Neurocognitive Complications of Cancer Therapy

By Michelle Monje, MD, PhD

Overview: Oncologic therapies frequently result in a spectrum of neurocognitive deficits that include impaired learning, memory, attention, and speed of information processing. In addition to classical mechanisms of neurotoxicity associated with chemotherapy and radiotherapy, such as radiation necrosis and leukoencephalopathy, damage to dynamic progenitor cell populations in the brain are emerging as important etiologic factors. Radiation and chemotherapy-induced damage to progenitor populations responsible for maintenance of white matter integrity and adult hippocampal neurogenesis are now believed to play major roles in the neurocognitive impairment many cancer survivors experience.

TREATMENT STRATEGIES designed to target cancer cells are commonly associated with damaging effects to normal cell types, including those of the central nervous system (CNS). Cognitive dysfunction has been long recognized as a major problem in long-term survivors in the pediatric population.[1,2] There is growing evidence that cancer chemotherapy-associated cognitive dysfunction, commonly referred to as "chemobrain," appears to be a real phenomenon in many adults undergoing treatment for cancer and cannot simply be attributed to stress, fatigue, or affective distress.[3-5]

Radiotherapy and chemotherapy are both associated with neurocognitive complications, and the deleterious effects on cognition can be combinatorial and even synergistic. As treatment regimens advance and survival is prolonged, neurologic complications are likely to be observed with increasing frequency.

Great progress has recently been made in understanding the cellular mechanisms of neurologic dysfunction following cancer therapy. The identification and characterization of progenitor cell populations in the adult mammalian CNS has highlighted physiologic processes particularly vulnerable to damage from cancer therapies. Neural stem and neural precursor cell (NPC) populations are believed to be crucial to normal memory function and to play key roles in the maintenance of white matter integrity. Experimental studies have revealed that toxicity to NPCs may be central in understanding delayed treatment side effects, including cognitive impairment and white matter disease.[6]

NPCs in the Childhood and Adult Brain

Neural stem cells—self-renewing cells that generate neurons, astroglia, and oligodendroglia, as well as lineage-restricted neural progenitor cells—exist in the postnatal and adult brains of all mammals studied to date, including humans.[7,8] Neural stem cells, neuronal progenitor cells, and glial progenitor cells are collectively known as NPCs. Prominent populations of neural stem cells exist in the subventricular zone throughout the CNS[9] and in the hippocampus.[8] Lineage-restricted glial progenitor cells are found throughout the subcortical white matter and, in fact, the process of postnatal myelination of the frontal lobes continues from birth through the end of the third decade of life. Maintenance of white matter tract integrity is thought to depend on the ongoing generation of glial cells (oligodendrocytes and astrocytes) from glial progenitor cells. Once thought to be a relatively static organ, it is now recognized that the health of the adult brain requires ongoing cell generation from diverse precursor cell populations in multiple germinal zones (Fig. 1).

Hippocampal Neurogenesis and Cognition

In the hippocampus, a major site of postnatal/adult neurogenesis, NPCs generate newborn dentate gyrus granule cell neurons throughout life (Fig. 2). These newborn hippocampal granule cell neurons migrate into the granule cell layer proper, integrate, and become electrophysiologically functional. (For review, see Zhao et al.[8])

Although the electrophysiologic properties of the mature newborn neuron (approximately 4 weeks after new neuron generation) are identical to those of the established granule cell neurons, electrophysiologic properties of the immature newborn neuron (age 1 to 3 weeks) are distinct, and therefore possess particularly powerful capabilities to alter the performance of a circuit.[9]

New neuron generation is believed to be crucial for certain types of memory function. In rodents, increased hippocampal neurogenesis results in improved performance in certain hippocampal-dependent memory tasks. Neurogenesis is increased by voluntary physical exercise, exposure to an enriched environment, and by hippocampal-dependent learning.[8] The mechanism by which cognitive challenges increase neurogenesis appears to be mediated by increased activity flow through the hippocampal circuit.[10,11] In this way, use of the hippocampal circuit, at the right time and in the right way, strengthens the circuit, much as weight lifting strengthens muscles.

Conversely, disruption of hippocampal neurogenesis generally results in decreased performance in certain hippocampal-dependent memory tasks, such as finding the way out of a maze.[8] Discussed in more detail later, several exogenous and endogenous conditions negatively regulate neurogenesis in the hippocampus, including chemotherapy,[12] radiotherapy,[13,14] the glucocorticoid hormones (e.g., prednisone and dexamethasone),[15] and certain inflammatory states.[16,17] Cranial radiation has been repeatedly proven to cause defects in hippocampal-dependent behavioral tests in rodents.[18-20]

Ongoing hippocampal neurogenesis is likely important for human cognition as well; although experimental manipulation of neurogenesis in humans is not ethically possible, conditions known to alter neurogenesis for better or worse,

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Author's disclosure of potential conflicts of interest is found at the end of this article.

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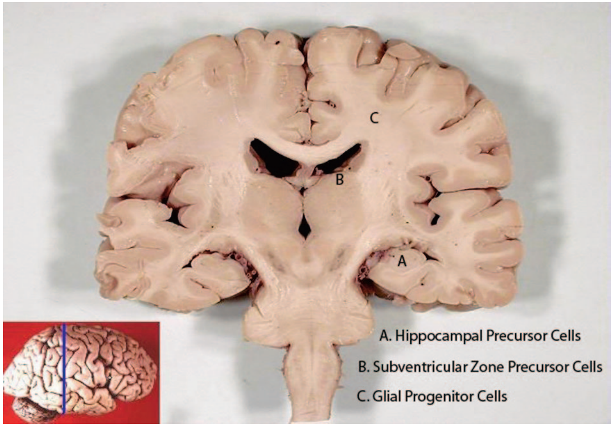

Fig. 1. Germinal zones of the brain vulnerable to cancer therapies, seen on coronal section of the human adult brain. (A) Hippocampus, containing neural stem cells and lineage-restricted progenitors that give rise to new dentate gyrus granule cell neurons throughout life. (B) Subventricular zone of the lateral ventricle, containing neural stem cells and lineage-restricted progenitors. (C) Frontal lobe white matter, containing glial progenitor cells that give rise to myelinating oligodendrocytes. Figure adapted from image courtesy of WikiCommons.

such as voluntary physical exercise or aging, are associated with corresponding changes in memory function in humans.[21]

Microenvironmental determinents of neurogenesis. The process of neurogenesis requires a specific neurogenic microenvironment, referred to as the neurogenic niche. Transplantation experiments demonstrate that neurogenesis is restricted in the postnatal brain to regions in which it occurs naturally, namely the subventricular zone and the subgranular zone of the hippocampus.[8] Microenvironmental determinants of neurogenesis include the presence of the trophic signals required for progenitor cell proliferation, differentiation and survival, and the absence of inhibitory factors. NPCs form a close anatomic relationship with the microvasculature in the neurogenic region, and this neurovascular relationship is believed to be crucial not only for nutritional support, but also for trophic support.[8] Hippocampal astrocytes play key roles in creating and maintaining the neurogenic niche.[8] Many of the signaling pathways central to prenatal neural development are conserved in postnatal neurogenesis, including Wnt, Shh, and Notch.[8] Additional molecules with potent proneurogenic effects include fibroblast growth factor, vascular endothelial growth factor, and certain neurotransmitters.[8]

An important negative regulator of the neurogenic microenvironment is microglial inflammation, particularly in disease states. Proinflammatory cytokines elaborated by microglial cells in certain states of activation, including interleukin (IL)-6 and tumor necrosis factor-alpha, inhibit neurogenesis through a specific blockade in neuronal differentiation, as well as a nonspecific increase in precursor cell death.[16,22] The effects of inflammatory cells on neurogenesis are complex and depend on the microglial phenotype involved; microglia stimulated by cranial irradiation or systemically administered lipopolysaccharide (also known as endotoxin) inhibit neurogenesis,[16] whereas microglia stimulated by IL-4 or interferon-gamma promote neurogenesis.[23]

KEY POINTS

- Chemotherapy and cranial radiotherapy frequently result in neurocognitive deficits, including memory and executive dysfunction.
- Damage to dynamic cell populations in the subcortical white matter and hippocampus are thought to cause much of the cognitive toxicity induced by cancer therapies.

Neurocognitive Sequelae of Cancer Therapy

Cancer treatment usually involves multiple modalities, including surgery, traditional chemotherapy, and radiation. In addition, hormonal agents, steroids, and other novel chemotherapeutic agents (e.g., angiogenesis inhibitors, tyrosine kinase inhibitors) are increasingly used in patients with cancer.

Adult patients typically report cognitive symptoms, such as difficulties with memory and attention, soon after initiating treatment. Frequently, these symptoms persist after completion of therapy and result in difficulty returning to previous academic, occupational, or social activities. Both radiation and many chemotherapeutic agents have been shown to cause acute and delayed injury to the CNS. (For review, see Dietrich et al.[6])

Radiation

Cranial radiotherapy is among the best-recognized risk factors for cognitive dysfunction following cancer therapy. Currently, reported risk factors for developing neurologic complications of radiation include younger than age 7 or older than age 60, more than 2 Gy dose per fraction, cumulative dose, volume of brain irradiated, hyperfractionation schedules, shorter overall treatment time, concomitant or subsequent use of chemotherapy, and the presence of comorbid vascular risk factors (e.g., diabetes).[6] Radiation encephalopathy has been separated into three stages: (1) acute reaction, (2) early-delayed reaction, and (3) late-delayed reaction.[6] Within the first several weeks of therapy, patients may experience acute focal neurologic deficits. These effects are possibly from increased edema, which has been supported by the observation that glucocorticoid steroid treatment often results in clinical improvement. Early-delayed adverse effects, such as the “somnolence syndrome,” usually occur within 1 to 6 months of treatment, and are thought to be from demyelination.[6] This syndrome is characterized by somnolence, fatigue, and cognitive deficits consistent with dysfunction of frontal network systems. Slowed information processing speed, word, and memory retrieval deficits; diminished executive function and attention; and decreased fine motor dexterity are characteristic of the early-delayed syndrome.[6]

Late-delayed side effects occur months to years after cessation of treatment, and are largely irreversible and progressive. Cranial radiotherapy frequently causes a debilitating cognitive decline in both children and adults.[6] Months to years after cranial radiation exposure, patients exhibit progressive deficits in short-term memory, spatial relations, visual motor processing, quantitative skills, and attention.[6] Hippocampal dysfunction is a prominent feature of these neuropsychologic sequelae. In fact, the severity of the cognitive deterioration appears to depend on the radiation dosage delivered to the medial temporal lobes.[6]

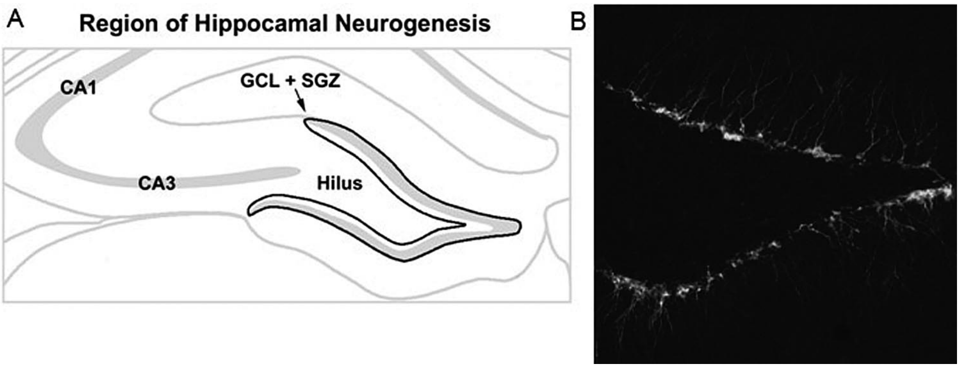

Fig. 2. Region of hippocampal neurogenesis. (A) Schematic representation of the hippocampal formation. The granule cell layer (GCL) of the dentate gyrus in highlighted in gray. The subgranule zone (SGZ), where neural precursor cells reside, is the thin lamina in between the GCL and the hilus. (B) Confocal micrograph illustrating the newborn neuron-specific marker doublecortin lining the neurogenic region of the rodent dentate gyrus. Figure adapted from Monje et al.[16]

The incidence of radiation-induced impairment in cognition has been very well described in children. It is estimated that, when children younger than age 7 are irradiated, nearly 100% require special education; after age 7, approximately 50% of children require special education. Some degree of memory dysfunction is thought to occur in the majority of children. The incidence of memory dysfunction in adult patients has been difficult to quantify, largely because of a lack of uniformity in neuropsychometic testing methodology in the literature. However, because adults are surviving longer after treatment and the long-term consequences of radiation are becoming more important for this population, an extremely high rate of cognitive dysfunction of varying degrees has been recognized.

Mild-to-moderate cognitive dysfunction is inconsistently associated with radiologic findings and frequently occurs in patients with normal-appearing neuroimaging.[6] Clinically significant memory deficit in the absence of radiologic findings implicates damage to a subtle process with robust physiologic consequences. One such process is hippocampal neurogenesis, discussed in detail below.

On the more severe end of the spectrum, a devastating dementia syndrome is associated with diffuse leukencephalopathy, with or without radionecrosis.[24] The dementia is typically a subcortical dementia characterized by deficits in memory, attention, and executive function. Gait disturbance, urinary incontinence, and personality changes may occur. Cortical functions, such apraxis and language, are relatively spared. Typical onset is within 2 years of radiation exposure, and the course is usually progressive. A large meta-analysis of the literature found an incidence of postradiation dementia to be 12%.[25] Risk factors are the same as for leukencephalopathy, including radiation dose, fractions size, volume of brain irradiated, older age, and concomitant chemotherapy. Methylphenidate[26] and anticholinesterases, such as donepezil,[27] are sometimes used for symptomatic relief. As the survival of patients with brain tumors improves, an increasing number develop impairment of normal cerebrospinal fluid reabsorption through the arachnoid granulations. This leads to a communicating hydrocephalus with cognitive impairment, gait unsteadiness, and urinary symptoms. A subset of these patients may benefit from placement of a ventriculoperitoneal shunt.[28]

Chemotherapy

Chemotherapy-induced cognitive impairment, known among patients with cancer and oncologists as "chemofog" or "chemobrain," is characterized by deficits in memory function and concentration, and is an increasingly recognized complication.[6] A recent meta-analysis estimates that mild cognitive impairment occurs in 10% to 40% of breast cancer survivors,[29] and other estimates of cognitive dysfunction incidence range from 15% to 70%.[3,30,31] It is important to note that some degree of memory impairment in patients with breast cancer has been shown to be present before initiation of adjuvant chemotherapy and correlates with affective distress.[32] In contrast to the cognitive dysfunction that follows cranial irradiation, chemotherapy-induced deficits in memory and concentration appear to be transient in many cases, but may only resolve slowly over a number of years.[29]

Similar to the radiation-induced syndrome, patients undergoing chemotherapy experience difficulty with memory, attention, information processing speed, and organization (components of executive function). Deficits in attention account for patient reports of "spacing out" and losing concentration at times. Inefficiency of working memory, information processing speed, and executive function corresponds to patient reports of disorganization, difficulty multitasking, and overall slowness in performing tasks. Memory testing generally reveals reduced learning efficiency and memory retrieval problems with relatively better memory consolidation. This pattern of cognitive performance after chemotherapy indicates prominent dysfunction of frontal lobe networks and relatively less severe dysfunction of limbic (e.g., hippocampal) networks.

The Cellular Basis of Radiation-induced Cognitive Dysfunction

Located in the medial temporal lobes, the hippocampal formation plays a central role in learning and memory[33]—functions prominently affected by radiation. Neural stem cells, self-renewing cells that generate neurons, astroglia, and oligodendroglia, as well as lineage-restricted progenitor cells, exist in the postnatal and adult brains of all mammals studied to date, including humans.[7,8] In the hippocampus, a major site of postnatal/adult neurogenesis, NPCs generate newborn dentate gyrus granule cell neurons throughout life, and this process of hippocamal neurogenesis is thought to be critical for normal hippocampal function. (For review, see Zhao et al.[8]) Animal studies have elucidated the pathologic effects of radiation on hippocampal progenitor cell biology. Work in such models has demonstrated that exposure to therapeutic doses of irradiation results in increased apoptosis,[13,34,35] decreased cell proliferation, and decreased neuronal differentiation in the neurogenic region of the

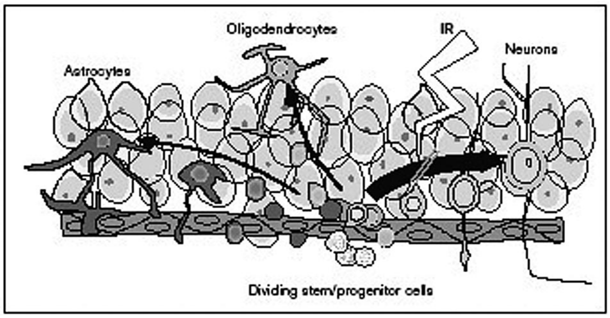

Fig. 3. Irradiation causes a specific blockade in neuronal differentiation. Stem/progenitor cells in the subgranular zone of the hippocampus can self-renew or differentiate into neurons, astrocytes or oligodendrocytes. Following radiation exposure, neuronal differentiation is selectively blocked. Figure adapted from Monje et al.[16]
Abbreviation: IR, irradiation.

hippocampus.[13,14,34] A single clinically relevant dose of radiation in the rat results in a greater than 95% decrease in absolute production of new neurons throughout the entire volume of the hippocampus,[14] essentially ablating neurogenesis in these animals (Fig. 3).

The direct isolation of equivalent numbers of NPCs from hippocampi 1 month after exposure to increasing doses of irradiation demonstrated that an acute ablation of the NPC population does not occur.[14] However, NPCs exhibited impaired growth potential in a radiation dose-dependent manner,[14] possibly because of radiation-induced DNA damage and subsequent mitotic catastrophe. The striking decrease in cell proliferation within the neurogenic region in the months following radiation probably results from both acute cell death and impaired proliferative potential of the precursor pool.

In contrast to the effects on neurogenesis, gliogenesis appears to be relatively preserved following irradiation.[14] The disproportionate deficit in neurogenesis could be from a stem cell-intrinsic defect or a failure of the neurogenic microenvironment. To test the intrinsic ability of irradiated precursor cells to make neurons, NPCs were isolated from rat brains exposed to radiation and allowed to differentiate in vitro. NPCs from irradiated brains could, in fact, make neurons, and newborn cells were generated in the same neuron to glia ratio as those from nonirradiated NPCs.[14] This suggests that alterations in the microenvironment of the irradiated hippocampus may be the cause of a near complete absence of neurogenesis. To test the integrity of the irradiated neurogenic microenvironment, healthy, nonirradiated NPCs were transplanted into the irradiated hippocampus. These transplanted, nonirradiated NPCs similarly failed to produce neurons,[14] indicating that radiation disrupts the microenvironment necessary for neurogenesis.

Two prominent alterations in the neurogenic niche have been observed in the hippocampus following irradiation. First, there is a disruption of the close anatomic relationship of NPCs to the microvasculature within the neurogenic region.[14] Second, radiation causes a striking microglial inflammatory response.[14,16] This finding is intriguing because microglial inflammation and subsequent elaboration of proinflammatory cytokines inhibit neurogenesis.[16,17] Furthermore, microglial inflammation alone is sufficient to cause disruption of the neurovascular relationship,[16] and treatment with an anti-inflammatory agent restores the anatomic relationship of NPCs with microvasculature in the neurogenic region. Notably, anti-inflammatory therapy restores neurogenesis following systemic inflammatory challenge with lipopolysaccharides.[16] The nonsteroidal agent indomethacin, which functions both as a cyclooxygenase I/II inhibitor and as a direct peroxisome proliferator-activated receptor-gamma agonist, was administered during and after cranial radiation. Indomethacin therapy resulted in a 35% decrease in activated microglia within the neurogenic region of the hippocampus and a 250% increase in the absolute number of newly generated neurons relative to animals irradiated without anti-inflammatory intervention.[16] Despite significant improvement, however, anti-inflammatory therapy alone did not restore neurogenesis to baseline levels. The effect on hippocampal function remains unclear. More potent anti-inflammatory/antimicroglial agents may confer a greater benefit in restoring neurogenesis. Experiments are currently ongoing to identify the most efficacious agent. It should be noted that steroidal anti-inflammatory agents (e.g., prednisone, dexamethasone) are themselves deleterious to neurogenesis, thus only nonsteroidal agents should be considered for restoration of neurogenesis following radiotherapy. Of nonsteroidal anti-inflammatory agents, those that do not inhibit cyclooxygenase enzymes will likely prove to be the most efficacious because of the beneficial effects of prostaglandin E2 on neurogenesis.[36]

Recent work suggests that observations made in animal models of radiation-induced neurotoxicity may extend to patients with cancer.[37] Postmortem analysis of hippocampal neurogenesis in patients with medulloblastoma, performed 2 to 23 years following the completion of radiotherapy, revealed a 10-fold decrease in neurogenesis, compared with age and sex-matched controls. These findings suggest long-lasting damage to hippocampal neurogenesis caused by the cumulative effects of treatment, including cranial irradiation, chemotherapy, steroid therapy, as well as endogenous factors related to the disease process itself.[37] One of the cases in this study, however, offered a unique opportunity to examine the effects of radiotherapy alone. One patient suffered a unilateral recurrence of her tumor adjacent to, but not invading, one hippocampus and therefore received additional focal radiotherapy to that region. The contralateral hippocampus thus served as an internal control for systemic factors, such as chemotherapy. Relative to the internal control hippocampus, the side with the additional radiation exposure exhibited a 79% reduction in neurogenesis, a 59% reduction in overall cell proliferation within the neurogenic region, a 200% increase in activated microglia, and relative preservation of gliogenesis.[37] These findings mirror those from the rodent model of radiotherapy and confirm ablation of human neurogensis following cranial radiotherapy.

The Cellular Basis of Chemotherapy-induced Cognitive Dysfunction

Many chemotherapeutic agents have now been demonstrated to have toxic effects on multiple neural cell types, affecting both proliferating and static cells of the CNS. For example, methotrexate, an antimetabolite with a particularly high incidence of neurotoxic effects induces cell death in multiple neural cell types, including neurons, in both cell culture and in vivo rodent model systems.[38] Particularly vulnerable to methotrexate toxicity are the glial progenitor cells that form myelinating oligodendrocytes and astrocytes, both critical to white matter integrity.[39] Further studies have confirmed and delineated the particular chemosensitivity of NPCs, including both neural stem cells, as well as lineage-restricted progenitor cells that form, among other cell types, the myelinating oligodendrocytes in the frontal white matter.[40] A wide range of agents, including carmustine, cisplatin, and cytarabine have proven to be more toxic to NPCs than to the cancer cells their use targets.[40] In addition to their precursor cells, mature myelinating oligodendrocytes are exquisitely sensitive to chemotherapeutic agents at doses lower than required to kill most tumor cell types.[40,41] Following single-drug exposures in an in vivo animal model, rebound cell proliferation in germinal zones imply that compensatory mechanisms may replace the cells lost; disturbingly, repetitive drug exposures (carmustine, cisplatin, or cytarabine) ablate this proliferative response, suggesting a depletion of the precursor pool.[40] Consistent with this finding, toxicity to oligodendrocyte progenitors and myelinating oligodendrocytes causes progressive damage to white matter tracts in the rat after short-term fluorouracil exposure at clinically relevant doses.[41]

Multiple chemotherapeutic agents similarly affect the precursor cells that contribute to hippocampal neurogenesis. Like radiation exposure, systemic methotrexate administration causes a persistent decrease in cell proliferation within the germinal region of the hippocampus and associated poor performance on hippocampal-dependent cognitive tasks in rodent models.[42,43]

Conclusion

Damage to neural progenitor cell populations offers a compelling explanation for delayed neurologic toxicities, such as progressive dementias, cerebral atrophies, and white matter disease. There are likely a number of cofactors and mechanisms that mediate the risk for an individual patient of developing neurotoxicity and cognitive dysfunction.

Chemotherapy and radiotherapy remain central to the management of cancer. Many patients experience a debilitating cognitive syndrome that severely affects their long-term quality of life. Although progress in oncology is leading to more targeted therapeutic agents, these new and emerging therapies that alter signaling pathways active in cancer cells and their niche are likely to further affect the normal neural stem and progenitor cells that share dependence on many of these very same pathways. Mitigating the cognitive sequelae of cancer therapies will require specific and targeted intervention aimed at protecting or replacing compromised NPC populations. For example, the neuroprotective value of anti-inflammatory strategies for patients undergoing cranial radiation is currently being explored. Symptomatic interventions, such as the use of stimulants (e.g., methylphenidate) or acetylcholinesterase inhibitors (e.g., donezepil) can improve cognition. Cognitive and behavioral intervention strategies, such as the use of external memory aids (memory notebooks, pagers), can prove very useful to daily functioning.[44] Hopefully, as we advance in our understanding of the mechanisms responsible for neurocognitive dysfunction following cancer therapy, new strategies will emerge to limit the extent and effect of treatment-related cognitive symptoms.

Author's Disclosure of Potential Conflicts of Interest

Author	Employment or Leadership Positions (Commercial Firms)	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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