Chemotherapy and Cognitive Impairment: Treatment Options

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Chemotherapy has improved survival rates in patients with many of the common cancers. However, there is reliable evidence that, as a result of treatment, a subset of cancer survivors experience cognitive problems that can last for many years after the completion of chemotherapy. The etiology of this phenomenon is largely unknown, and currently there are no proven treatments. This article explores the clinical and preclinical literature on potential therapies for chemotherapy-induced cognitive impairments. Emerging results suggest that both pharmacological and behavioral approaches may offer patients some benefits. However, research in this area has been limited and is sometimes fraught with methodological flaws. As a result, it is difficult to draw definite conclusions regarding treatment efficacy. These issues, along with predictors of cognitive decline, are discussed in the light of possible interventions.

The effect of anticancer treatments on cognition is receiving increasing attention from researchers because some patients report cognitive difficulties long after anticancer treatment has been completed. However, there are no proven treatments or preventive measures for this side effect, and oncology service providers may not consider themselves sufficiently knowledgeable or well equipped to deal with the cognitive changes that patients may experience.1 In a qualitative study, Munir et al.1 found that the majority of the breast cancer survivors interviewed reported memory loss and attention problems, yet less than one-third of this survey population had received any information about the possible effects of chemotherapy on cognition or any advice about methods of coping with these problems. Although cognitive impairment in such patients is generally subtle, even a small degree of difficulty in everyday functioning can have a significant impact on quality of life.2 In view of this, the International Cognition and Cancer Taskforce has identified a need for well-validated treatments and interventions.3 The purpose of this article is to review the literature on treatment options for chemotherapy-induced cognitive deficits. (A recent review by Joly et al.4 discusses therapies for cognitive difficulties experienced as a result of childhood malignancies and anticancer treatments and therefore are not discussed here.)

CHEMOTHERAPY-INDUCED COGNITIVE IMPAIRMENT: PRESENTATION AND INCIDENCE

Improvements in treatments for many cancers have led to longer survival times for patients, and researchers have moved toward investigating and improving quality of life for survivors. During and shortly after chemotherapy for cancer, many patients report attention deficits, memory loss, and confused thought processes. Up to 70% of patients with cancer report that these cognitive difficulties persist well beyond the duration of treatment,3,5,6 and for some the impact on daily functioning is the most troublesome survivorship issue that they face.2 Focus-group research and qualitative interviews with breast cancer survivors have found that many of these women are no longer able to perform at their previous levels of competence and frequently do not feel confident about returning to their jobs.1 Also, survivors frequently describe social situations as daunting, and interpersonal relationships may suffer as a result.2 Clearly, cognitive problems resulting from chemotherapy are related to a significant decline in quality of life.

Studies that have measured cognitive function using standardized neuropsychological assessments have found mild to moderate effects of chemotherapy on cognitive performance in 15–50% of the survivors after treatment.4,7 Longitudinal studies have shown that, in a subset of survivors, cognitive difficulties
can persist for between 1 and 2 years after the completion of chemotherapy, and cross-sectional studies have found cognitive impairments lasting between 4 and 10 years after chemotherapy. Although most of the studies evaluated cognitive function in breast cancer survivors, more recent work has shown that similar effects also occur in patients with other types of cancer. For example, Vardy et al. found that patients treated for colorectal cancer experience cognitive impairment up to 6 months after the completion of treatment.

When cognitive impairments occur, they are typically seen in processing speed, attention/concentration, and executive functioning—all of which are widely associated with the function of the frontal lobes of the brain—and in visual and verbal memory, which are believed to be under the control of the hippocampus (for a review, see ref. 7). In support of this pattern of cognitive impairment, several brain-imaging studies found chemotherapy-related decreases in the integrity of white matter in the brain area associated with changes in processing speed, and others reported changes in electrophysiological indexes of processing speed (e.g., ref. 11). Inagaki et al. discovered structural brain changes in cancer survivors 4 months after the completion of chemotherapy treatment, with reduced superior frontal gyri and parahippocampal gyrus volume being correlated with poor attention/concentration and impaired memory performance, respectively. Corresponding functional brain changes have also been reported; de Ruiter et al. found hyporesponsiveness in both the prefrontal cortex and parahippocampal gyrus during executive functioning and episodic memory tasks in cancer survivors who had received chemotherapy almost 10 years previously. Overall, imaging studies have found both structural and functional changes in brain regions that are believed to be involved in the cognitive deficits experienced by cancer survivors who received chemotherapy.

Complicating the issue somewhat, recent prospective studies show that ~20% of cancer patients experience cognitive dysfunction even before commencement of chemotherapy (e.g., refs. 15,16). This suggests that the cancer itself and/or the cancer diagnosis may have an impact on cognition. Indeed, cancer induces systemic changes that may influence cognition. For example, patients with cancer exhibit increased circulating levels of cytokines; in both preclinical and clinical studies, increased levels of cytokines and inflammation have been shown to be associated with impairment of cognition. Although receiving a diagnosis of cancer is associated with increased stress, depression, and anxiety, the studies that evaluated cognitive function before chemotherapy did not find an association between depression/anxiety and objectively measured cognitive impairment (e.g., refs. 9,15). Similarly, research has consistently demonstrated that there is only a weak relationship between self-reported cognitive impairment and cognitive performance as assessed by formal neuropsychological testing (e.g., ref. 5). However, self-reported cognitive symptoms appear to be associated with increased anxiety and depression (e.g., refs. 5,6) and may reflect, at least in part, the stress of cancer diagnosis and treatment.

Chemotherapy agents that are commonly used in clinical practice produce significant cognitive impairment in laboratory animals that are free from cancer as well as from other treatment- and diagnosis-related factors. The pattern of cognitive deficits observed in rodents in these studies is virtually identical to that experienced by human patients after chemotherapy. Research studies in animals have shed considerable light on the potential underlying neurobiological mechanisms linking chemotherapy with cognitive impairment (Figure 1; for reviews, see refs. 18,19). Healthy rodents that are given chemotherapy show increase in cell death in the central nervous system, increase in oxidative stress, increase in microglia activity, suppression of hippocampal neurogenesis, decreases in levels of neurotrophic factors, and decreases in levels of hippocampal catecholamines, as compared to baseline values. Taken together, this evidence strongly indicates that, although cancer and/or a cancer diagnosis may affect cognition in human patients, chemotherapy induces both central nervous system changes and measurable cognitive impairments in rodents and humans. There is a clear need to develop effective interventions that target the cognitive domains affected and their underlying neurobiological causes.

**PHARMACOLOGICAL INTERVENTIONS**

**Erythropoietin**

Several studies have investigated the therapeutic potential of the glycoprotein erythropoietin (EPO) in preventing chemotherapy-induced cognitive deficits. EPO stimulates the production of red blood cells, and, in anemic patients, EPO treatment increases hemoglobin levels and reduces the need for blood transfusions, thereby contributing to better quality-of-life outcomes. However, the relationship between cognition and hemoglobin levels is not clear-cut; Vearncombe reported that reduced hemoglobin levels, together with increased anxiety, predict a decline on measures of cognitive function. Massa et al. evaluated EPO therapy in 10 elderly cancer patients who had hemoglobin levels between 10 and 12 g/dl during the period of chemotherapy. Each of the patients received 10,000 U twice a day, 6 days a week, for 2 weeks, followed by 10,000 U three times a week for the following 10 weeks of chemotherapy treatment. After 4 weeks of treatment, 9 of the 10 patients demonstrated cognitive improvements from baseline, as measured by the Mini-Mental State Examination (MMSE), and the improvements in hemoglobin levels in these patients showed significant correlation with the improvements in cognition. In a larger study of 50 anemic cancer patients, Iconomou et al. found small but statistically significant improvements in cognition, as measured by the MMSE, after 12 weeks of combined chemotherapy and EPO. Interestingly, Iconomou et al. failed to find a relationship between hemoglobin levels and cognition, despite a significant positive association between hemoglobin levels and quality of life.

Two studies have examined the effect of EPO treatment (given during chemotherapy) on long-term cognitive outcomes. O’Shaughnessy et al. conducted a double-blind, placebo-controlled, pilot trial in which 100 patients with breast cancer were randomized to receive EPO (40,000 U subcutaneously) or placebo once a week throughout the duration of
doxorubicin/cyclophosphamide treatment. At the beginning of the study, hemoglobin levels in EPO and control groups were between 12 g/dl and 14 g/dl. The study was not powered to find statistical differences between treatment and control groups; however, in agreement with the findings of Massa et al.28 and Iconomou et al.29 executive functioning, as measured by the Executive Interview prior to cycle 4 of chemotherapy, improved in EPO-treated patients relative to placebo patients. Similarly, hemoglobin levels increased in EPO patients and decreased in placebo patients, but the association between hemoglobin changes and cognition was not directly tested. At the 6-month follow-up, executive functioning scores were similar in the two groups; however, patients receiving EPO appeared to have lower levels of fatigue and better quality of life. Mar Fan et al.31 assessed cognition in breast cancer survivors with hemoglobin <12 g/l who had received (neo)-adjuvant chemotherapy with or without weekly EPO (40,000 U) by comparing their cognition scores with those of patients who had received standard care without EPO. Cognitive function was assessed at a single time point, 12–30 months after completion of chemotherapy, using the MMSE and High Sensitivity Cognitive Screen. Patients who had received EPO during chemotherapy reported better quality of life than those who had received standard care. Mar Fan et al. tested the subjects 2 years after completion of chemotherapy. In agreement with the results of the study by O’Shaughnessy et al.,30 Mar Fan et al.31 also did not find any difference in cognitive function between patients who had received EPO and those who had not.

Taken together, the available results provide some evidence that EPO may be effective in improving cognition in the short term.28–30 However, several methodological issues are worth noting. In particular, two of the studies that offer support28,29 to this hypothesis employed only brief cognitive screening tests, which are probably inappropriate for detecting the subtle impairments generally found in cancer survivors.32 In addition, three of the four studies reported here assessed pretreatment cognitive function28–30 and short-term cognitive outcomes, whereas Mar Fan et al.31 assessed cognition at 2 years after the conclusion of the treatment. It is unclear whether EPO treatment during chemotherapy confers longer-term protection of cognitive function after chemotherapy. Finally, the studies conducted to date have been underpowered and/or lacking appropriate control groups (e.g., ref. 28) and have therefore been unable to establish whether EPO treatment during chemotherapy has any effect on cognition. From the available research, it is still not clear what impact changes in systemic hemoglobin levels have on cognition in patients after chemotherapy. Indeed, research suggests that EPO treatment may be beneficial and neuroprotective only in patients in whom local brain damage is present, for instance, because of hypoxia or ischemia.26 Therefore, testing the efficacy of EPO treatment in a sample with heterogeneous cognitive capacity seems unlikely to yield definitive answers.

Figure 1 A schematic representation of the putative pathology underlying chemotherapy-induced cognitive impairment associated with hippocampal and frontal-lobe dysfunction. Chemotherapy may have both direct and indirect effects on the central nervous system (CNS), affecting cognition.
**Methylphenidate**

The stimulant methylphenidate (MPH) is typically used to treat attention-deficit/hyperactivity disorder and may also mitigate cancer-related fatigue. MPH acts by modulating catecholaminergic tone in the prefrontal cortex and striatum and increases dopamine signaling through multiple pathways (for a review, see ref. 34). By contrast, methotrexate (MTX) chemotherapy has been shown to decrease hippocampal catecholamine levels in healthy rats. In humans, MPH treatment has been shown to enhance memory in healthy individuals and overall cognitive function in patients with primary brain tumors. Gagnon et al. found that treatment with 20–30 mg MPH per day improved psychomotor, language, and attention deficit in patients with advanced cancer who had cognitive deficits and associated hypoactive delirium. However, two recent randomized, placebo-controlled studies failed to find a clear benefit of MPH on cognition in cancer patients receiving chemotherapy. Mar Fan et al. conducted a double-blind, placebo-controlled trial of d-methylphenidate (dMPH) in women with breast cancer receiving adjuvant chemotherapy. All the participants received a placebo for one cycle of chemotherapy and were then randomized to receive 5 mg of dMPH (n = 29) or placebo (n = 28) twice a day. If this dose was well tolerated, after 1 week the dMPH dose was increased to 10 mg twice a day, until the completion of chemotherapy. Cognitive function was assessed using the High Sensitivity Cognitive Screen and the Revised Hopkins Verbal Learning Test prior to randomization, at the end of chemotherapy and 4–6 months thereafter. There were no significant differences between the dMPH and control groups with respect to either of the cognitive measures at any of the time points; however, the results may have been confounded by a trend that showed more cognitive impairment at baseline in placebo-receiving patients than those receiving dMPH. Unfortunately, because of poor accrual, the study closed early; as a result, conclusions from these results must be regarded as tentative. Lower et al. also found little benefit of dMPH on cognition in patients with sustained cancer-related fatigue. In this study, patients had completed four cycles of chemotherapy 25 months previously (on average) and had received dMPH for 8 weeks. Fatigue and cognitive function were assessed prior to starting and at completion of dMPH treatment. Fatigue, which was the primary end point, was reduced after dMPH treatment, but there was no effect on cognition.

Neither of these studies was sufficiently powered to detect a difference, and it therefore remains unclear what effect continuing MPH treatment beyond chemotherapy completion would have on late cognitive outcomes. It is possible that treatment benefits may accrue with time and continued use and may therefore not be apparent in the time frames assessed here. However, a recent review found little evidence to support continued use of MPH in patients with Alzheimer's disease, vascular dementia, or frontotemporal dementia in an attempt to improve cognitive function. The available evidence does not indicate that MPH is useful for the prevention or treatment of chemotherapy-induced cognitive deficits. However, until sufficiently powered trials are completed with appropriate sample populations, this conclusion is tentative.

**Modafinil**

Modafinil is commonly used to treat narcolepsy and shift-work sleep disorders. Like MPH, it is a central nervous system stimulant that appears to exert its effects through the release of the catecholamines norepinephrine and dopamine, and histamine. In healthy adults, modafinil acts as an enhancer of cognition, primarily improving attention; in cancer patients, it has been shown to reduce fatigue. Two studies have investigated the effect of modafinil on cognition in cancer patients. Lundorff et al. examined 28 patients with advanced cancer in a double-blind, single-dose, crossover trial. The patients were randomly assigned to receive 200 mg oral modafinil on day 1 and placebo on day 4, or the reverse of that order. On both days, they were tested with the Finger Tapping Test for psychomotor speed and Trail Making Test B for visual information processing and mental flexibility, before and at 4.5 h after drug administration. Performance on both tests was significantly improved after modafinil treatment as compared with placebo, and there was a parallel reduction in depression and drowsiness. In a secondary analysis, Kohli et al. examined the effects on cognition after 4 and 8 weeks of modafinil treatment in patients with breast cancer (n = 82) who were continuing to experience fatigue after completing chemotherapy 22 months (on average) earlier. Participants receiving modafinil demonstrated improved speed and quality of episodic memory on the computerized Cognitive Drug Research assessment. These preliminary results are promising; however, larger longitudinal, randomized, controlled studies are needed to confirm short- and long-term efficacy, the duration for which improvement persists, and whether any benefit is seen in patients who do not have ongoing fatigue.

**Donepezil**

Donepezil is a cholinesterase inhibitor that is widely used to treat cognitive impairment in populations free of cancer. It has been shown to slow the progression of dementia and act as a neuroprotectant through a number of different mechanisms, including reduction of inflammation, regulation of catecholamines, and enhancement of neuroplastic activity. Interestingly, preclinical studies have shown that chemotherapy affects these same pathways in healthy laboratory rodents. Winocur et al. investigated the cognition-enhancing effects of donepezil in mice that had received a combination of the anticancer drugs MTX and 5-fluorouracil (5-FU). Groups of donepezil-treated and control mice (receiving saline) were administered a series of cognitive tests that assessed various aspects of learning and memory. Mice that had received only chemotherapy showed impairment on tests of hippocampus-dependent memory (e.g., spatial memory) and a test of nonmatching-to-sample rule learning, known to be sensitive to frontal lobe impairment. The cognitive deficits were significantly reduced when mice receiving the anticancer drugs were treated with donepezil during chemotherapy/control treatment and throughout the experiment. On some measures, the performance of the chemotherapy + donepezil group...
matched that of the control groups receiving saline. Although these results need to be replicated in future studies, they clearly point to the potential usefulness of donepezil as a treatment for chemotherapy-induced cognitive impairment.

Only one study has attempted to examine the effect of donepezil on cognitive function in patients with cancer. Jatoi et al.46 administered donepezil in combination with vitamin E to patients with small-cell lung cancer who had previously received chemotherapy and prophylactic radiation. Cognition was assessed using the MMSE and the Blessed Dementia Scale, with testing being carried out at study entry, 1 month later, and every 3 months thereafter. The trial was closed early because of poor accrual (n = 9), and the results remain inconclusive.

**Fluoxetine**

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is used primarily in the treatment of depression. It increases extracellular levels of serotonin within the brain by inhibiting its reuptake by serotonin transporters and is reported to improve memory function in patients with depression, as well as in patients with neurodegenerative conditions.37 In addition, preclinical studies have found that treatment with fluoxetine upregulates brain-derived neurotrophic factor and increases the rate of neurogenesis (for a review, see ref. 47). Studies in rodents have shown that both these mechanisms are impaired by chemotherapy.23,24 The findings from preclinical studies by Wigmore and colleagues48,49 suggest that SSRIs such as fluoxetine may be beneficial in mitigating chemotherapy-induced cognitive impairments. Specifically, healthy rats that were administered fluoxetine (10 mg/kg/day in drinking water) prior to and throughout treatment with 5-FU chemotherapy showed improved performance on object location recognition relative to rats treated with 5-FU alone.48 Similar effects were observed in animals treated with MTX chemotherapy.49 Interestingly, in these same animals, decreases in proliferation and survival of neuronal cells in the hippocampus resulting from chemotherapy were reversed with fluoxetine treatment.48,49

Although these results are promising, they should be interpreted with caution. First, the dose employed in these animal studies may be far higher than the dose normally employed in the clinic.47 Second, the use of SSRIs including fluoxetine during chemotherapy may not be desirable, given the side effects of this class of drugs. A preclinical pilot study investigating the neuroprotective effects of 5 mg/kg/day paroxetine, an SSRI, on MTX-induced cognitive impairments in our laboratory had to be aborted because of excessive weight loss and diarrhea in a significant number of the animals (Fardell et al., unpublished data). Indeed, weight loss due to fluoxetine treatment was significant in both the study by ElBeltagy et al. and the work of Lyons et al.48,49

Taken together, the results of these preclinical studies suggest that fluoxetine may protect against chemotherapy-induced cognitive deficits. However, the findings need to be replicated in cancer patients so as to validate the efficacy and safety of fluoxetine and other SSRIs in preventing cognitive impairments caused by chemotherapy.

**Antioxidants and diet**

Preclinical studies have shown that several commonly used chemotherapy agents can induce central oxidative stress in healthy rodents (for a review, see ref. 19). By contrast, consumption of foods high in antioxidants and antioxidant supplementation appear to slow the rate of cognitive decline associated with aging and disease in humans and rodents.50 Little clinical work has been conducted on the usefulness of antioxidants and supplements in treating chemotherapy-induced cognitive impairments. However, several preclinical studies have shown that antioxidant treatment prevents chemotherapy-induced oxidative stress and cognitive deficits when administered prior to and during chemotherapy. For example, Joshi et al.21 found that, in healthy mice, systemic treatment with γ-glutamyl cysteine ethyl ester prior to doxorubicin treatment significantly decreased markers of oxidative stress, namely, protein oxidation and lipid peroxidization. However, because behavior was not assessed, it is unclear whether these changes in the brain were associated with concomitant changes in cognition in the treated mice.

Two studies have assessed the cognitive-behavioral outcomes of pretreatment with an antioxidant and found protective effects against chemotherapy-induced cognitive deficits. Helal et al.51 found that prior intracerebroventricular treatment with the antioxidant zinc sulfate (ZnSO4) prevented short-term memory impairments induced by systemic carmustine (BCNU) treatment. Specifically, BCNU treatment caused rats to make more errors during learning and recall of the radial arm maze, whereas treatment with ZnSO4 prior to BCNU prevented these deficits in learning and memory. In addition, hippocampal cell death and inflammation induced by BCNU treatment were prevented in rats pretreated with ZnSO4. Konat et al.52 investigated the impact of 4 weeks of cyclophosphamide and doxorubicin treatment on memory in rats, using the passive avoidance test. They found that cyclophosphamide + doxorubicin treatment impaired memory function. However, when rats were treated with the antioxidant N-acetyl cysteine during chemotherapy, there was no short-term memory impairment.

Taken together, the results of these preclinical studies suggest that treatment with antioxidants prior to and during chemotherapy prevents the occurrence of cognitive deficits shortly after chemotherapy. However, the usefulness of antioxidants in preventing cognitive impairments needs to be evaluated in cancer patients receiving chemotherapy. Furthermore, it is possible that overall diet is more important than antioxidant supplementation alone. It is well established that dietary patterns can have a direct impact on cognitive function in animals and humans. Diets that are low in calories and saturated fat are associated with better cognition in old age, particularly when this is coupled with consumption of foods high in antioxidants, such as berries and walnuts.50 In rodents, the consumption of foods (rather than supplements) high in antioxidants increases hippocampal neurogenesis and neurotrophic factors such as insulin growth factor 1 and concomitantly improves performance on measures of learning and memory.53 Conversely, diets that are high in saturated or hydrogenated fats adversely affect...
both brain function and cognitive performance in rodents and elderly humans. For example, consumption of a high-fat diet by rodents was shown to induce inflammation, decrease neurogenesis and brain-derived neurotrophic factor levels, and cause poor maze performance. In the absence of reliable data, it is not possible to predict the effect of an improved diet on cognitive outcome in patients with cancer receiving chemotherapy; however, it is likely to be positive in terms of overall health benefits.

Herbal supplements

The Chinese herb Ginkgo biloba is commonly used in the community for treatment of dementia, memory, and difficulties in concentrating. Constituents of a standardized extract of Ginkgo biloba, EGb761, have demonstrated neuroprotective effects in several in vitro and in vivo models. EGb761 appears to have a mode of action similar to that of antioxidants; it protects brain tissue from damage by oxidative stress, reduces apoptosis, regulates cerebral blood flow, and interacts with catecholaminergic neurotransmitters implicated in cognition. A recent review of 29 placebo-controlled randomized control trials comparing psychometric tests by cognitive domain confirmed that the greatest benefits of Ginkgo biloba were found in executive functioning, selective attention, and memory for both verbal and nonverbal material, all of which are neuropsychological domains in which cancer survivors have deficits. These findings make Ginkgo biloba a compound of interest in the prevention and/or alleviation of cancer-related cognitive impairment. The results of a randomized controlled study to evaluate its efficacy is currently under way in Sydney, Australia, and should provide important insight.

BEHAVIORAL INTERVENTIONS

Cognitive rehabilitation

Cognitive rehabilitation refers to behavior-oriented interventions in which individuals receive noninvasive training designed to improve performance in a range of cognitive and functional domains. Traditional models of cognitive rehabilitation emphasize any of the following approaches: (i) retraining to retrieve apparently lost cognitive abilities; (ii) teaching compensatory techniques that encourage the use of residual abilities to develop alternative ways of performing cognitive tasks; and (iii) holistic methods that take a broader approach and address social, emotional, and functional issues related to cognitive impairment.

Rehabilitation scientists have also developed programs that focus on strategic processing and attempt to improve the use of strategies that are most effective in responding to cognitive challenges. Participants are not taught new strategies; rather, they are guided in the use of previously formed strategies. The assumption is that many well-established strategies survive brain impairment but that the individuals require instruction and support in consciously applying them in an effective manner. There is evidence that such programs can improve memory and overall cognitive function in elderly adults who experience significant cognitive decline. In general, programs that take a strategic approach to cognitive rehabilitation are designed for individuals with frontal-lobe impairment that affects executive functioning and related cognitive processes (e.g., attention, conscious recollection). Consequently, this approach may be particularly well suited to patients who have received chemotherapy, whose cognitive deficits are typically in the mild-to-moderate range, and who are sufficiently functional to fulfill the program’s requirements and apply the strategic training to real-world demands.

Although cognitive rehabilitation, in one form or another, is extensively used in many clinical populations that experience cognitive impairment, its use in cancer patients has been extremely limited. In one of the few examples, Ferguson and colleagues developed a cognitive training program, Memory and Attention Adaption Training (MAAT), which focuses on helping participants to develop compensatory strategies for everyday activities. During the course of four individual face-to-face visits, either once a month or once every 2 weeks, MAAT covers four key cognitive-behavioral components in which participants (i) are educated on the effects of chemotherapy on cognition; (ii) learn self-awareness, and also how to self-monitor and identify “at-risk” situations in which cognitive failures are likely to occur; (iii) learn self-regulation through relaxation training; and (iv) learn and rehearse cognitive compensatory strategies. In a single-arm pilot study of 29 women who had received chemotherapy 8 years earlier for breast cancer, Ferguson et al. found improvements in quality of life, self-reported cognitive function, and performance on standard neuropsychological tests, for up to 6 months after undergoing the MAAT program. Similar results were found in a waitlist control trial; at a 2-month follow-up, patients participating in MAAT had significant improvements on the spiritual subscale of the quality-of-life measure and on verbal memory, relative to controls; however, there were no differences in self-reported cognitive function.

Poppelreuter et al. compared the effects of group-based cognitive training and individualized training on cognitive impairment in breast cancer patients who had received adjuvant chemotherapy. Neither form of training resulted in cognitive improvements over and above those observed over time in a nontreatment control group. Several factors may have contributed to the null results. Patients were recruited shortly after they had completed chemotherapy, which is when spontaneous recovery of cognitive function is most likely to occur. By contrast, Ferguson et al. evaluated participants who had completed chemotherapy at least 18 months or 3 years previously. Poppelreuter et al. concluded that, during this narrow time frame immediately after chemotherapy, interventions aimed at improving cognitive outcomes may not be effective or necessary. Immediately after completion of treatment, patients are likely to be dealing with many other important issues, and confronting cognitive deficits at this time may be psychologically disturbing.

Clearly, the limited evidence precludes a conclusive statement about cognitive rehabilitation as a treatment for chemotherapy-induced cognitive impairment; however, the experience with
these approaches has been very encouraging in other clinical populations with similar cognitive deficits, and there is no a priori reason that patients who have undergone chemotherapy for cancer would not benefit from such intervention.

**Physical activity**

Physical-activity programs and interventions have been successful at mitigating fatigue in cancer survivors. Interestingly, programs that call for increased physical activity have been effective at improving cognitive function in both healthy individuals and in those with acquired cognitive dysfunction (e.g., patients with depression or Alzheimer’s disease). Similar results have been obtained in preclinical studies in animals. In a case series, Galantino et al. found that an 8-week yoga intervention improved performance on measures of cognition and perceived cognitive function in three breast cancer survivors who had completed chemotherapy less than 6 months earlier. Recently, Fardell et al. found a significant association between physical activity and cognition after chemotherapy in rodents. Rats treated with 5-FU plus oxaliplatin displayed impairments in object recognition and spatial reference memory. However, when the animals were given access to running wheels for 4 weeks after 5-FU plus-oxaliplatin treatment, these deficits in object recognition and spatial reference memory were prevented. Physical exercise acts on a number of neurological mechanisms that contribute toward maintaining cognitive function. Research in animals has found that physical activity increases levels of neurotrophic factors such as brain-derived neurotrophic factor, enhances the proliferation and survival of neural cells in the hippocampus, and decreases central nervous system inflammation and oxidative stress, while concurrently improving performance on measures of learning and memory (for a review, see ref. 65). Many of these factors have been shown to be affected in rodents treated with chemotherapy.

From the viewpoint of prevention, individuals with high lifetime levels of physical activity have slower cognitive decline in old age and a reduced likelihood of developing dementias later in life, as well as better overall quality of life. Importantly, aerobic exercise in elderly persons has been shown to improve executive functioning and memory, which are the cognitive domains affected by chemotherapy. The beneficial effects of exercise on cognition are associated with concomitant improvements in markers of brain health. For instance, individuals with higher levels of physical activity have larger hippocampal volume in later life. By contrast, individuals with low levels of activity have greater levels of systemic inflammation. The impact of lifetime levels of physical activity on chemotherapy-induced cognitive impairments has yet to be investigated. However, like good diet, higher levels of physical activity may be neuroprotective and lessen the impact of chemotherapy on cognition.

**PREDICTORS OF CHEMOTHERAPY-INDUCED COGNITIVE DEFICITS**

**Treatment factors**

To identify those who will benefit from interventions in order to reverse or reduce chemotherapy-induced cognitive deficits, one should be able to identify those who are most likely to develop these impairments. Several treatment-related factors may increase the likelihood of cognitive impairment (for a review, see ref. 7), although the results at this stage are not conclusive. Two studies have reported that high-dose chemotherapy is associated with worse cognitive outcomes. In a longitudinal study, Schagen et al. found that breast cancer patients who had received high-dose chemotherapy experienced greater cognitive decline over time. A cross-sectional study conducted by Scherwath et al. failed to support these results. In fact, they found that, at 5 years after completion of treatment, patients who had received high-dose chemotherapy were less likely to experience cognitive impairments than those who had received standard-dose chemotherapy. Wiernek et al. found that treatment duration was associated with degree of cognitive decline; those receiving longer courses of chemotherapy displayed more cognitive impairment. Several studies have reported that adjuvant hormonal treatment may increase the likelihood of cognitive impairment after chemotherapy (e.g., refs. 5,8). Finally, the regimen of cyclophosphamide, MTX, and 5-FU (CMF) may increase the likelihood of chemotherapy-induced cognitive deficits, with MTX in particular contributing to neurotoxicity.

**Individual characteristics**

Some individual differences appear to increase the likelihood of chemotherapy-induced cognitive impairments. The presence of the APOE e4 allele and low levels of pretreatment cognitive reserve have been associated with worse cognitive outcomes after chemotherapy. In the general population, aging is associated with declines in processing speed, and increased age at diagnosis may increase the impact of chemotherapy on cognition. In their longitudinal study on patients with breast cancer, Ahles et al. found an interaction between age and pretreatment cognitive reserve; older patients with less cognitive reserve showed poorer performance on measures of processing speed as compared with younger patients with higher levels of pretreatment cognitive reserve. Eberhardt et al. found that older patients with hematologic disease or cancer of the intestinal tract had greater memory impairments shortly after the start of chemotherapy but that these impairments resolved by 6 months after completion of treatment. Adams-Price and colleagues found that older survivors of breast cancer who had received chemotherapy between 3 and 45 months prior to the evaluation showed greater impairments in a test of processing speed than younger survivors and age-matched healthy controls. These preliminary results need to be expanded on with further research to investigate other cognitive domains that are commonly affected by chemotherapy over the long term.

The overwhelming majority of the studies have failed to find any association between psychological well-being and chemotherapy-induced cognitive impairments as measured by traditional neuropsychological assessment. In their 2007 review, Vardy et al. report that only 1 of the 15 studies that they reviewed reported a positive relationship between affective stress and cognitive performance and that this finding too could be attributable to statistical chance alone. In contrast, Vearncombe et al. reported that patients who had undergone chemotherapy for cancer were associated with concomitant improvements in overall cognitive function.
found that, together with declines in hemoglobin levels, increased anxiety predicted impairment on two or more cognitive tests in women with breast cancer who had received chemotherapy an average of 6 weeks earlier. This study also found that baseline fatigue, depression, and functional well-being were significantly associated with executive functioning and attention. Although these results warrant further investigation, they should be interpreted with caution. Cognitive ability in these patients was assessed shortly after the completion of chemotherapy treatment, and the results may not be sustained, particularly because the cognitive difficulties experienced may spontaneously resolve.

**Lifestyle factors**
In other at-risk populations, cognitive competency has been related to various lifestyle factors. These factors have not been investigated in cancer patients, but they merit attention because they may similarly affect the degree to which cognitive performance is affected by chemotherapy. On the basis of the evidence described earlier, we may expect that individuals with high levels of physical activity, and who have diets that are low in fat and calories and high in antioxidants, may be protected against the cognition-related detrimental effects of chemotherapy to a greater extent than those who are inactive and have poor dietary habits. Psychosocial factors should also be taken into consideration; research has shown that elderly patients and brain-damaged patients perform much better on neuropsychological tests of cognition and enjoy a higher quality of life when surrounded by caring family members and caregivers.

A positive environment, in itself, may not be sufficient to prevent chemotherapy-related cognitive deficits, but it could help in minimizing the impairments. Effective management of psychosocial issues could also render the patient more responsive to counseling and cognitive rehabilitation programs.

**FUTURE DIRECTIONS AND SOME CONSIDERATIONS**

**Two cognition-related syndromes: acute or long-term effects of chemotherapy on cognition?**
As noted early in this article, although changes in cognitive capacity are commonly experienced during chemotherapy, a subset of patients experience cognitive impairment lasting several years after the completion of treatment. It is unclear from the available research whether these represent different temporal aspects of the same underlying condition or whether they are two separate phenomena. Therefore, interventions that target cognitive impairments during or shortly after chemotherapy may not be as effective in those with sustained impairment. For example, the studies reviewed here suggest that, although EPO may be effective at improving cognitive function during and shortly after chemotherapy, there is little evidence to suggest that EPO protects or improves cognitive function for up to 2 years after completion of the treatment (O’Shaughnessy et al. and Mar Fan et al.). The reverse was true of cognitive rehabilitation; Poppelreuter et al. found little evidence that cognitive rehabilitation was beneficial shortly after completion of chemotherapy, and Ferguson et al. found positive effects of MAAT on longer-term cognitive impairment.

**Timing and duration of intervention: prevention or treatment**
If an intervention is designed to prevent cognitive impairment, it needs to occur before and/or during chemotherapy. However, patients are understandably reluctant to take additional medications during chemotherapy because of potential side effects and the risk of interactions with their anticancer treatments.\(^9\) In addition, prevention may not be the most efficient approach, given that only a subset of patients receiving chemotherapy will go on to develop sustained problems with cognition, and one cannot accurately predict which patients will belong to this subset. Careful examination of a broad range of cancer patients receiving chemotherapy in preventive drug trials may help to explain why some studies failed to find positive effects of various interventions.\(^9,39\)

From the results of preclinical studies, donepezil, fluoxetine, and antioxidants are potential interventions to prevent, and possibly treat, chemotherapy-induced cognitive deficits.

For survivors who have completed their chemotherapy and have ongoing cognitive impairment, appropriate treatments need to be identified. Based on the results of the clinical studies reviewed here, there appears to be tentative evidence for the positive effects of modafinil and cognitive rehabilitation in ameliorating cognitive deficits experienced long after the completion of chemotherapy, and preclinical research suggests that increased physical activity after chemotherapy may be effective.

However, it is not clear, from either clinical or preclinical research, whether treatment needs to be ongoing for any cognitive improvements to be maintained.

**Methodological considerations**
One of the factors that precludes strong conclusions being drawn on the basis of the research conducted so far in this area is the choice of study populations and control groups. Studies that recruited patients with cognitive deficits as identified by either standard neuropsychological testing or self-report found that their interventions had successful outcomes. Those that recruited participants regardless of their cognitive status, failed to find positive effects of the intervention (e.g., refs. 29,38,39). If patients are not recruited on the basis of cognitive criteria, particularly for prevention approaches, the sample size needs to be sufficiently large. This is because only the patients who go on to develop cognitive difficulties after chemotherapy would potentially benefit from the intervention. The smallness of the samples may also explain why several of the trials failed to find a positive intervention effect. Furthermore, the side effects of some of the pharmacological interventions can be bothersome, and this aspect needs to be considered before deciding to give all the patients additional medication during chemotherapy, particularly because sustained cognitive impairment will affect only a subset of these patients. As mentioned, several studies assessed cognitive function using brief screening tests (e.g., the MMSE) that are unlikely to detect cognitive impairment efficiently. Although these tests are quick and easy to administer, they are generally inappropriate for this setting.

In addition, the positive results of preclinical studies need replication in both animal cancer models and clinical study samples. As highlighted above, it is sustained cognitive impairment...
that is most problematic for cancer survivors, and yet the majority of rodent studies have assessed the efficacy of interventions only immediately after completion of chemotherapy and over relatively short periods of time. It is not clear whether any of the candidate interventions offer long-term protection from cognitive problems experienced as a result of chemotherapy. This issue, as well as appropriate dose, duration, and timing of the intervention, warrant careful examination because all these factors are likely to influence the efficacy of the treatment.

**CONCLUSION**

Ferguson et al.\textsuperscript{61} suggest that low-risk treatments (such as cognitive-behavioral interventions) that emphasize functional improvements in both cognition and quality of life may provide

<table>
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<tr>
<th>Treatment</th>
<th>Potential central nervous system neuroprotective effects</th>
<th>Balance of evidence on chemotherapy-induced cognitive deficits</th>
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</table>
| Erythropoietin (EPO)      | EPO has many central nervous system effects that may confer neuroprotection;\textsuperscript{26} the most relevant, given the current research, on underlying mechanisms associated with chemotherapy-induced cognitive loss are presented here:  
  - Increased expression of enzymes protecting against oxidative stress and decreases in levels of nitric oxide-mediated free radicals  
  - Modification of neurotransmission  
  - Increase in neoangiogenesis/normalization of cerebral blood flow | Three studies found positive effects of EPO treatment during chemotherapy on cognition shortly after the completion of treatment\textsuperscript{28–30}  
Two randomized control studies evaluated longer-term cognitive outcomes. Neither found any effect of EPO treatment on cognition at 6 months\textsuperscript{29} and 2 years\textsuperscript{31} |
| Methylphenidate (MPH)    | Influences the catecholaminergic system—inhibits the DA transporter\textsuperscript{34};  
  - May protect against the formation of DA-associated reactive oxygen species (as occurs in Parkinson’s disease and methamphetamine-induced neurotoxicity) by attenuating or preventing abnormal accumulation of cytoplasmic DA  
  - Increases extracellular levels of DA in the prefrontal cortex and striatum and modulates catecholaminergic tone | Two randomized control trials failed to find any positive effects of MPH on cognition in breast cancer survivors\textsuperscript{38,39} |
| Modafinil                 | Modafinil is a psychostimulant that inhibits both the DA transporter and the norepinephrine transporter; its primary effects appear to be through the catecholaminergic system\textsuperscript{51};  
  - It significantly increases extracellular levels of DA, norepinephrine, serotonin, glutamate, and histamine and decreases levels of γ-amino-butyric acid | Two randomized control trials found positive effects of modafinil on cognition.\textsuperscript{42,43} Positive effects were seen in quality of episodic memory,\textsuperscript{43} processing speed,\textsuperscript{42,43} and visual processing and mental flexibility\textsuperscript{42} |
| Donepezil                 | Donepezil is a cholinesterase inhibitor that has many neuroprotective actions in animal models of Alzheimer’s disease;\textsuperscript{66} the most relevant, given the current research on underlying mechanisms associated with chemotherapy-induced cognitive decline, are presented here:  
  - Mitigates the effects of oxidative stress  
  - Modulates neurotransmission  
  - Improves cerebral blood flow and activity coupling  
  - Enhances neuroplasticity  
  - Reduces levels of pro-inflammatory cytokines | One preclinical study showed that mice treated with donepezil during chemotherapy displayed improved spatial memory and rule learning\textsuperscript{55} |
| Fluoxetine                | Fluoxetine is a selective serotonin reuptake inhibitor that increases extracellular serotonin and appears to modulate important cellular functions that are thought to be important for neuronal cell survival and neuroplasticity\textsuperscript{47};  
  - Regulation of the transcription factor cAMP-responsive element binding protein  
  - Production of neurotrophic factors (e.g., BDNF)  
  - Regulation of neuronal energy supply | Two preclinical studies found that administration of fluoxetine during chemotherapy prevented object location recognition memory deficits and prevented suppression of neurogenesis due to either 5-fluorouracil or methotrexate\textsuperscript{54,49} |
| Antioxidants              | The primary mode of action of antioxidants is through their ability to prevent the formation of reactive oxygen species and/or scavenge reactive oxygen species. Foods containing antioxidants, such as blueberries, have additional neuroprotective effects\textsuperscript{50};  
  - Activate cAMP-responsive element binding protein  
  - Increase levels of BDNF in the hippocampus  
  - Reduce central nervous system levels of pro-inflammatory cytokines and cell death | Three preclinical studies showed that antioxidant administration during chemotherapy reduces markers of oxidative stress;\textsuperscript{21,51,52} two found concomitant protection of cognitive function in animals co-treated with antioxidants and chemotherapy\textsuperscript{51,52} |
| Physical activity         | Exercise has many central nervous system effects,\textsuperscript{65} the few most relevant given the current research on underlying mechanisms associated with chemotherapy-induced cognitive decline are presented here:  
  - Decreases inflammation  
  - Increases levels of neurotrophic factors (BDNF, insulin growth factor 1, vascular endothelial growth factor)  
  - Increases neuronal cell proliferation and survival | One preclinical study found that physical activity after chemotherapy prevented the occurrence of spatial reference memory impairments and recognition memory impairments caused by chemotherapy\textsuperscript{67} |

BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; DA, dopamine.
the most benefit for patients with cognitive impairment after cancer treatment. The etiology of chemotherapy-induced cognitive impairments is likely to be multifactorial, and more than one treatment modality may be required. Patients with cognitive impairments may benefit from the administration of a cognition-enhancing drug to aid their ability to both encode and recall cognitive compensatory strategies learned during rehabilitation training.

In summary, emerging pharmacological and behavioral therapies offer some hope for cancer survivors who are experiencing chemotherapy-induced cognitive impairments (Table 1). However, although progress is being made, insufficient data and methodological limitations in some of the trials reported here make it difficult to arrive at solid conclusions and recommendations. More research is clearly required; studies must be adequately powered to detect an effect and should specify a priori the aims of the intervention and recruit a sample accordingly. Therapies that have broad neurobiological and psychological effects, and that have been shown to be beneficial in other populations with cognitive impairments similar to those reported after chemotherapy, may offer the best hope for cancer survivors in this regard.

**CONFLICT OF INTEREST**

The authors declared no conflict of interest.

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