidomide.^{2,3} The cumulative toxic dose associated with clinical manifestations varies according to chemotherapy (greater than 30 to 50 mg for vinca alkaloids, greater than 175 to 200 mg/m² for taxanes, and greater than 300 to 400 mg/m² for platinum analogs).¹ Pathophysiology also varies accord-

ing to chemotherapy. Mechanisms include disruption of microtubule assembly and axonal transport. CIPN is often characterized by a painful sensory neuropathy, initially presenting as paresthesias and dysesthesias in the fingers and toes. The symptoms may spread proximally to affect upper and lower extremities in a stocking-glove distribution. Nerve conduction studies demonstrate a length-dependent axonal pattern or a sensory neuronopathy, depending on the mechanism of the peripheral neuropathy toxicity.¹ Other patterns of PNS involvement include autonomic neuropathy with vincristine, ataxic neuropathy with cisplatin, cranial neuropathies with vinca alkaloids, proximal motor neuropathy with taxanes, and transient neuromyotonia with oxaliplatin.¹ The neurotoxic effects of chemotherapy may be compounded by other causes of peripheral neuropathy, such as diabetes, alcoholism, nutritional deficiencies (e.g., thiamine, vitamin B₁₂), metabolic disorders (e.g., hypothyroidism), compressive injuries, and vascular damage. Therefore, diagnostic workup should include a search for such disorders, especially in patients with more severe manifestations than anticipated from chemotherapy alone.

Symptoms from CIPN often improve with drug discontinuation or dose reduction, but these options may not be available for patients who depend on the chemotherapeutic agent for disease control. Several agents—such as amifostine, glutathione, and Org 2766—have been investigated in clinical trials as neuroprotectants, but data are insufficient to warrant routine use in clinical practice.⁴ Calcium and magnesium infusions may reduce the severity of oxaliplatin-induced chronic peripheral neuropathy without reducing response rates.⁵ Accumulating data also suggests that vitamin E may reduce CIPN, but further studies are needed.⁵ Randomized, placebo-controlled, double-blinded studies of tricyclic antidepressants, gabapentin, and lamotrigine for established CIPN failed to demonstrate benefit over placebo.⁵

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Table 1. Central and Peripheral Nervous System Complications of Common Chemotherapeutic Agents

Agent	Central Nervous System	Peripheral Nervous System
Carboplatin	Cortical blindness, cortical infarcts	Sensory neuropathy (less toxic than cisplatin)
Cisplatin	Headache, encephalopathy, cortical blindness, focal deficits, strokes, seizures	Sensory neuropathy
Cyclosporine	Posterior reversible leukoencephalopathy syndrome	
Cytarabine	Acute cerebellar dysfunction with high dose Intrathecal administration: aseptic meningitis, myelopathy, encephalopathy, seizures	Rarely associated with painful sensory neuropathy
Fluorouracil	Encephalopathy (risk increased for patients with a deficiency of dihydropyrimidine dehydrogenase) Acute cerebellar dysfunction	Rarely associated with neuropathy
Ifosfamide	Acute but reversible encephalopathy with high doses	Severe, painful axonal neuropathy with high doses
Interferon-alpha	Neuropsychiatric symptoms, such as depression Rarely cognitive dysfunction	
Methotrexate	Delayed leukoencephalopathy (with or without neurocognitive impairment) Intrathecal administration: aseptic meningitis	Intrathecal administration: anterior lumbosacral radiculopathy
Oxaliplatin		Acute, reversible sensory neuropathy and neuromyotonia Chronic sensory peripheral neuropathy
Paclitaxel	Acute encephalopathy at very high doses	Sensory greater than motor length-dependent neuropathy Acute pain syndrome with arthralgias and myalgias
Tacrolimus (FK506)	Posterior reversible leukoencephalopathy syndrome	
Thalidomide		Sensory, length-dependent neuropathy Rarely sensorimotor neuropathy
Vincristine	Encephalopathy, seizures, cortical blindness, ataxia, parkinsonian-like symptoms	Sensory greater than motor, length-dependent neuropathy Autonomic neuropathy (especially paralytic ileus) Mononeuropathies Cranial nerve palsies

aseptic meningitis, which can be ameliorated with prophylactic dexamethasone. Rarely, these intrathecal agents can also produce transverse myelopathy or seizures. Leukoencephalopathy occurs commonly with high-dose methotrexate, but has also been described with vincristine, fluorouracil, and ifosfamide. Specific agents—such as thymidine for fluorouracil, methylene blue for ifosfamide, and folinic acid for methotrexate—may minimize the encephalopathy caused by these chemotherapies.³ Posterior reversible encephalopathy syndrome is typically associated with uncontrolled hypertension or immunosuppressants, such as cyclosporine and tacrolimus, but may also be caused by a variety of combination and single anticancer agents, such as gemcitabine, cisplatin, and cyclophosphamide.⁸

More recent evidence suggests that chemotherapy may produce cognitive dysfunction.⁹⁻¹¹ This has been termed

“chemobrain” to describe the problems with memory and/or concentration that occur during and after chemotherapy.¹⁰ Even though most patients improve after completing chemotherapy, subsets of patients continue to experience cognitive impairments. Symptoms may be subtle, but they can adversely affect quality of life. Neuropsychologic profiles suggest disruption of frontal-subcortical networks, including problems with short-term memory, executive function, working memory, and sustained attention.¹¹ Studies have demonstrated conflicting results and may be difficult to interpret for a variety of reasons, including the lack of cognitive evaluation before chemotherapy and inconsistency in defining what constitutes cognitive dysfunction. In one of the few prospective longitudinal studies with a control group, the neuropsychologic performances of 85 women with early-stage breast cancer receiving chemotherapy, 43 women receiving endocrine therapy and/or radiotherapy, and 49 healthy controls were assessed at baseline, following completion of chemotherapy, and at 18 months.¹² After controlling for age and intelligence, no significant differences in cognitive decline were seen between the groups. Only a small minority of women receiving adjuvant treatments experienced objective measurable change in their concentration and memory, with women who experienced treatment-induced menopause most at risk for a decline in cognitive performance. However, the chemotherapy regimens administered in this study were heterogeneous, and many received a relatively low-dose regimen of fluorouracil, epirubicin, and cyclophosphamide. Conditions that may mimic or confound studies on cognitive dysfunction include fatigue, anxiety, depression, stress, hormonal agents, opioids, glucocorticoids, brain metastases, and antiepileptics. Possible mechanisms include direct neurotoxic effects on the CNS, including neural stem cells from chemotherapy,¹³ anemia with cerebral hypoxia, oxidative stress, immune dysregulation with release of cytokines, altered neurotransmitter levels, induced hormonal changes, and genetic pre-

KEY POINTS

- Neurologic complications from cancer therapies affect quality of life and remain an important source of dose-limiting toxicity.
- Anticancer treatments can adversely affect any part of the nervous system, and some neurotoxic effects can present years after completion of treatment.
- The neurotoxicities of chemotherapy and radiation are widely known, but several newer targeted agents (e.g., bortezomib and bevacizumab) are also associated with neurologic complications.
- Cognitive dysfunction from cancer therapies is an active area of research, but the epidemiology and pathophysiology are still poorly understood.
- Early recognition and prevention may help avoid permanent neurologic damage.

Table 2. Risk Factors for Radiation-induced Nervous System Injury

Treatment-related Factors	Patient-related Factors
Fraction dose (> 200 cGy)	Age (< 7 years and > 60 years)
Cumulative dose (> 5,000 cGy)	Genetic predisposition (neurofibromatosis, ataxia telangiectasia)
Shorter overall treatment time	Preexisting central nervous system damage
Volume of brain irradiated	Vascular risk factors (hypertension, diabetes, smoking)
Hyperfractionation schedules	Duration of survival following completion of radiation
Concomitant or subsequent chemotherapy	
Proximity to susceptible neural tissues (hypothalamus, retina, optic nerves)	

disposition.^{10,11} Data regarding prevention or treatment of chemotherapy-induced cognitive impairment are limited.

Neurologic Complications of Radiation

Radiation neurotoxicity is a well-known complication of cancer therapy. Although radiation treatment fields and regimens are carefully planned to prevent damage to normal neural structures, the effectiveness of radiotherapy is frequently limited by the tolerance of the nervous system. The incidence of radiation-induced nervous system complications varies according to several risk factors, including cumulative radiation doses and doses per fraction (Table 2).^{14,15} Radiation can affect any part of the neuroaxis resulting in encephalopathies, myelopathies, brachial and lumbosacral plexopathies, malignant peripheral nerve sheath tumors, and a variety of other neurologic disorders. The cerebrovascular system is also susceptible to delayed effects from radiation producing vascular malformations, aneurysms, accelerated atherosclerosis, and strokes.

Cranial irradiation is an important component of primary and metastatic brain tumor management, but can cause acute, subacute, and chronic complications. Acutely, patients may experience progressive fatigue and signs of in-

creased intracranial pressure attributed to disruption of the blood–brain barrier and cerebral edema. These symptoms may respond to corticosteroids. Subacute effects occurring 6 to 12 weeks following radiation include reversible generalized weakness and somnolence caused, in part, by transient demyelination. The most severe complications of radiation neurotoxicity are delayed or chronic.

Delayed cerebral radionecrosis (Fig. 1) occurs months to years after radiation to brain parenchyma, either directly from cranial irradiation or indirectly as in the case of temporal lobe necrosis following radiation for head and neck cancer.¹⁵ Although best characterized following external beam radiation, cerebral radionecrosis may be relatively more common after stereotactic radiosurgery or interstitial brachytherapy.¹⁵ In patients with glioblastoma, the combination of temozolomide with fractionated radiotherapy increases the risk of an intracranial radiation reaction and can produce changes on imaging that mimic tumor progression.¹⁶ Presenting signs and symptoms are nonspecific and include headaches, confusion, seizures, or focal neurologic deficits. Both vascular and glial damage have been implicated in the pathophysiology.¹⁷ Cerebral radionecrosis may be difficult to distinguish from tumor recurrence. Occasionally, biopsy is needed for definitive diagnosis. Clinical improvement has been reported in small series following treatment with corticosteroids, anticoagulation, hyperbaric oxygen therapy, or bevacizumab, but further studies are needed.¹⁸

The more common manifestation of delayed radiation injury is cognitive dysfunction. Varying degrees of cognitive impairment have been reported, although as many as 12% of patients may develop frank dementia.¹⁹ Cognitive dysfunction may not become apparent for several years. In a longitudinal study of low-grade gliomas, comparing irradiated patients with nonirradiated patients, no differences in cognitive function were detected at a mean of 6 years after

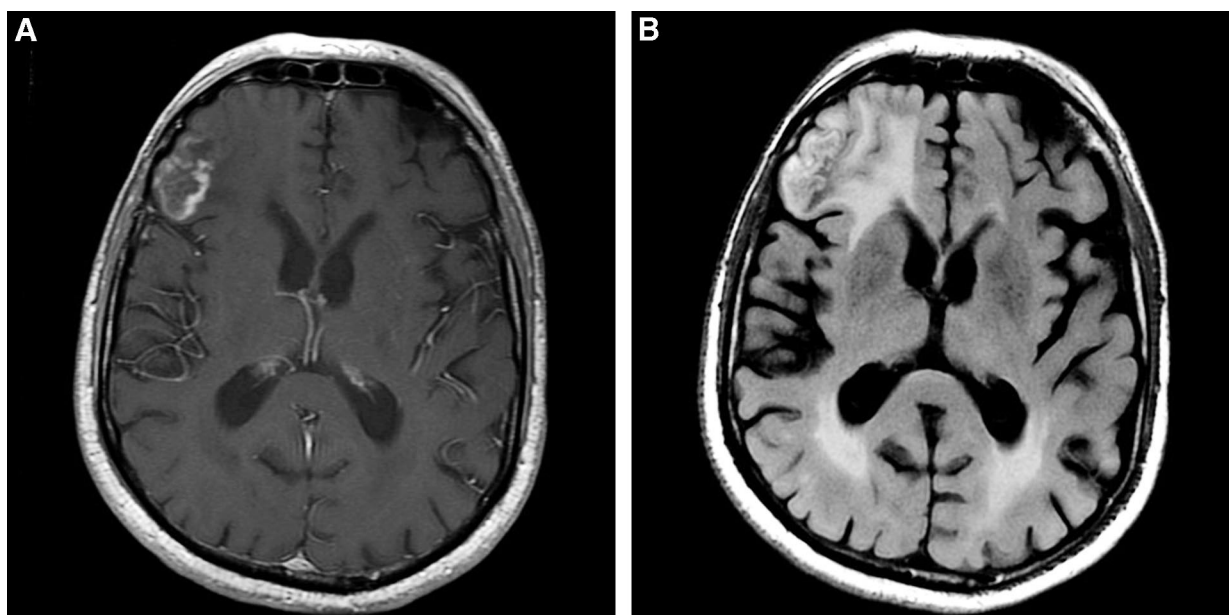


Fig 1. Post contrast T1-weighted (A) and FLAIR (B) MRI show geographic enhancement with vasogenic edema caused by radiation necrosis. One year before presenting with confusion and seizures, this patient received radiation to the right temple for poorly differentiated squamous cell carcinoma.

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

diagnosis.²⁰ Yet, re-evaluation of the same cohort at a mean of 12 years after diagnosis did reveal cognitive disabilities in 53% of the patients who had radiation, compared with 4% of the patients who were radiotherapy-naïve.²¹ Typically, in patients with radiation-induced cognitive dysfunction, neuropsychologic testing reveals deficits in memory, visual motor processing, quantitative skills, and attention.¹⁴ Brain magnetic resonance imaging may demonstrate leukoencephalopathy, progressive brain atrophy, or radiation necrosis, but patients with mild-to-moderate cognitive dysfunction often have normal-appearing neuroimaging.^{14,19} The underlying pathology may be related to inflammation, metabolic derangements, and long-term damage of various neural cell types, including stem and progenitor cells.¹⁴ In addition, cranial irradiation can profoundly inhibit neurogenesis in the hippocampus, an area of the brain essential to learning and memory.¹⁹ Both methylphenidate and donepezil improve cognition in brain tumor patients.^{14,22} Ventriculoperitoneal shunting may benefit patients with radiation-induced hydrocephalus.²³

Because of concerns regarding long-term toxicity of whole-brain radiation (WBRT), many have advocated withholding adjuvant WBRT in patients with limited brain metastases and good performance status in favor of more aggressive local therapy, such as surgery and stereotactic radiosurgery.^{24,25} However, patients who do not receive adjuvant WBRT have a higher rate of intracranial relapse, which can worsen neurologic, as well as cognitive, function. Phase III studies are currently underway to evaluate the effect of adjuvant WBRT on quality of life, neurocognition, and survival.

Neurologic Complications of Novel Therapies

Advances in our molecular understanding of tumorigenesis and progression have led to an explosion of novel therapies, including small molecule receptor tyrosine kinase inhibitors and monoclonal antibodies targeting specific pathways. These agents represent the majority of anticancer drugs currently in clinical trials. As our clinical experience with targeted agents expands, toxicities are uncovered. A few agents thus far have been associated with neurologic complications.

Bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma, causes injury to the dorsal root ganglion and a small-fiber sensory neuropathy that is one of its main dose-limiting toxicities.^{16,26} The incidence ranges from 30% to 40%, and the prevalence increases through the first five treatment cycles.²⁶ Neuropathic pain is more prominent than sensory loss or paresthesias. Examination may be relatively normal, but can reveal loss of pain and temperature distally with preservation of vibration sense, muscle strength, and ankle reflexes. As with other small-fiber

neuropathies, nerve conduction studies may be unremarkable. Most patients experience resolution or improvement of their neuropathy symptoms with dose reduction or drug discontinuation.

Antiangiogenesis agents that target vascular endothelial growth factor (VEGF) and its receptor (VEGFR) have emerged as important therapies in several cancers. Three U.S. Food and Drug Administration–approved agents that primarily inhibit the VEGF/VEGFR pathway are a monoclonal antibody against VEGF (bevacizumab) and two tyrosine kinase inhibitors (sunitinib and sorafenib). Neurotoxicities associated with VEGF/VEGFR inhibitors include arterial thrombotic events, bleeding events, posterior reversible encephalopathy syndrome, and optic neuropathy.^{16,27,28} Two distinct types of hemorrhages are associated with anti-VEGF/VEGFR agents: (1) mild spontaneous mucocutaneous bleeding and (2) serious tumor-related bleeding.²⁷ Until recently, patients with brain metastases were often excluded from clinical trials of VEGF/VEGFR inhibitors because of the concern for intratumoral hemorrhage. However, the risk of CNS hemorrhage may not be as high as anticipated. Two recent retrospective studies of anti-VEGF therapy found relatively low rates of intracranial hemorrhage, even in the presence of CNS metastases.^{29,30} Bevacizumab can likely be given in patients with brain metastases, but caution should be used in tumors with a strong hemorrhagic tendency, such as renal cell carcinoma.¹⁶ In patients with high-grade gliomas, the risk of hemorrhage in bevacizumab-treated patients appears to be only slightly elevated over the baseline risk.³¹ Bevacizumab can also be safely combined with anticoagulation in this patient population.³²

Imatinib, a tyrosine kinase inhibitor of bcr-abl used to treat Philadelphia chromosome-positive leukemia and c-kit used to treat gastrointestinal stromal tumors, has been associated with muscle cramps and myalgias.^{16,33} Symptoms are typically mild to moderate and respond to dose reduction or treatment with calcium, magnesium, or quinine. Cramps usually occur in the hands, feet, calves, and thighs. Rarely, imatinib has been associated with rhabdomyolysis.³⁴ The mechanism for these musculoskeletal manifestations is unknown.

Conclusion

As cancer therapies improve and life expectancies increase, patients are encountering treatment-related neurologic complications with increasing frequency. The ongoing challenge is to find treatment regimens that can control disease without damaging normal neural structures. Further research is needed to adequately prevent and treat neurologic complications from cancer therapy.

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REFERENCES

- Antoine JC, Camdessanche JP. Peripheral nervous system involvement in patients with cancer. *Lancet Neurol*. 2007;6:75-86.
- Dietrich J, Wen PY. Neurologic complications of chemotherapy. In: Schiff D, Kesari S, Wen PY, eds. *Cancer Neurology in Clinical Practice*. 2nd ed. Totowa, NJ: Humana Press; 2008:287-326.
- Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol*. 2009;63:761-767.
- Albers J, Chaudhry V, Cavaletti G, et al. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev*. 2007;CD005228.
- Wolf S, Barton D, Kottschade L, et al. Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies. *Eur J Cancer*. 2008;44:1507-1515.
- Verstappen CC, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy in patients with cancer: Clinical signs and optimal management. *Drugs*. 2003;63:1549-1563.
- DeAngelis LM, Posner JB. Side effects of chemotherapy. In: *Neurologic Complications of Cancer*. 2nd ed. New York, NY: Oxford University Press; 2009: 447-510.
- Marinella MA, Markert RJ. Reversible posterior leukoencephalopathy syndrome associated with anticancer drugs. *Intern Med J*. 2008. [Epub ahead of print]
- Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: A review of published studies and recommendations for future research. *J Clin Oncol*. 2007;25:2455-2463.
- Vardy J, Tannock I. Cognitive function after chemotherapy in adults with solid tumours. *Crit Rev Oncol Hematol*. 2007;63:183-202.
- Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev*. 2008;18:121-131.
- Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer*. 2006;94:828-834.
- Dietrich J, Han R, Yang Y, et al. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo [abstract]. *J Biol*. 2006;5:22.
- Dietrich J, Monje M, Wefel J, et al. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *Oncologist*. 2008;13:1285-1295.
- Cross NE, Glantz MJ. Neurologic complications of radiation therapy. *Neurol Clin*. 2003;21:249-277.
- Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol*. 2009;6:596-603.
- Yoshii Y. Pathological review of late cerebral radionecrosis. *Brain Tumor Pathol*. 2008;25:51-58.
- Torcuator R, Zuniga R, Mohan YS, et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. *J Neurooncol*. 2009;94:63-68.
- Monje M. Cranial radiation therapy and damage to hippocampal neurogenesis. *Dev Disabil Res Rev*. 2008;14:238-242.
- Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: A comparative study. *Lancet*. 2002;360:1361-1368.
- Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: Long-term follow-up. *Lancet Neurol*. 2009;8:810-818.
- Shaw EG, Rosdhal R, D'Agostino RB, Jr., et al. Phase II study of donepezil in irradiated brain tumor patients: Effect on cognitive function, mood, and quality of life. *J Clin Oncol*. 2006;24:1415-1420.
- Thiessen B, DeAngelis LM. Hydrocephalus in radiation leukoencephalopathy: Results of ventriculoperitoneal shunting. *Arch Neurol*. 1998;55:705-710.
- Brown PD, Asher AL, Farace E. Adjuvant whole brain radiotherapy: Strong emotions decide but rational studies are needed. *Int J Radiat Oncol Biol Phys*. 2008;70:1305-1309.
- Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol*. 2009;10:1037-1044.
- Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol*. 2006;24:3113-3120.
- Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol*. 2009;6:465-577.
- Sherman JH, Aregawi DG, Lai A, et al. Optic neuropathy in patients with glioblastoma receiving bevacizumab. *Neurology*. 2009;73:1924-1926.
- Besse B, Lasserre SF, Compton P, et al. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res*. 2010;16:269-278.
- Carden CP, Larkin JM, Rosenthal MA. What is the risk of intracranial bleeding during anti-VEGF therapy? *Neuro Oncol*. 2008;10:624-630.
- Norden AD, Drappatz J, Wen PY. Antiangiogenic therapies for high-grade glioma. *Nat Rev Neurol*. 2009;5:610-620.
- Nghiemphu PL, Green RM, Pope WB, et al. Safety of anticoagulation use and bevacizumab in patients with glioma. *Neuro Oncol*. 2008;10:355-360.
- Guilhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist*. 2004;9:271-281.
- Penel N, Blay JY, Adenis A. Imatinib as a possible cause of severe rhabdomyolysis. *N Engl J Med*. 2008;358:2746-2747.