Pharmacologic management of cognitive impairment induced by cancer therapy

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Cognitive dysfunction is a challenging adverse effect of chemotherapy and radiotherapy that has limited treatment options. Clinical trials for proposed pharmacotherapeutic interventions to help manage these cognitive symptoms have had conflicting results and no standard of care has yet been established. Pharmacotherapeutic approaches for cancer therapy-induced cognitive symptoms include CNS stimulants (eg, methylphenidate and modafinil), medications used in patients with memory impairment (eg, donepezil, memantine, and ginkgo biloba), and bone marrow supporting agents (eg, erythropoietin). Whilst the beneficial effects of CNS stimulants have been mainly reported in children, efficacy in adults has been varied. Antidementia drugs have emerged as promising compounds in the management of cognitive dysfunction, but clinical experience of their use remains limited. Therefore, large clinical trials for these putative memory-enhancing drugs are needed to establish their clinical value in an oncology setting. Several clinical trials testing novel pharmacotherapeutic interventions for the management of cognitive dysfunction are ongoing, as well as numerous preclinical studies. With an increasing understanding of the molecular and cellular mechanisms underlying cognitive deficits in patients with cancer, novel treatment strategies are emerging.

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Introduction

Recent therapeutic advances have greatly improved survival in some patients with cancer, such as in melanoma, lung cancer, and breast cancer, with a growing number of long-term survivors.[1–3] However, cancer therapy can be associated with harmful effects to numerous organ systems, including the CNS. Cognitive dysfunction has emerged as one of the most concerning and poorly understood adverse effects of cancer and its treatment from radiotherapy and chemotherapy, in which reported symptoms and deficits identified on cognitive evaluation are often denoted as chemobrain. Reported incidence of cognitive impairment on objective testing in patients treated for non-CNS cancers ranges from 10–65% because of varying sensitivities of cognitive assessment methods, patient populations studied, and drugs used.[4,5] Results from a small longitudinal study of patients with breast cancer showed that 21% of patients had cognitive impairment before treatment, 65% were impaired shortly (3 months) after chemotherapy, and 61% had persistent cognitive deficits (7 months after treatment).[6] Results from a much larger study of patients with colorectal cancer showed cognitive impairment in 43% of patients before chemotherapy and in 46% of patients 12 months later.[7] The most common cognitive deficits are in the domains of executive function, memory, psychomotor speed, and attention.[8–10]

Importantly, neurocognitive impairment might be of delayed onset and, in some patients, can be progressive even years after cessation of cancer therapy. These symptoms can occur whether treatment was directed at the CNS or non-CNS tumour.[11,12] Brain irradiation and virtually all categories of chemotherapeutic regimens have been linked to varying degrees of neurocognitive changes. Affected patients are difficult to evaluate as the severity of cognitive dysfunction are not necessarily associated with imaging findings on conventional MRI.[13–15] Although individual factors such as age, cerebrovascular comorbidities, cognitive reserve, and genetic polymorphisms have been shown to explain varying degrees of symptoms in otherwise similar patient populations,[16–18] in general useful biomarkers indicative of patients at high risk of poor outcomes are not available.

The precise pathological mechanisms of cancer therapy-induced cognitive dysfunction are elusive.[19–21] Therapeutic interventions for these cognitive symptoms would ideally prevent side-effects of cancer therapy, minimise the extent of symptoms, or stimulate repair after treatment-induced functional and structural neural injury. Non-pharmacological interventions, such as meditation or physical exercise, have also been considered useful strategies.[22] Various pharmacotherapeutic interventions (such as CNS stimulants and anti-dementia drugs) have been tested in clinical trials; however, no guidelines pertaining to the management of patients with cancer therapy-induced cognitive dysfunction are available. In this Review, we provide a critical summary of the available data on drugs proposed for the treatment of cancer therapy-induced neurocognitive symptoms. Treatment interventions for patients undergoing brain directed-cancer therapy will be discussed separately from pharmacotherapeutic management of patients undergoing systemic cancer therapy.

CNS stimulants

Methylphenidate

Craniospinal radiotherapy in combination with chemotherapy is frequently delivered to children with acute lymphoblastic leukaemia for CNS prophylaxis or in patients with medulloblastoma. Such treatments have substantially improved survival, and many of these children live well into adulthood without evidence of disease. Unfortunately, patients often have persistent deficits in attention and working memory, with associated decline in intelligence quotient and academic achievements.[23] As attention is one of the most frequently

affected cognitive domains in patients presenting with chemotherapy-related cognitive concerns, cognitive deficits in patients with medulloblastoma but also with other types of cancer have been compared with those found in children with the primary inattentive type of attention deficit hyperactivity disorder.[24] Consequently, the use of methylphenidate, a CNS stimulant, has emerged as a possible intervention in children with cancer for the treatment of chemotherapy-induced cognitive dysfunction. Methylphenidate is a dopaminergic and noradrenergic agonist influencing the frontostriatal network that regulates attention and is commonly used in the treatment of attention deficit hyperactivity disorder.

Methylphenidate for patients with CNS cancer and brain-directed cancer therapy

A double-blinded N-of-1 crossover trial[25] studying the immediate effects of methylphenidate among cancer survivors with cognitive dysfunction has been done within a paediatric population. N-of-1 trials have a within subject design in which each patient receives active treatment and placebo in alternating order and, therefore, acts as his or her own control.[26] 122 long-term survivors of acute lymphoblastic leukaemia or malignant brain tumours, with a median age of 11·8 years, were treated with placebo or methylphenidate (0·6 mg/kg once, maximum dose of 20 mg). Participants received chemotherapy with or without cranial radiotherapy (39% received chemotherapy only, 14% received cranial radiotherapy ≤24 Gy with or without chemotherapy, and 47% received cranial radiotherapy >24 Gy with or without chemotherapy) for at least 12 months before the intervention. The methylphenidate group compared favourably with the placebo group when tested 90 min after taking the medication, showing improved attention, cognitive flexibility, and information processing (T-score difference in the mean Stroop Colour-Word Association Test 3·9 [SE 1·5], p=0·01).

The same group of researchers did another double-blinded N-of-1 crossover study[27] among a paediatric cohort of survivors of acute lymphoblastic leukaemia or brain tumour with a median age of 11·9 years who received 3 weeks of alternating placebo, low-dose (0·3 mg/kg, maximum dose of 10 mg) methylphenidate, and moderate-dose (0·6 mg/kg, maximum dose of 20 mg) methylphenidate. Behaviour and social skills were defined as primary endpoints for short-term efficacy of methylphenidate and were evaluated weekly by parents and teachers. Both methylphenidate-treated subgroups showed improved results compared with the placebo group (difference in Conners' Rating Scale for attention and cognitive problems between groups of −3·4 [SE 1·4] for low-dose methylphenidate [p=0·017] and −4·1 [1·4] for moderate-dose methylphenidate [p=0·004] when evaluated by parents; −3·6 [1·0] for low-dose methylphenidate [p=0·001] and −3·1 [1·0] for moderate-dose methylphenidate [p<0·004] when evaluated by teachers) and the Social Skills Rating System was not significant when evaluated by parents (mean normative score difference between groups 2·3 [1·7] for low-dose methylphenidate and 2.8 [1·8] for moderate-dose methylphenidate, both p>0.05), but significant when evaluated by teachers (4·2 [1·5], p=0·006 for low-dose methylphenidate, 5·7 [1·5], p=0·001 for moderate-dose methylphenidate). No statistically significant difference was observed between moderate-dose and low-dose methylphenidate.

The same group did a third trial[28] studying patients with the same inclusion criteria (ie, survivors of acute lymphoblastic leukaemia or brain tumour, same age as previous study [about 11 years], and same pretreatment [chemotherapy, CNS-directed radiotherapy, or both]), although doses have differed from those in the other methylphenidate trials in the peadiatric population: dose of methylphenidate was weight-adjusted (starting dose for <30 kg bodyweight: 5 mg once or twice daily; ≥30 kg bodyweight: 18 mg daily) and titrated upon clinical response (up to 36 mg daily). The assessment of the methylphenidate group at the end of the 12-month period was administered while patients were still on methylphenidate. The control group consisted of 54 cancer survivors (31 patients with brain tumour and 23 patients with acute lymphoblastic leukaemia) who had previously participated in the study of Conklin and colleagues[25] testing short-term efficacy of methylphenidate, but refused to participate in the long-term study for the following reasons: declined participation in a study medication phase of the trial; were previously classified as methylphenidate non-responder; had adverse effects and, therefore, discontinued; or refused for other reasons. The positive effects of open-label prescribed methylphenidate were durable over 1 year: after 12 months of treatment, 68 childhood cancer survivors did significantly better when tested for attention and behaviour using a broad test battery compared with a cancer control group. Therefore, the authors concluded that methylphenidate has the potential to benefit long-term in treating cognitive dysfunction in paediatric patients with cancer. However, response to methylphenidate in improving cognitive function was 45% lower than typically measured in patients with attention deficit hyperactivity disorder.

Although compelling evidence exists for the beneficial effects of methylphenidate on cognitive symptoms induced by CNS-directed cancer therapy in paediatric patients with cancer, only one study[24] has been done in adults with brain cancer. Gehring and colleagues[29] treated 24 adult patients with primary brain tumour, who were randomised to either open-label modafinil (200 mg daily) or open-label methylphenidate (18 mg daily or 10 mg twice daily) for 4 weeks. Almost all patients had completed chemotherapy and radiotherapy and 60% underwent chemotherapy during the study. Cognition and fatigue were tested at

baseline and after the end of cancer treatment to evaluate the general and differential efficacy of the two CNS stimulants. Following the fixed daily dose of medication, all treated patients showed significant improvement in processing speed, executive function, and fatigue without favouring one treatment group. However, patients in this study had active disease and the study was not placebo-controlled. Accordingly, the study was not designed to exclude the possibility that CNS stimulants treated direct tumour effects on cognition rather than the effects of chemotherapy or radiotherapy. It is also possible that improvement in cognition was due to response of the tumour to therapy and decrease in tumour burden.

Methylphenidate for patients with non-CNS cancer and systemic cancer therapy

The effects of methylphenidate were studied in clinical trials among adult cancer survivors who received systemic chemotherapy for non-CNS cancer. Mar Fan and colleagues[30] enrolled 57 women (29 women received the drug and 28 placebo) undergoing adjuvant chemotherapy for fully resected breast cancer in a randomised, placebo-controlled trial studying the effect of concomitant methylphenidate (10 mg or 20 mg daily) on cognitive dysfunction and fatigue. Although the study did not show any significant differences between the groups at the end of treatment and 6 months after chemotherapy, the trial did not meet its accrual goal of 170 patients and the authors concluded that the study was underpowered for analysis. Indeed, another randomised controlled trial was done in 154 adult patients with predominantly breast or ovarian cancer who were administered placebo or methylphenidate (10 mg daily) 2 months or more receiving four cycles or more of chemotherapy.[31] After 8 weeks of treatment, fatigue was assessed with the self-rating functional assessment of chronic illness therapy-fatigue subscale questionnaire and cognition domains were assessed with the high sensitivity cognitive screen, a brief objective cognitive screening measure. Although fatigue improved significantly in the treatment group, no difference in cognitive function was measured between both groups. Although these results did not support a positive effect of methylphenidate on cognitive impairment, the high sensitivity cognitive screen assessment tool might have had inadequate sensitivity, and the authors noted that their study was not powered to reliably assess the secondary endpoint of cognitive function and regarded it as explanatory only. Escalante and colleagues[32] did a double-blinded N-of-1 crossover trial with 33 women who underwent chemotherapy or hormonal therapy for breast cancer. One group received methylphenidate (18 mg daily) for 2 weeks followed by placebo for 2 weeks; the second group received placebo followed by methylphenidate. No significant difference between the treatment group and the placebo group was seen by assessing the worst level of fatigue, which was the primary endpoint of this study. Of note, secondary measures of response at that timepoint showed that patients who received methylphenidate did significantly better when tested for verbal learning, memory, visual perception, analysis, and scanning speed compared with patients who received placebo.[32] Patients were also able to work more hours weekly and indicated a subjective overall health improvement. However, the sample size was small (only 33 patients completed all study visits), and p-values were just short of the significance threshold.

Collectively, existing clinical trial data appear to support the potential use of methylphenidate for treating cognitive dysfunction in childhood cancer survivors; however, data in adult patients with cancer remain controversial. Only one study has shown beneficial effects of methylphenidate in patients with brain tumours.[29] Although two randomised control trials did not show a positive effect of methylphenidate on neurocognitive deficits in the context of chemotherapy-induced impairment,[30,31] the most recent study by Escalante and colleagues[32] reported an improvement in neurocognitive deficits following methylphenidate in patients undergoing systemic chemotherapy, albeit only slightly (table 1). A phase 2 trial (NCT02970500) to assess methylphenidate for cognitive dysfunction management is ongoing for a cohort of patients with breast cancer undergoing systemic cancer therapy and might provide further insight on the potential effects of methylphenidate.

Modafinil

Modafinil is a CNS stimulant established as a first-line treatment for improving wakefulness in the context of narcolepsy, obstructive sleep apnoea, or shift work sleep disorder.[46] In contrast to methylphenidate, modafinil is exclusively approved for adults. Modafinil acts primarily on hypothalamic sleep-regulating centres through the decrease of gamma-amino butyric acid (GABA) in the sleep-inducing preoptic area. This selective interaction with the sleep–wake cycle, as opposed to generalised excitation, might be the reason that modafinil is associated with fewer side-effects and lower likelihood of drug tolerance than other CNS stimulants such as methylphenidate.[46] The effect of modafinil on cognitive function in patients with cancer remains controversial: although some pilot studies have shown that modafinil appears superior compared with placebo in improving psychomotor dysfunction, resulting in faster task switching ability and improved fine motor skills,[47] other randomised controlled trials did not find clear evidence to support this hypothesis.[48] However, previous or active cancer therapy were not inclusion criteria in these studies.

Modafinil for patients with CNS cancer and brain-directed cancer therapy

The open-label trial done by Gehring and colleagues[29] comparing modafinil and methylphenidate in 24 patients

with brain tumours is the only study of modafinil in patients undergoing brain directed-cancer therapy. A significant positive effect of modafinil (200 mg daily) was seen on processing speed, executive function, and fatigue compared to methylphenidate (10 mg methylphenidate twice daily, or 18 mg once daily). However, the absence of a placebo group restricts the interpretation of the results as it does not allow to rule out non-specific treatment effects (such as placebo effect) as an explanation for the observed positive effects after stimulant treatment.

	Study design	Study population	Study focus	Treatment and placebo duration	Cognitive assessment methods and significantly improved cognitive domain
Methylphenidate					
Patients with brain-directed cancer therapy					
Conklin and colleagues[25] (2007)	N-of-1 crossover	Children (n=122): leukaemia or brain tumour	Symptoms	2 days	Stroop word-colour association test: processing speed, attention, cognitive flexibility
Mulhern and colleagues[27] (2004)	N-of-1 crossover	Children (n=83): leukaemia or brain tumour	Symptoms	3 weeks	Conners' rating scales: attention or hyperactivity; social skills rating system: social skills
Conklin and colleagues[28] (2010)	Open-label, single group with non-placebo control group	Children (n=68): leukaemia or brain tumour	Symptoms	52 weeks	Conners' Rating Scales and Conners' continuous performance test: attention; social skills rating system and child behaviour checklist: social skills or behaviour
Gehring and colleagues[29] (2012)	Open-label, two groups, without placebo	Adults (n=24): brain tumour	Symptoms	4 weeks	WAIS-III digit symbol test: processing speed; trail making test part B: executive function (after stimulant treatment with methylphenidate or modafinil)
Patients with systemic cancer therapy					
Mar Fan and colleagues[30] (2008)	Double-blind RCT	Adults (n=57): breast cancer	Prevention	3–20 weeks	No significant differences (high sensitivity cognitive screen: cognitive screening test; revised Hopkins verbal learning test: memory; self-reported fatigue and quality of life)
Lower and colleagues[31] (2009)	Double-blind RCT	Adults (n=154): breast cancer or ovarian cancer	Symptoms	8 weeks	No significant differences (high sensitivity cognitive screen, and modified Swanson, Nelson and Pelham attention deficit and hyperactivity scale: attention)
Escalante and colleagues[32] (2014)	N-of-1 crossover	Adults (n=33): breast cancer	Symptoms	4 weeks	WAIS-III digit span test: attention.
Modafinil					
Patients with brain-directed cancer therapy					
Gehring and colleagues[29] (2012)	Open-label, two groups, without placebo	Adults (n=24): brain tumour	Symptoms	4 weeks	WAIS-III digit symbol test: processing speed; trail making test part B: executive function (after stimulant treatment with methylphenidate or modafinil)
Patients with systemic cancer therapy					
Kohli and colleagues[33] (2009)	Phase 1: open-label single arm; phase 2: RCT	Adults (n=82): breast cancer	Symptoms	Phase 1 or 2: 4 weeks each	Cognitive drug research computerised assessment system: speed and quality of memory, and attention
Donepezil					
Patients with brain-directed cancer therapy					
Shaw and colleagues[34] (2006)	Open-label, single-arm	Adults (n=24): brain tumour	Symptoms	24 weeks	WAIS-III digit span test: attention; California verbal learning test-II and modified Rey-Osterrieth figure test recall: verbal or figural memory
Rapp and colleagues[35] (2015)	Double-blind RCT	Adults (n=198): brain tumour	Symptoms	24 weeks	Revised Hopkins verbal learning Test: memory; grooved pegboad for the dominant hand: motor speed and dexterity
Castellino and colleagues[36] (2012)	Open-label, single-arm	Children (n=11): brain tumour	Symptoms	24 weeks	Dellis-Kaplan executive function tower test: executive function; wide range assessment of memory and learning, second edition: memory
Correa and colleagues[37] (2016)	Open-label, single-arm	Adults (n=15): brain tumour	Symptoms	24 weeks	WAIS-III digit span test: attention; WAIS-III digit symbol test: attention or processing speed; revised brief visuospatial memory test: memory
Patients with systemic cancer therapy					
Lawrence and colleagues[38] (2016)	Double-blind RCT	Adults (n=62): breast cancer	Symptoms	24 weeks	Revised Hopkins verbal learning test: memory
Memantine					
Brown and colleagues[39] (2013)	Double-blind RCT	Adults (n=508): brain metastases (lung, breast, and colon cancer)	Prevention	24 weeks	Revised Hopkins verbal learning test: memory; trail making test part A: processing speed; controlled oral word association: language and executive function; mini mental state exam: cognitive screening

(Table 1 continues on next page)

	Study design	Study population	Study focus	Treatment duration	Cognitive assessment methods and improved cognitive domain
(Continued from previous page)					
Ginkgo biloba					
Patients with brain-directed cancer therapy					
Attia and colleagues[40] (2012)	Open-label, single-arm	Adults (n=34): brain tumour	Symptoms	24 weeks	Trail making test part A: processing speed; trail making test part B: executive function; modified Rey-Osterrieth figure test recall: memory
Patients with systemic cancer therapy					
Barton and colleagues[41] (2013)	Double-blind RCT	Adults (n=166): breast cancer	Prevention	During and 1 month after chemotherapy	No significant differences (high sensitivity cognitive screening and trail making test parts A and B: processing speed, executive function; perceived health scale, cognitive subscale, and profile of mood state, confusion or bewilderment subscale: subjective rating of cognition)
Erythropoietin					
Massa and colleagues[42] (2006)	Open-label, single-arm	Adults (n=10): patients with cancer and concurrent anaemia	Prevention	12 weeks	Mini mental state examination: cognitive function
Iconomou and colleagues[43] (2008)	Open-label, single-arm	Adults (n=50): patients with cancer and concurrent anaemia	Prevention	12 weeks	No significant differences (mini mental state examination: cognitive screening)
O'Shaughnessy and colleagues[44] (2005)	Double-blind RTC	Adults (n=94): breast cancer	Prevention	12 weeks	No statistical comparison done (executive Interview [EXIT25] and clock drawing tasks: executive screening)
Fan and colleagues[45] (2009)	Open-label, two groups, without placebo	Adults (n=87) : patients with breast cancer and concurrent anaemia	Prevention	16–28 weeks	No significant differences (mini mental state examination and high sensitivity cognitive screening: cognitive screening; revised Hopkins verbal learning test: memory)

WAIS=Wechsler adult intelligence scale. RCT=randomised clinical trial.

Table 1: **Clinical studies of pharmacotherapy for cancer therapy-induced cognitive symptoms**

Modafinil for patients with non-CNS cancer and systemic cancer therapy

A study to evaluate the effects of modafinil on systemic cancer therapy-induced cognitive deficits was done by Kohli and colleagues.[33] The effects of modafinil on cognitive dysfunction were analysed in 82 patients with breast cancer who completed chemotherapy or chest radiotherapy more than 1 month before the study. All patients received modafinil (200 mg daily) for 4 weeks (phase 1), and patients with a favourable response were randomised to receive an additional 4-week intervention with either modafinil or placebo (phase 2). Memory and attention were tested at baseline and after phase 1 and phase 2 with tests for memory and attention selected from the cognitive drug research computerised assessment system. Modafinil significantly improved memory during phase 1 (mean change in speed of memory index from baseline to end of phase 1 was of 240·003 seconds, p=0·0073; mean change in quality of episodic memory from baseline to end of phase 1 was 26·826, p<0·0001), and only patients who were assigned modafinil in phase 2 continued to show significant improvement in memory (p=0·029 for memory speed; p=0·015 for quality of episodic memory) and attention (p=0·010 for continuity of attention). On a cautionary note, the study by Kohli and colleagues exclusively included patients who presented with fatigue, as the primary goal was to evaluate the effects of modafinil on post-treatment fatigue. Therefore, the generalisation of the results from this study might be restricted.

The role of CNS stimulants, such as modafinil and methylphenidate, in treating chemotherapy-induced cognitive dysfunction in adult patients with cancer remains, therefore, inconclusive (table 1).

Anti-dementia drugs

Donepezil

Donepezil is an acetylcholinesterase inhibitor and among the few drugs approved by the US Food and Drug Administration for the treatment of Alzheimer's disease. Donepezil reduces atrophy of the basal forebrain cholinergic system, a network projecting to the cortex, entorhinal cortex, and hippocampus.[49] Impairment of memory is commonly seen in patients with brain tumours,[50] brain-directed therapies,[39] and following systemic chemotherapy.[24] Loss of hippocampal neural progenitor cells has been shown in numerous preclinical studies testing the effects of chemotherapy and radiotherapy,[51] suggesting that hippocampal dysfunction might underlie these memory deficits.[52]

Donepezil for patients with CNS cancer and brain-directed cancer therapy

The potential benefit from donepezil is supported by a prospective, open-label, single-arm phase 2 trial of donepezil in 24 patients with brain tumours and cognitive impairment who completed cranial radiotherapy.[34] Cognitive functions, such as concentration and verbal memory, significantly improved following a 24-week course of donepezil. The positive results were ratified in a

phase 3 double-blinded randomised controlled trial done by the same group in a cohort of 198 survivors of brain cancer after cranial irradiation,[35] showing that a 24-week treatment with donepezil was superior to placebo in improving cognitive functions. Significant differences after 24 weeks between the groups were observed in the Grooved Pegboard for the dominant hand testing motor speed and dexterity (least square mean scores 105·1 [3·4] for donepezil *vs* 117·0 [3·5] for placebo, p=0·016), and the Revised Hopkins Verbal Learning Test (HVLT-R) assessing memory (least square mean scores for HVLT-R recognition 10·9 [0·2] for donepezil *vs* 10·3 [0·2] for placebo, p=0·027; least square mean scores for HVLT-R discrimination 10·1 [0·2] for donepezil *vs* 9·2 [0·2] for placebo, p=0·007). Perhaps, most importantly, this study showed an interaction between treatment effect and individual cognitive impairment, in that those patients who had more significant memory deficits before treatment showed a greater benefit of donepezil when compared with patients with less memory deficits before treatment.

Castellino and colleagues[36] did an open-label pilot study in 11 survivors of childhood brain tumour with a median age of 11·1 years who completed cranial radiotherapy more than 22 months before enrolment, of which eight (73%) of those patients had also completed concurrent chemotherapy. All patients received age-adjusted doses of donepezil for 24 weeks. Neurocognitive outcome was evaluated at baseline and after 12 weeks, 24 weeks, and 36 weeks after the intervention with objective cognitive measurements. Visual memory, executive function, and working memory showed significant improvement 24 weeks after treatment compared with baseline. The largest effect was measured with the Dellis-Kaplan Executive Function Test Tower Test, which changed from mean baseline scaled score of 8·3 to 11·7 at week 24 (p<0·001). Moreover, after a washout period of 12 weeks, a trend towards decline in some cognitive domains was observed. Another open-label, single-arm pilot study with 15 adult patients with brain tumour who had completed chemotherapy or radio-chemotherapy was previously published.[37] A daily dose of donepezil (5 mg daily for 4 weeks, and subsequently 10 mg daily for 20 weeks) was administered for 24 weeks, and cognitive evaluation was done at baseline, and 12 weeks and 24 weeks after the intervention. A beneficial treatment effect was seen after 12 weeks, and a treatment duration of 24 weeks had a significant positive effect on attention, graphomotor speed, and visual memory.

Donepezil for patients with non-CNS cancer and systemic cancer therapy

One double-blinded randomised controlled trial evaluated donepezil in systemic chemotherapy-induced cognitive dysfunction.[38] 62 female survivors of breast cancer who completed more than four cycles of chemotherapy and had cognitive dysfunction were enrolled and treated with 24 weeks of donepezil (5 mg daily for 4 weeks, and subsequently 10 mg daily for 20 weeks) or placebo. Neurocognitive function was assessed with several standardised neuropsychological tests that included the Revised Hopkins Verbal Learning Test (HVLT-R), Rey-Osterreith Complex Figure Test, Controlled Oral Word Association Test, Trail Making Tests, Digit Span Test, and Grooved Pegboard test at baseline (N=60) and at 24 weeks after the intervention (N=46). Donepezil produced significantly greater improvements than placebo on two measurements of memory, HVLT-R total recall (improvement of 2·1 points for donepezil *vs* decline of 0·4 points for placebo, p=0·033) and HVLT-R delayed recognition discrimination index (improvement of 0·5 points for donepezil *vs* decline of 0·4 points for placebo, p=0·036). Notably, other measures of cognitive function remained stable, suggesting that donepezil might have had a preferential effect on the hippocampal memory system. According to the authors, positive effects of donepezil were sustained at the 36-week timepoint but were not reported in further detail in the original manuscript. The results of an ongoing phase 3 trial (NCT02822573) for treatment of cognitive symptoms in survivors of breast cancer after systemic chemotherapy promises to provide further insight into the usefulness of donepezil in this patient population.

Although clinical data on using donepezil in cancer therapy-induced cognitive dysfunction is restricted, the existing studies suggest a benefit in this patient population. Based on findings from donepezil treatment of patients with both CNS and non-CNS cancer,[35] the decision to treat an individual patient might be based on the nature and severity of cognitive dysfunction. Specifically, those patients with memory impairment (as opposed to deficits in attention, processing speed, or other cognitive domains) and those who are more severely affected appear to have a great likelihood of benefit. Future clinical trials potentially testing higher doses of donepezil might face dose-dependent side-effects with this treatment;[53] however, the available studies found only minimal toxicities that mainly included fatigue, insomnia, and gastrointestinal symptoms, resulting in low dropout rates.[34,38]

Memantine

The N-methyl-D-aspartate receptor (NMDA) antagonist memantine is an anti-dementia drug, acting through amelioration of glutamatergic neurotransmission, and is a treatment option for various subtypes of dementia, including Alzheimer's disease and dementia with Lewy body.[54]

Memantine for patients with CNS cancer and brain-directed cancer therapy

Brown and colleagues[39] randomised a large cohort of 508 patients with brain metastases to either receive 24 weeks of placebo or memantine (20 mg daily), within 3 days of the initiation of whole-brain radiotherapy. About

half of patients in the double-blinded randomised controlled trial had received chemotherapy previously, and a third had chemotherapy while on the study. Cognition was evaluated at baseline and weeks 8, 16, 24, and 52 after treatment. Although the predefined primary endpoint of reduced decline in delayed recall was not reached, several findings favoured the memantine group. Memantine reduced probability of cognitive failure at 24 weeks (53·8% *vs* 64·9%, hazard ratio [HR] 0·78, p=0·01) and fewer patients had a decline in delayed recognition (HVLT-R delayed recognition median decline in standardised scores at 24 weeks 0 *vs* –1, p=0·0149), executive function (group scores not available), and processing speed (group scores not available). Notably, an intent-to-treat analysis was done but only 29% of all eligible patients completed the 24-week assessment. Because a careful objective neuropsychological test battery was used in this study, the findings, though of marginal statistical significance, might be interpreted as showing only modest neuroprotective effects from memantine. The results were ratified in a second analysis of this cohort that also found that dynamic contrast enhanced-MRI might be a possible imaging biomarker for the radioprotective properties of memantine.[55] More clinical trials are ongoing in this regard: a phase 2 or 3 trial to investigate the effects of memantine on cognitive function in patients after head or neck radiotherapy (NCT03342443), and a phase 3 trial of patients undergoing brain radiotherapy (NCT02360215).

No data exist so far to specifically comment on the effect of memantine in non-CNS cancer and systemic chemotherapy-induced cognitive dysfunction (table 2).

	Potential targets or mechanisms of action	Clinical trial registry numbers
CNS stimulants		
Methylphenidate[56]	Activation status of the frontostriatal network	NCT02970500
Anti-dementia drugs		
Donepezil[49]	Basal forebrain cholinergic system protection	NCT02822573
Memantine[54]	Glutamatergic neurotransmission	NCT03342443 NCT02360215
Potentially neuroprotective drugs		
Patients with brain-directed cancer therapy		
Lithium[57]	Protection against hippocampal neuron apoptosis	NCT01486459
Pioglitazone[58]	Anti-inflammatory, less oxidative neuron injury	NCT01151670
Ramipril[59]	Anti-inflammatory, less oxidative neuron injury	NCT03475186
Patients with systemic cancer therapy		
Fluoxetine[60]	Protection of dividing cells in the hippocampus	NCT01615055
Docosahexaenoic acid[61]	Functional recovery, reduction of microglia infiltration	NCT02517502
Ibuprofen[62]	Anti-inflammatory, less oxidative neuron injury	NCT03186638
Nicotine[63]	Glutamatergic neurotransmission	NCT02312934

Table 2: **Ongoing clinical trials of pharmacotherapy for cancer therapy-induced cognitive symptoms**

Ginkgo biloba

Ginkgo biloba for patients with CNS cancer and brain-directed cancer therapy

An open-label phase 2 trial with 34 patients with brain tumour who completed radiotherapy and were all consecutively treated with ginkgo biloba (120 mg daily) for 24 weeks showed positive effects on cognitive function.[40] Significant improvements were found on cognitive tests assessing the domains of processing speed, executive function, and memory. However, this study was limited because of the absence of a placebo control and because it did not control for practice effects that might account for improvement in test scores over time.

Ginkgo biloba for patients with non-CNS cancer and systemic cancer therapy

Results from a double-blind randomised controlled trial with 166 patients with breast cancer treated with ginkgo biloba (120 mg daily) during chemotherapy and 1 month after completion of chemotherapy, showed no benefit for the treatment group on subjective report of cognitive symptoms or objectively tested cognitive function.[41] These negative results line up with other randomised control trials that reported no beneficial effect of ginkgo biloba for cognitive dysfunction in other settings, such as for the prevention of progressive memory complaints in Alzheimer's disease or slowing the rates of global cognitive declines in patients over the age 72 years.[64,65]

Erythropoietin

Erythropoietin is an endogenous hormone stimulating the proliferation of red blood cells. It exhibits inhibitory properties on apoptotic cell death in haematopoietic tissue, as well as non-haematopoietic tissue.[66] It is not only used for the treatment of anaemia, but also for neuroprotection in preterm infants. Although no studies exist specifically for the use of erythropoietin in patients with brain tumours or brain directed-cancer therapy, the potential for prevention or treatment of systemic chemotherapy-induced neurocognitive decline has been examined in several studies.

Erythropoietin for patients with non-CNS cancer and systemic cancer therapy

Massa and colleagues[42] administered erythropoietin (20 000 international units subcutaneously, 6 days per week for 2 weeks, subsequently 10 000 international units 3 days per week for 10 weeks) to 10 patients with cancer and who had anaemia who were undergoing 12 weeks of chemotherapy. After 4 weeks, 8 weeks, and 12 weeks of treatment, the authors found that erythropoietin significantly improved anaemia, as well as cognitive function, with significant correlation between these two parameters (Spearman's rank correlation test, p=0·049 at 4 weeks, p=0·044 at 8 weeks, and p=0·031 at 12 weeks). Therefore, the study might have shown that improving haemoglobin levels is associated with improved neurocognition, but was not designed to prove the neuroprotective properties of erythropoietin in

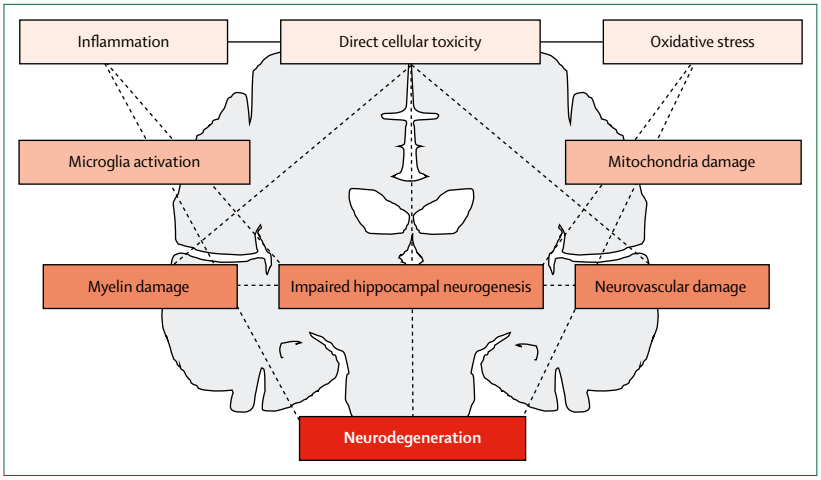

Figure: **Structural and cellular basis of cancer therapy-induced neurotoxicity**
Loss of hippocampal neural progenitor cells is considered a key mechanism for cancer therapy-induced cognitive impairment. Damage to neurovascular units and myelin might also contribute to neurodegeneration. The structural effects are thought to be mediated by direct cellular treatment toxicity, inflammation, and oxidative stress. Cancer therapy-induced mitochondrial damage and microglia activation further enhance neurodegenerative processes. However, definitive molecular mechanisms remain to be elucidated. All these potential mechanisms are interconnected in a downstream dynamic process of structural and cellular changes. The accumulated damage results, ultimately, in neurodegeneration.

chemotherapy patients. Moreover, the study was limited because of its very small sample size of only 10 patients. Indeed, an open-label single arm study with 50 patients with cancer who had anaemia did not show a positive effect of erythropoietin on haemoglobin levels after 12 weeks of treatment (40 000 international units subcutaneously, once weekly).[43]

A multicentre double-blinded randomised controlled trial placed 94 patients with breast cancer on erythropoietin (40 000 IU subcutaneously once weekly) or on placebo at the beginning of four cycles of adjuvant anthracycline-containing chemotherapy administered over 12 weeks.[44] Anaemia at baseline was not a criterion for inclusion in this study. Cognitive function was measured at baseline, 1 week before cycle 4, and 6 months after completion of chemotherapy. Although a mild difference in cognitive function before cycle 4 was seen between the two groups favouring the treatment group (Executive interview [EXIT25] score-difference from baseline to cycle 4 of chemotherapy: –1·3 [SD 3·3] in the erythropoietin group and 0·3 [2·4] in the placebo group; negative changes indicate improved executive function), the authors concluded that the study was not powered adequately nor designed to reliably test for statistically significant differences between the intervention and the placebo. Therefore, the authors of this study did not do a statistical comparison.

A study focusing on the long-term neuroprotective effects against chemotherapy-induced damage using erythropoietin was done by Fan and colleagues.[45] 87 patients with breast cancer and anaemia undergoing chemotherapy received erythropoietin (40 000 international units subcutaneously once weekly) for 16–28 weeks versus standard of care, and cognitive function was assessed 12–30 months after treatment. This study also did not show a clear significant protective effect of erythropoietin against delayed cognitive dysfunction.

Collectively, although improvement in haemoglobin levels might have a an effect on cognitive function in patients with cancer, no study so far has conclusively showed a definite neuroprotective effect of erythropoietin in patients undergoing chemotherapy. Moreover, concerns remain of potentially increasing the risk of thromboembolic complications in patients treated with erythropoietin.[67,68] Prospective clinical trials designed to specifically study potential neuroprotective properties and associated cardiovascular risks of erythropoietin using objective cognitive tests and placebo-controlled groups are needed to elucidate this point further (table 1).

Future directions

Management of cancer therapy-induced cognitive dysfunction remains highly challenging because of the heterogeneity of symptoms and paucity of effective treatment options. Hippocampal dysfunction is considered a key mechanism of cancer therapy-induced neurotoxicity, whereas other cellular and molecular mechanisms appear less clear and remain to be elucidated as possible targets for treatment (figure).[11,52] Although some drugs, such as CNS stimulants and antidementia drugs have been proposed as useful agents for this patient population, well controlled prospective clinical trials are urgently needed to elucidate the true potential of candidate drugs (table 2).

Drugs used in other neurologic conditions have recently drawn the attention of researchers in the field of neuroprotection and neurocognition. For example, in-vitro data have encouraged the use of lithium, pioglitazone, and ramipril for neuroprotection following brain-directed therapy. Accordingly, clinical phase 1 trials for the prevention of radiotherapy-induced cognitive dysfunction are ongoing for lithium (in patients with lung cancer undergoing prophylactic cranial radiotherapy, NCT01486459) and pioglitazone, an antidiabetic drug (in patients with brain tumour, NCT01151670). A phase 2 trial for ramipril (NCT03475186), a centrally acting angiotensin-converting enzyme inhibitor, is planned in patients with brain tumour. Other promising drugs for patients that received brain-directed cancer therapy are AT1 receptor antagonists, a group of antihypertensive drugs that have been shown to ameliorate radiotherapy-induced cognitive dysfunction in preclinical settings.[69]

Fluoxetine, a selective serotonin reuptake inhibitor, was found to exhibit protective properties in the CNS against systemic chemotherapy in a rodent model,[60] and a phase 1 trial (NCT01615055) is scheduled to elucidate potential protective effects in patients with breast cancer or lymphoma undergoing systemic chemotherapy. Two more potentially neuroprotective drugs are being analysed in clinical studies for patients with systemic

chemotherapy: docosahexaenoic acid in a phase 1 trial (patients with breast cancer, NCT02517502), and ibuprofen in a phase 2 trial (patients with colorectal cancer, NCT03186638). A clinical trial using nicotine dermal patches was recently planned for patients with breast cancer after chemotherapy (NCT02312934), on the basis that nicotine, a cholinergic agonist, might affect alertness and have some neuroprotective effects. Therefore, these drugs might provide new options for the prevention or treatment of cancer therapy-induced cognitive dysfunction in the future.

Another potential avenue for neuroprotection is the use of novel drugs developed to minimise oxidative stress or mitochondrial dysfunction caused by radiotherapy or chemotherapy. Astaxanthin is a naturally occurring carotenoid with antioxidant properties and was found to protect memory in a rodent model of chemotherapy-induced cognitive dysfunction.[70] Other drugs that have successfully prevented chemotherapy-induced cognitive decline in animal models are KU-32, which inhibits chaperones and is thought to repair mitochondrial damage,[71] and PAN-811, a ribonucleotide reductase inhibitor with the capability of scavenging free radicals.[72] The use of antioxidants as a strategy to prevent neurotoxicity or enhance neural repair will have to be carefully evaluated in the context of the potential concern that such drugs might also alter the effects of chemotherapy or radiotherapy on tumour cells.[73] Although controversial data exist on the use of antioxidants and the role of oxidative stress to promote carcinogenesis and tumour growth,[74–77] it will be crucial to show whether the use of a specific antioxidant might enhance or reduce the tumour-killing properties of existing cancer therapies.

An unanticipated connection between bone marrow function and brain plasticity has emerged, suggesting an alternative strategy for neural repair. Using a mouse model, our group showed that bone marrow-derived G-CSF-responsive cells are a crucial component of endogenous brain repair following radiation injury.[78] Cells of monocyte-macrophage origin are able to migrate to the CNS, where they eventually mature and integrate into the cellular microenvironment. Accordingly, irradiated mice treated with G-CSF showed improved restoration of cerebral white matter and improved cognitive function.

The potential for combined therapies that integrate pharmacological interventions with non-pharmacological approaches has not been well studied. Most treatment studies, in seeking to control confounds and maximise power of direct head-to-head comparisons, have chosen to explore the effect of either pharmacotherapy or non-pharmacological treatments. However, new clinical trials are being designed to explore the potential for complementary effects of these treatment strategies. For example, an ongoing randomised controlled trial is combining the potential anti-inflammatory effects of ibuprofen versus placebo using a physical exercise programme for patients with cancer (NCT01238120). It will be important to integrate maximally effective pharmacological approaches with other treatments that have showed efficacy in this population, such as cognitive rehabilitation and stress reduction therapy, in future studies.[79,80]

Conclusion

Numerous drug therapies have been proposed for the treatment of cancer therapy-induced cognitive dysfunction. Prospective and placebo-controlled clinical trials are few at this point. Although open-label, single-arm studies have suggested trends towards drug efficacy, they are at risk of generating false-positive results caused by placebo and repetitive cognitive testing-induced practice effects. Of the nine open-label trials highlighted in this Review, only one corrected for practice effects using the reliable change index.[29] Another limitation is the substantial heterogeneity in the patient cohorts among the studies. Trials analysing cognitive improvement based on therapeutic drugs as secondary objectives might not indicate if the patient's cognition is impaired at baseline, complicating the interpretation of study results.[32] This point is a crucial issue as it has been suggested that patients with cognitive impairment at baseline have greater potential for treatment-induced improvement compared with those without an impairment at baseline.[34] Also, inclusion criteria, such as receipt of previous cancer therapies, vary between clinical trials and pathomechanisms might differ for patients who have undergone chemotherapy or radiotherapy alone from those who received combined treatment. Moreover, numerous risk factors, comorbidities, and medications (eg, neuroleptics, anti-epileptics, and mood stabilisers) that might adversely affect brain plasticity and vulnerability to cancer therapies will need to be controlled for in prospective studies. An increasing understanding of the basic mechanisms underlying cognitive deficits in patients with cancer will be crucial to identify novel treatment strategies that can specifically target molecular or cellular pathomechanisms to help mitigate or potentially alleviate cognitive dysfunction for patients with cancer.

Contributors

PK and JD did the study concept and design. All authors participated in the data analysis and interpretation, and drafting and revising of manuscript.

Declaration of interests

MWP is a consultant for Monteris Medical Inc and earns royalties from the American Psychological Association. PK and JD have nothing to declare.

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