



Review Article

## Neurocognitive Effects of Cancer: A New Surrogate End Point

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### ABSTRACT

The longer survival of a subset of cancer patients treated with chemotherapy (CT) or CNS directed radiotherapy (RT) has revealed that these treatments can impair cognitive functions. Following this discovery, researchers and clinicians have a new challenge on their table: to improve the quality of life of cancer survivors. Neurocognitive effects of cancer defined by problems with thinking, learning, remembering and executive function (i.e. the ability to organize, plan, hold information in mind and manipulate it and self-monitor behavior) have become an expanding area of scientific interest. These deficits significantly impair the daily life of the patient causing decreased independence, interference in academic or vocational pursuits, and increased caregiver distress and burden. Subtle cognitive deficits can also significantly limit a patient's ability to perform usual activities, although it may not be evident on casual observation or detectable via routine medical examinations. Neurocognitive outcomes are considered important end points in clinical trials of new agents; the U.S. Food and Drug Administration considers improvement in neurocognitive function or delay in expected decline as the approved end points in registration trials, as these end points directly relate to clinical benefit.

The purpose of this review is to discuss neurocognitive impairment in cancer patients and various neuroprotective strategies available to minimize this neurocognitive deficit.

**Key words:** neurocognitive, chemotherapy, WBRT, cancer

### INTRODUCTION

Cognitive changes are a documented consequence of cancer therapies, including chemotherapy and radiotherapy. The ability to inhibit cell division, the key element in cancer therapies, causes reduction in neurogenesis, which is implicated in cognitive disorders. Radiotherapy is delivered to the brain for the treatment of primary brain tumors and brain metastases, and also prophylactically to decrease the occurrence of CNS relapse in patients with

small cell lung cancer (SCLC) and certain hematological malignancies with known high rates of CNS relapse. Brain radiotherapy has been shown to have profound negative impact on cognitive functions. [1]

Chemotherapy induced cognitive impairment is noted in 30% patients. The exact underlying mechanism of the impairment is currently unknown. Most of the cognitive research has been in breast cancer survivors although there are currently

ongoing studies investigating cognitive function in patients with colorectal, testicular and prostate cancer. Longitudinal studies with baseline cognitive assessments have been published in the last few years. These have reported that up to 30% of patients with solid tumors may have cognitive impairment before receiving chemotherapy. [2] This has been attributed as a paraneoplastic manifestation of cancer and is closely related to the area involved in case of brain tumors.

The impact of primary tumor itself on neurocognitive functions and role of surgery alone in causing neurocognitive deterioration is being studied extensively.

The present scenario justifies the routine use of cognitive rehabilitation programmes in cancer survivors and use of preventive strategies to minimize the neurocognitive deficit.

#### ***Neurocognitive late effects in childhood cancer survivors***

Neurocognitive late effects most commonly follow treatment of malignancies that require central nervous system (CNS)-directed therapies, such as cranial radiation, systemic therapy with high-dose methotrexate or cytarabine, or with intrathecal chemotherapy. Children with brain tumors or acute lymphoblastic leukemia are most likely to be affected. Risk factors for the development of neurocognitive side effects are female gender, young age at the time of treatment, higher radiation dose, and treatment with both cranial radiation and chemotherapy (systemic or intrathecal). [3][4]

#### ***Pediatric brain tumors***

Brain tumors are the most common pediatric solid tumor with an annual incidence of 2.7 per 100,000 children under the age of 20 years. [5] Survival rates have increased over recent decades for children with brain tumors; however, long-term cognitive effects due to their illness and

associated treatments are emerging. Cranial irradiation used in management of these tumors has consistently shown a link to symptoms of neurocognitive deficit. Upon neuropsychological testing, 40-100% of long-term brain tumor survivors have been found to have some form of cognitive dysfunction. [6]

Neurocognitive deficits are inversely related to age at the time of irradiation and correlate directly with both site (supratentorial irradiation > posterior fossa irradiation) and radiation dose. [7][8] Detailed assessment of neuropsychological function usually identifies multiple areas of damage in information processing. Some studies have found specific neurocognitive deficits in attention, memory, coordination, fine motor speed, visual motor processing, mathematics, and spatial relations. [7][8] The negative impact of radiation treatment has been characterized by changes in intelligence quotient (IQ) scores, which have been noted to drop about 2 to 5 years after diagnosis and an attenuation of the decline 5 to 10 years afterward, followed by stabilization of the IQ scores 20 to 40 years after diagnosis. [9][10][11] Affected children may experience information-processing deficits resulting in academic difficulties, and are prone to problems with receptive and expressive language, attention span, and visual and perceptual motor skills. These changes in intellectual functioning may be partially explained by radiation-induced or chemotherapy-induced reduction of normal white matter volume as evaluated through magnetic resonance imaging (MRI). [12]

Extent of surgical resection has been found to have a positive relation with intellectual function. [13] as well as no relation at all. [14] Brain tumor patients with hydrocephalus at diagnosis are at higher risk for intellectual deficits than those with no hydrocephalus at diagnosis. [15]

The resultant increased intracranial pressure due to hydrocephalus can give rise to declining academic performance, fatigue, personality changes and vague intermittent headaches.

Additionally, there is preliminary evidence to suggest that survivors of medulloblastoma with glutathione S-transferase M1 and T1 gene polymorphisms may be at an increased risk of neurotoxicity and intellectual impairment.<sup>[16]</sup> A report from St. Jude Children's Research Hospital showed that age at time of irradiation was more important than radiation dose in predicting cognitive decline. Children younger than 5 years showed the most cognitive decline.<sup>[17]</sup>

Using lower doses of radiation and more targeted volumes have demonstrated improved results minimizing the neurocognitive effects of therapy. Recent studies indicated that patients with medulloblastoma exposed to lower doses of whole-brain irradiation (23.5 Gy) are at reduced risk of neurocognitive dysfunction.<sup>[18]</sup> Treatment of neurocognitive deficits with pharmacologic and/or rehabilitative interventions may ameliorate the learning and memory difficulties associated with declines in IQ. Methylphenidate has been shown to reverse attentional problems and improve memory/learning at least in time-limited measures.<sup>[19]</sup> Ongoing studies are being performed to address prospective interventions during and immediately after irradiation.

#### ***Acute lymphoblastic leukaemia***

The increase in cure rates for children with ALL over the past decades has resulted in greater attention to the neurocognitive morbidity and quality of life of survivors. In survivors of ALL, cranial radiation therapy leads to considerable neurodevelopment late sequelae. Although these abnormalities are mild in some patients (overall IQ fall of approximately 10

points), those who have received higher doses at a young age may have significant learning difficulties.<sup>[20][21]</sup> Deficits in visual-motor integration, processing speed, attention, and short-term memory are reported in children treated with 1800 cGy to 2400 cGy.<sup>[22][23]</sup> Girls and younger children are more vulnerable to cranial irradiation.<sup>[24]</sup> The decline in intellectual functioning appears to be progressive, showing more impairment of cognitive function with increasing time since radiation therapy.<sup>[25]</sup> Most studies of chemotherapy-only CNS-directed treatment display good neurocognitive long-term outcomes. However, few longitudinal studies evaluating long-term neurocognitive outcome report a decline in global IQ after treatment with chemotherapy alone.<sup>[26][27]</sup> The academic achievement of ALL survivors in the long term seems to be generally average for reading and spelling with deficits mainly affecting arithmetic performance.<sup>[28][29]</sup> During long-term follow-up of children treated for ALL that had CNS-directed RT [18 Grey (Gy) in 10 fractions] and chemotherapy using intrathecal methotrexate, parents commonly report that children are unable to attend to simple tasks or their eye-hand coordination is poor or their memory is unsatisfactory or their arithmetic ability is inadequate. These reports are substantiated by the school teachers' reports of these children. Because of its penetrance into the CNS, systemic methotrexate has been used in a variety of low-dose and high-dose regimens for leukemia CNS prophylaxis. Systemic methotrexate in high doses can lead to an infrequent but well-described leukoencephalopathy, in which severe neurocognitive deficits are obvious.<sup>[30]</sup>

Neurocognitive assessment in children can be done by using the Bender gestalt test (BGT)<sup>[31]</sup> colored progressive matrices (CPM)<sup>[32]</sup> and the Binet Kamat test

(BKT) of intelligence.<sup>[33]</sup> The BGT is a nonverbal test of visuo-spatial perception and visuo-motor coordination and integration. It consists of simple geometrical figures which the subject has to copy as they are presented one by one. The test is scored on the basis of certain errors made. The total number of errors made provides an age equivalent, which is a measure of the cognitive function. The CPM is also a nonverbal test. It is designed to assess a child's ability to form comparisons and reason by analogy. It comprises three sets of 12 problems each, represented as patterns with a missing piece, where the subject has to find the missing piece from the alternatives given. It provides a percentile score on analytical reasoning, which is also a measure of the child's intelligence level. The BKT measures general intelligence and provides a global IQ (verbal and nonverbal) of the subject. Pattern analysis of the test items provides estimates of specific cognitive functions.

The goal of current ALL treatment is to minimize adverse late effects while maintaining high survival rates. Patients are stratified for treatment according to their risk of relapse. Avoiding cranial radiation in standard risk patients and using the 12-Gy preventive cranial radiotherapy regimen in medium risk and high risk patients has been shown to provide sufficient central nervous system prophylaxis.<sup>[34]</sup>

Since the life expectancy of these children has increased and most children have long-term survival and even cure, identifying children with cognitive difficulties and parental counseling could be important in the rehabilitation of these children, so that they may benefit from early educational intervention directed towards using cognitive strengths to overcome difficulties. In exceptional cases, admission into special schools for slow learners is another option, where remedial training in

scholastic skills can be tried.<sup>[35]</sup>

### **Other cancers**

Neurocognitive abnormalities have been reported in other groups of cancer survivors besides patients with CNS tumors and ALL. In a study of adult survivors of childhood non-CNS cancers (including ALL, n = 5,937), 13% to 21% of survivors had impairment in task efficiency, organization, memory, or emotional regulation. Patients with lymphoma and neuroblastoma were particularly affected. This rate of impairment was approximately 50% higher than that in the sibling comparison. Factors such as diagnosis before age 6 years, female gender, cranial radiation therapy, and hearing impediment were associated with impairment. This neurocognitive impairment was associated with important life outcomes in adults, such as unemployment, marriage status, and lack of independent living. Thus, monitoring all non-CNS cancer survivors, particularly those with leukemia, lymphoma, and neuroblastoma, for difficulties in learning and academic performance is essential so that the appropriate intervention may be given during childhood. Focused screening is especially important for children who received any cranial radiation therapy, who are female, who are treated in the preschool age range, and who have hearing deficits.<sup>[23]</sup>

### **Neurocognitive effects of chemotherapy in adults**

There is growing evidence that a subset of patients suffer cognitive impairment after chemotherapy.<sup>[36-38]</sup> Survivors have coined the terms 'chemobrain' and 'chemofog' to describe this symptom, although recent studies have found that some patients' cognitive impairment may predate the chemotherapy<sup>[39]</sup> and hormonal treatment for cancer may also impact on cognitive function.<sup>[40]</sup> Fortunately, the problem is generally subtle and often improves after ceasing

chemotherapy. However, for some survivors the symptoms are sustained and can impact significantly on their quality of life and ability to function in their everyday activities.<sup>[41]</sup> Most of the cognitive research has been in breast cancer survivors although there are currently ongoing studies investigating cognitive function in patients with colorectal, testicular and prostate cancer. Studies have reported a 15–50% incidence of cognitive impairment in patients who received chemotherapy for solid tumors.<sup>[36,37]</sup> The studies were mainly cross-sectional in design with no evaluation of cognitive function before treatment and no longitudinal data. Comparison between studies is hampered by lack of clear definition of cognitive impairment and standardization of neuropsychological tests used. Despite methodological problems and small sample size, the studies consistently showed a sub-group of people who suffered subtle cognitive impairment, with diffuse yet patchy deficits after chemotherapy. The cognitive domains most consistently impaired were attention, concentration, verbal and visual memory and processing speed.<sup>[36,37]</sup>

The cause of cognitive impairment in cancer patients after chemotherapy is unknown, but is likely to be multi factorial. Possible mechanisms by which chemotherapy might lead to cognitive dysfunction include direct neurotoxic effects; oxidative damage induced hormonal changes; immune deregulation with release of cytokines and blood clotting in small vessels of the central nervous system. Some patients may have a genetic predisposition for developing cognitive impairment (for example, due to problems with DNA or neuronal repair, changes in neurotransmitter activity).<sup>[2]</sup> It is likely that the regimen, the dose and the duration of chemotherapy influence the incidence and severity of cognitive impairment. According to one

study, objective rates of impairment have been higher following treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) than after anthracycline-containing regimens.<sup>[42]</sup> Studies comparing high-dose chemotherapy for breast cancer with standard-dose chemotherapy have generally found higher rates of cognitive dysfunction in patients who received high doses.<sup>[43]</sup> However, another study found no significant difference between high-dose and standard-dose chemotherapy.<sup>[44]</sup>

Methotrexate is a chemotherapeutic agent used in treatment of primary CNS lymphoma as well as other malignancies. It is often used in high doses and administered intravenously and intrathecally. Methotrexate therapy has been associated with cognitive dysfunction, including severe disseminated necrotizing leukoencephalopathy, which is more common in the elderly and in young children. Much of the toxicity of methotrexate has been attributed to alteration in normal blood brain barrier and brain architecture secondary to tumor infiltration.<sup>[45]</sup> However, there have been reports of leukoencephalopathy after low-dose, oral administration of methotrexate for benign disease such as rheumatoid arthritis.<sup>[46]</sup> Neurocognitive testing of primary CNS lymphoma patients after treatment with methotrexate (without cranial radiotherapy) has revealed conflicting results, with one small study of 10 patients observing mild cognitive dysfunction.<sup>[47]</sup> and another small study of 10 patients found no gross cognitive deterioration.<sup>[48]</sup> Unfortunately there has been only limited research to examine the neurocognitive effects of specific chemotherapy regimens in primary brain tumor patients. Hilverda et al.<sup>[49]</sup> in their study of cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment concluded that non progressed glioblastoma patients did not have neurocognitive deterioration with



concomitant temozolomide and adjuvant use. Immunotherapy, particularly interferon (IFN)-alpha, can cause significant cognitive impairments and organic mood disturbance. One prospective study of 30 chronic myelogenous leukemia patients examined before and during treatment with IFN-alpha alone or IFN-alpha and chemotherapy, found a significant decline in cognitive function in 53.3% of patients. [50] Several physiological mechanisms have been

proposed for the neurotoxic effects of IFN, including actions mediated through neuroendocrine, neurotransmitter, and cytokine pathways. Patients with IFN neurotoxicity have been reported to exhibit mild-to-moderate symptoms of frontal-subcortical brain dysfunction, including cognitive and behavioral slowing, apathy, impaired executive functions, and decreased memory.

Table 1: Chemotherapy and cognitive deficit: studies comparing breast cancer patients with matched healthy controls.

Study	Participants	Evaluation	Results
Castellon et al [51]	17 breast cancer patients; 19 healthy subjects	2-5 years post-treatment [baseline assessment not done]	Chemo-treated patients significantly worse in domains of verbal learning, visuospatial functioning, and visual memory than those who had surgery only; No significant difference between chemotherapy treatment regimens.
Brezden et al [52]	40 breast cancer patients; 36 healthy controls	Pts currently receiving CT; Patients completed CT on average 2 years previously	More patients who were receiving or had received chemo in past had moderate or severe impairment than in the control group; No significant differences between CMF and CEF groups.
Tchen et al [53]	100 breast cancer patients; 100 patient- matched healthy controls	Patients reassessed at 1 to 2 years after initial treatment; Assessment done in conjunction with matched breast cancer patients	Patients experienced a higher incidence of moderate or severe cognitive impairment (16% patients vs. 4% controls). Patients self-reported quality of life was poorer than controls, especially in areas of physical and functional domains.

CEF = cyclophosphamide, epirubicin, and Fluorouracil, CMF = cyclophosphamide, methotrexate and Fluorouracil.

Table 2: Hormonal treatment and cognitive deficit.

Study	Participants and Treatment given	Evaluation	Results
Bender et al [54]	19 breast patients (stage I,II) treated with Chemotherapy only; 15 breast patients (stage I, II) treated with Chemotherapy and tamoxifen; 12 breast carcinoma patients with only surgical treatment (no chemotherapy or tamoxifen)		Recipients of chemo plus tamoxifen displayed the broadest declines with changes in visual memory and verbal working memory; Women treated solely with chemotherapy exhibited declines in working memory only
Phillips et al [55]	22 patients received Tamoxifen ( T ) for 5 years ; 37 pts. Received Letrozole ( L ) for 5 years; 28 pts. Received 2 years of T followed by 3 years of L; 33 pts. Received 2 years of L followed by 3 years of T		Letrozole patients had better overall cognitive function than those taking tamoxifen; In comparison to tamoxifen, aromatase inhibitors are unlikely to impair cognition
Bender et al [56]	15 patients received Anastrozole for 5 years ; 16 pts. Received Tamoxifen for 5 years.		Treatment with anastrozole resulted in greater verbal/visual learning and memory impairment
Hermelink et al [57]	30 patients treated with Chemotherapy only; 62 patients treated with Chemotherapy and hormonal therapy (tamoxifen, anastrozole, or letrozole)		Antiestrogen treatment with tamoxifen, anastrozole, or letrozole did not impact Cognition

### *Neurocognitive impairment after whole brain radiotherapy (WBRT)*

Radiation therapy (RT) is a major treatment modality for malignant brain tumors and metastasis to brain. The major

limiting factor in its use is neurotoxicity. Radio-induced neurocognitive impairment evolves in a biphasic pattern: a subacute transient decline with a peak at four months, and a late delayed irreversible impairment of neurocognitive functions several months or years after completion of WBRT. [58,59] Late neurocognitive dysfunction prominently affects working memory, learning ability, executive function, and attention span.

Radiation-induced injury in cerebral tissue is a highly complex and interactive process. Early histopathologic changes in blood vessels after irradiation include dilation and thickening of blood vessels, endothelial cell nuclear enlargement, and hypertrophy of perivascular astrocytes. The dose-dependent endothelial cell death and apoptosis occur as early as 24 hours after irradiation. [60,61] The initial injury of vessels

is followed by the formation of platelet matrix and thrombi, which eventually results in occlusion and thrombosis in microvessels within weeks to months. [62,63] Furthermore, cerebral vascular injury is followed by degenerative structural changes in white matter. The time lag between vascular injury and demyelination and necrosis in white matter diminishes with increased dose. [64]

A number of studies have prospectively performed extensive neuropsychological testing on adult patients with low-grade neoplasm before (baseline) and after radiotherapy (up to 6 years after radiotherapy) and have not found significant neurocognitive deterioration when compared to either baseline or to a cohort of patients with low-grade brain neoplasms not treated with radiotherapy.

Table 3: Neurocognitive impairment after WBRT as assessed by MMSE

Study	Radiation Dose	Brain metastasis response	% patients impaired				
			2 months	3 months	6 months	12 month	18 months
Regine et al [65]	30 Gy/10 fractions/ 12 days	Controlled	0	0	NR	NR	NR
		uncontrolled	28	46			
Shibamoto et al [68]	40 Gy/20 fractions/33 days	Controlled	NR	7.4	11	12	0
Corn et al [66]	37.5 Gy/15fractions/19 days	Controlled	18	24	24	28	28
		Uncontrolled	23	23	33	38	40
Aoyama et al [67]	30 Gy/10 fractions/12 days		5	16	16	28	40

Several studies find that tumor progression is associated with deterioration of neurocognitive function after WBRT in patients receiving WBRT for unresectable brain metastasis. Regine et al [65] evaluated neurocognitive outcome as measured by the Mini-Mental Status Examination (MMSE) among patients with unresectable brain metastases randomly assigned to accelerated fractionation AF (3 Gy q.d. to 30 Gy) vs. accelerated hyper fractionated AH (1.6 Gy b.i.d. to 54.4 Gy) whole-brain radiation therapy (WBRT). The authors concluded that use of AH as compared to AF-WBRT was not associated with a significant

difference in neurocognitive function as measured by mini mental status examination (MMSE). However, control of brain metastases had a significant impact on MMSE. Corn et al. [66] also have reported that in patients receiving WBRT for brain metastasis those with progressive disease showed considerable drop in MMSE scores as compared with those who had response to WBRT.

Both Corn et al and Aoyama et al [67] showed that neurocognitive decline occurred continuously over time following WBRT. Shibamoto et al [68] observed no apparent decrease in mean MMSE score after WBRT.

Individually, MMSE scores decreased by four or more points in 11% at 6 months, 12% at 12 months, and 0% at 18 months. Patients with brain progression were excluded from the evaluation but patients

Based on Table 3, NCF as assessed by MMSE score is impaired after WBRT in the year following the completion of WBRT, but appears strongly related to uncontrolled brain metastases. Neurocognitive decline occurred continuously over time. For this reason, the authors subsequently attempted to isolate prognostic factors for brain recurrence in patients with expected long survival, with the objective to withhold WBRT. [69,70] They found that patients who had solitary brain metastasis in the absence of extracranial metastases were at lower risk of brain tumor recurrence compared with patients with multiple brain metastases or extracranial disease, and proposed to postpone WBRT in those cases, given that the brain tumor recurrence risk was 31% at 6 and 12 months in patients at lower risk without “up-front” WBRT, allowing 69% of patients to avoid unnecessary treatment. These patients with lower risk of brain tumor recurrence were treated with Stereotactic radiosurgery monotherapy without WBRT.

#### ***Impact of surgery on neurocognitive function***

Surgery for brain tumors leads to focal neurocognitive deficits. [71] The effects of surgery on neurocognitive functions has been observed in patients with benign tumors, such as pituitary adenomas with nearly half of the transfrontal resection and one third of the transsphenoidal resection demonstrating cognitive dysfunction compared to one quarter of the nonsurgical group. [72] In contrast, a study of 27 adult brain tumor patients that included extensive neurocognitive testing before surgery and after surgery found 84% improved in one or

with systemic progressive disease were included, and in about half the patients MMSE score decrease was associated with a decrease in performance status caused by systemic disease progression. more cognitive domains, and 36% worsened in one or more cognitive domains. If memory was impaired at baseline, it was most likely to improve, while executive function was most likely to decline. The authors postulated the improvements in cognitive function were primarily due to relief of mass effect and intracranial pressure. [73] Because the treatment of central nervous system tumors typically requires multimodality therapy, it has been difficult to assess the contribution of surgery to the cognitive dysfunction. Further studies are necessary to evaluate patients, especially those receiving surgery alone, with formal neurocognitive testing before and after surgery to help address this issue.

#### ***Impact of primary tumor on cognitive decline***

Whether the predominant cause of cognitive decline in patients with brain tumors is the treatment or the tumor itself is an important question. Older studies have emphasized that late neurotoxicity of treatment, especially radiotherapy is the culprit in cognitive decline. However, these studies have lacked baseline neurocognitive testing as the brain tumor itself is often the primary cause of cognitive difficulties. More recent studies that have included prospective baseline and serial neurocognitive testing have found tumor to be the dominant cause of cognitive decline in brain metastases. [74] low-grade glioma. [75] and high-grade glioma patients. [76] There is also mounting evidence that cognitive decline in brain tumor patients after therapy may frequently reflect subclinical tumor progression rather than neurotoxicity resulting from treatment. In an M. D. Anderson Cancer Center study of 56 patients with recurrent high-grade gliomas



treated on phase 1 and phase 2 trials, cognitive deterioration occurred 6 weeks prior to radiographic failure, highlighting the sensitivity and predictive value of neurocognitive assessments. [77]

### ***Neuroprotection***

Neuroprotection may be a viable and realistic goal in preventing neurocognitive sequelae in patients with cancer, especially in the setting of cranial irradiation. Modern radiotherapy techniques allow for sparing of sensitive areas of the CNS radiating only the brain area affected by cancer, and not the hippocampus, where the memory is located. Some of them are the intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and CyberKnife tomography. All allow radio-surgery with great accuracy and minimum error. Sparing of the hippocampus, which has a crucial role in short-term memory, can also be achieved with the use of IMRT. This approach can still deliver acceptable target coverage and homogeneous delivery to the tumor area in the case of brain metastases. [78] Obviously, short-term memory is only one of the cognitive aspects affected by hippocampal damage. Exposure of other parts of the brain, such as the frontal and prefrontal cortex, may have a more subtle effect. Declines in attention, executive function, and motor, language, and general intellectual skills have been reported. Therefore, prospective well-controlled studies are needed to validate the role of hippocampal sparing. The researchers now think of adding neuroprotective drugs to the current treatments of CT and RT to prevent brain damage and associated cognitive impairment in patients expected to survive beyond six months. The results are, by far, preliminary and disappointing. For example, in chemobrain erythropoietin has only been tested in a timely trial in women with breast cancer who were treated with chemotherapy

and it gave negative results. A phase III trial was recently completed comparing RT and donepezil with RT and placebo. The results are not favourable to the addition of donepezil. Methylphenidate has also been tried out, but in a less robust assay design, as it lacked a placebo control group. In many studies of the biochemical and behavioral models, lithium, antidepressants, atypical antipsychotics, and many substances such as vitamin A have been found to be neuroprotective. However, none has shown a significant effect size in subsequent adequately powered human clinical trials for this indication. Two very recent breast-cancer specific trials have shown that modafinil, a new eugeroic (wake-promoting) drug is useful for the prevention of chemotherapy-induced fatigue and cognitive changes. [79,80] However, further studies are needed to validate these results.

### **CONCLUSIONS**

As the efficacy of treatment for cancer patients continues to evolve and improve, long term treatment sequelae and quality of life issues have emerged as a new challenge for the treating clinicians. Particularly over the past few years neurocognitive effects of cancer have come under immense scrutiny. As we go into the depth of underlying mechanisms associated with neurocognitive deficits associated with cancer and its treatment, effective strategies to prevent and minimize it can be devised.

### ***Conflict of Interest***

The authors declare that there is no conflict of interests regarding the publication of this article.

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