REVIEW

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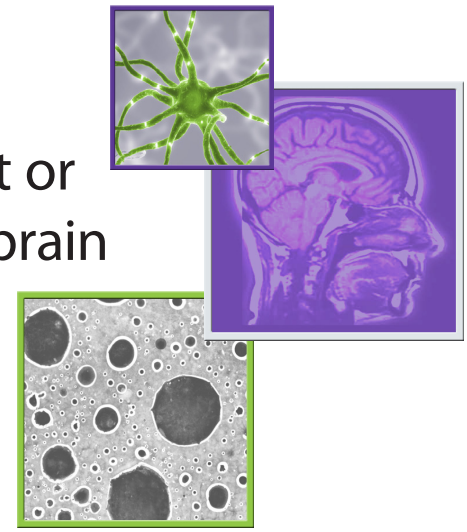

Pharmacological interventions to treat or prevent neurocognitive decline after brain radiation

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Practice Points

- Primary and metastatic brain tumors are common forms of cancer in adults and children and often require radiation treatment as a component of treatment.
- As survival increases with more effective treatment strategies, long-term cognitive effects become more problematic and treatment of these effects becomes more important.
- Several drug and lifestyle modifications have shown promise in helping to abrogate the cognitive effects of brain tumor treatments.
- Prevention of cognitive dysfunction can be attempted using more advanced radiotherapy techniques, as well as drugs given during and after radiotherapy treatment.
- There are currently several trials investigating drugs to prevent cognitive dysfunction following radiotherapy.

SUMMARY After surgery, radiation is the most effective treatment for the majority of brain tumors in both children and adults. Although improvements in radiotherapy delivery and targeting have resulted in reduction in neurologic morbidity, radiotherapy is still associated with acute and late toxicities that are dependent on a variety of treatment- and patient-specific variables. Variables of treatment include radiation dose, fractionation, volume, technique, photons or protons, and concomitant or adjuvant chemotherapy. Patient- and tumor-specific variables include tumor type, location and patient age. Side effects of treatment are also variable and can range from mild fatigue to significant memory difficulties and even death. This review will focus on the hypothesized mechanisms of cognitive dysfunction after radiation therapy and will discuss possible intervention strategies including behavioral and pharmacological prevention and treatment.

Brain metastases are the most common form of brain tumors in adults, with an estimated 150,000 new patients diagnosed each year in the USA alone. In addition, an estimated 24,620 new cases of primary malignant brain tumors and 4306 new cases of childhood primary brain tumors are expected to be diagnosed in the USA in 2013 [1]. Radiation remains an effective and necessary tool for helping to achieve symptom management and cure for many of these patients. For children, the effects of brain radiation are more prominent as radiation affects the developing brain more significantly [2]. Cure rates from childhood brain

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tumors have reached as high as 80% [3] and have resulted in a significant number of long-term survivors. Recent reports suggest that 60–80% of childhood cancer survivors are dealing with chronic health conditions [1]. As survival outcomes have improved and these patients are living longer, current research strategies have often shifted to identifying less toxic curative regimens and developed treatments for, and even more importantly, preventative strategies, to minimize treatment-related side effects.

The following review will summarize the neurologic symptoms associated with cranial radiation, review pathophysiologic mechanisms of neurologic and cognitive injury and discuss current strategies for treatment and prevention of radiation-related cognitive toxicity. Although proton radiotherapy (RT) is increasingly being used to treat cranial tumors, most of the historic toxicity data is based on photon RT. 'RT' as it is used in this review refers to photon RT unless otherwise specified.

Clinical symptoms

Clinical symptoms of cranial radiation are broken down into three categories: acute, early-delayed/subacute and late-delayed effects. Acute effects occur during or shortly after radiation treatment and are characterized by drowsiness, headache, nausea, emesis and worsening of pre-existing focal symptoms [4].

Early-delayed/subacute encephalopathy occurs 1–6 months after RT, is reversible, and is characterized by headache, somnolence, fatigability and deterioration of pre-existing deficits [4]. These effects are thought to be secondary to demyelination [5].

Late-delayed effects usually occur more than 6 months after radiation and are usually irreversible and often progressive [6] and, therefore, are the most worrisome. These effects are thought to be secondary to diffuse white matter injury, combined RT and chemotherapy-induced leukoencephalopathy and necrosis. Diffuse white matter injury is characterized by symptoms ranging from mild lassitude to significant memory loss and severe dementia [7]. Combined RT and chemotherapy-indued leukoencephalopathy is similar to diffuse white matter injury but has the additional symptoms of ataxia, confusion, dysarthria, seizures and incapacitating dementia or death [8]. Focal radiation necrosis symptoms include seizures, signs of increased intracranial pressure and neuroanatomical-specific effects. The tolerance dose 5/5, or the dose at which there is a 5% probability of necrosis, is 50 Gy for whole-brain RT and 60 Gy for partial-brain RT [9,10]. MRIs typically show an area of irregular enhancement with associated edema, which is difficult to distinguish from tumor progression [11]. A biopsy is generally required to determine whether these changes can be attributed to tumor progression versus radionecrosis [12].

Mechanisms of injury

Although clinical symptoms and syndromes have been well defined as acute, subacute and late effects, it is difficult to assign mechanisms of action specifically to each of these categories. It is thought that there is a continuum of effects and that although some acute effects completely resolve, others may continue or develop into late effects, likely resulting from the same mechanism of injury [13].

The mechanism of brain injury after radiation is still unclear but is likely multifactorial with many different cell lineages involved, including astrocytes, endothelial cells, microglia, neurons and oligodendrocytes [14,15]. Radiation causes neuroinflammation, prevents hippocampal neurogenesis and alters neuronal function [16].

Neuroinflammation

Inflammation is also thought to be responsible for both the early and late components of cognitive dysfunction following radiation therapy to the brain. Astrocytes and microglia have both been studied and thought to play a role in neuroinflammation following radiation.

Astrocytes have been shown to protect endothelial cells and neurons from oxidative injury [17]. When astrocytes are injured, they proliferate, express GFAP and secrete proinflammatory cytokines such as Cox-2 and ICAM-1 [18,19]. These cytokines may help to break down the blood–brain barrier to allow leukocyte infiltration [20].

Microglia are chiefly responsible for monitoring the brain microenvironment to maintain homeostasis [21]. When microglia are activated, which can occur within days after exposure to RT, they also produce reactive oxygen species and proinflammatory cytokines that leads to increased expression of TNF-α, IL-1β, IL-6, Cox-2 and the chemokines MCP-1 and ICAM-1 [20,22,23].

The production of the proinflammatory cytokines by activated astrocytes and microglia are thought to lead to inhibition of neurogenesis

and cognitive dysfunction. The preclinical evidence suggests this is an acute change and it is unclear if these inflammatory changes improve and resolve or if they contribute to late cognitive effects.

Hippocampal neurogenesis

As recently as the mid-1990s, many scientists believed neurons were incapable of neurogenesis past a certain point of brain development. The first experiments showing adult neurogenesis in animals were performed as early as the 1960s [24,25] but it was not until the last 20 years that this became a mainstream belief in the scientific community, with studies confirming human hippocampal neurogenesis [26]. It is now recognized that neurogenesis takes place throughout the human lifespan in at least two specific areas – the dentate gyrus of the hippocampus and the subventricular zone.

The hippocampus was initially proposed as the location for radiation-induced cognitive dysfunction after a correlation was drawn between cognitive function and dose delivered to the medial-temporal region of the brain [27]. New neurons that are born in the dentate gyrus of the hippocampus are thought to be important to normal memory function, possibly encoding new memories [28]. Mouse models have demonstrated disruption of this neurogenesis and memory decline after RT, which is thought to be mediated by microglial inflammation [29,30].

Researchers from Brigham and Women's Hospital (MA, USA) collected and examined human hippocampi from autopsy tissue. Four of their patients had undergone brain RT and were age and sex matched with control subjects. They observed a reduction of dentate gyrus neurogenesis in addition to an increase in microglial activation in the patients who had undergone brain RT [31]. The effects on neurogenesis have been seen in mouse models to be evident within 48 h after single fractions of 2 Gy, suggesting exquisite radiosensitivity of these neurons to RT [32]. The autopsy study suggests that these effects may be long lasting [30] and cognitive outcomes in patients receiving high doses to the medial temporal lobes suggests that injury to the hippocampus may also contribute to late cognitive toxicity [26].

To try to assess memory impairment following radiation assault on the brain, specifically, the hippocampus researchers at Stanford University (CA, USA) studied adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiation therapy as well as intrathecal and systemic chemotherapy [33]. These patients demonstrated poorer recognition memory, hippocampal atrophy and altered blood oxygenation level-dependent signals in the hippocampus, which showed long-term neuroimaging correlates of cognitive dysfunction, suggesting long-lasting damage to memory following RT and intrathecal chemotherapy.

Vascular hypothesis

It is hypothesized that radiation of vessels within the brain results in small vessel disease very similar to what is found in vascular dementia [34]. Accelerated atherosclerosis and mineralizing microangiopathy lead to vascular insufficiency and infarction of the brain tissue that, in turn, leads to injury and inflammation [4]. Electron microscopy of the brain microvasculature after radiation shows changes in the blood–brain barrier [35]. As the blood–brain barrier breaks down, it allows passage of leukocytes into the brain parenchyma leading to neuroinflammation and decreased neurogenesis. Histological studies reveal the beginning of endothelial cell death during RT and continuing over the ensuing few months [36,37]. As endothelial cells die, platelets stick to the exposed matrix, which leads to formation of clots. This reduced blood flow leads to ischemia, which is followed by necrosis of the brain tissue. For subacute or less severe reductions in blood flow, the vascular hypothesis has been equated to a resultant 'early aging' of the brain, resulting in accelerated atrophy compared with expected age-dependent changes.

It is increasingly recognized that radiation-related cognitive dysfunction is multifactorial and most likely involves a combination of all the pathways. For example, apoptosis of hippocampal neurons occurs at very low radiation doses and may be involved in early or acute radiation toxicity [31,38], whereas the inflammatory reaction may begin during radiation and continue on through the early-delayed period and result in long-term changes due to tissue demyelination and remodeling. The vascular changes after RT are typically late radiation changes that although may start early during RT, often do not become clinically apparent until months or years after treatment [7].

In addition, radiation effects on neurons, supportive cells and the vasculature are believed to be mediated by complex inflammatory cytokines and neurotransmitters [39]. Early research

focused more on behavioral modification and cognitive therapy strategies. Improved understanding of the mechanisms of radiation injury has lead to more targeted intervention strategies, and continued elucidation of pathways involved with the radiation injury is imperative for development of more effective strategies The following section will review the current outcomes of behavioral and medical treatments for radiation-induced cognitive dysfunction while the 'Prevention' section will review outcomes from recent efforts of preventative strategies.

Treatment

■ Behavioral

Physical activity has been hypothesized to help with cognitive dysfunction due to aging [40], following stroke [41], or in Alzheimer's disease [42]. Radiation-related cognitive dysfunction has similarities with all these types of dementia and it was hypothesized that exercise may help improve symptoms in a similar manner. In a prospective mouse model of radiation-induced cognitive injury, half the mice that had undergone whole-brain irradiation were offered access to a running wheel 1 month after their treatment [43]. They found mice that voluntarily ran on the treadmill daily had better spatial memory retention, as well as partial restoration of newborn neurons in the dentate gyrus of the hippocampus. Although the effects of physical activity have not been prospectively evaluated in humans, these results suggest exercise as a potential therapeutic intervention in patients hoping to maintain higher quality of life after brain radiation.

Mindful meditation has also been proposed to be helpful in both subjective and objective measures of cognitive function in patients having undergone treatment for cancer [44]. There have been several studies suggesting that meditation engages and modulates neural circuits involved in higher order cognitive processes that are often impaired in cancer-related cognitive deficits; however, randomized evidence is still required to help define the roll of mindful meditation in helping to abrogate cognitive effects of treatment [45,46]. It is thought that perhaps meditation practice provides mental training within the domains of attention, memory and executive function. This is proposed to work through regulation of emotional responses and sense of self [47], regulation of the immune system [48], stress reduction and improved sleep quality [49].

■ Pharmacological

PPAR agonists

PPARs are believed to play a role in modulation of inflammation. These receptors belong to the steroid/thyroid superfamily of nuclear receptors and regulate gene transcription by heterodimerizing with retinoid X receptors and binding to PPAR response elements on enhancer regions of genes [50]. In this way, they regulate inflammatory signaling (Table 1) [51]. As discussed above in the mechanisms of action section, activated astrocytes and microglia express increased *TNF-α* and *IL-1β* gene expression and increased Cox-2 protein levels. The promotor regions of these genes have numerous transcription factor binding sites, including AP-1 and NK-κB. PPARα agonists have been shown to significantly inhibit this proinflammatory response by preventing the activation of AP-1 (via inhibiting c-Jun phosphorylation) and NF-κB (by preventing p65 nuclear translocation) [51].

Pioglitazone is a PPARγ agonist that has been shown to prevent cognitive impairment in rats. In one report, pioglitazone was given to rats 3 days prior to, during and for 52 weeks following 40 Gy of fractionated whole-brain radiation (fWBI) [52]. Pioglitazone prevented radiation-induced perirhinal cortex-dependent cognitive impairment 1 year after treatment.

Fenofibrate is a PPARα agonist that has also been studied in animal models. In a study completed by Ramanan and colleagues, wild-type mice were assigned to one of four treatments: control diet and sham RT, fenofibrate and sham RT, control diet and 10 Gy whole-brain radiation (WBI), or fenofibrate and 10 Gy WBI [53]. Mice that had dietary fenofibrate did not have the typically seen decrease in the number of newborn hippocampal neurons or the increase in microglial activation, suggesting that fenofibrate promoted the survival of newborn cells following irradiation and prevented the activation of microglia. A similar experiment using rats used dietary fenofibrate given 1 week prior, during and 30 weeks after 40 Gy fWBI and was shown to prevent perirhinal cortex-dependent cognitive impairment at 26 weeks after RT as well as preventing an increase in activated microglia at 30 weeks after RT [16].

Although PPAR agonists have not been studied in radiated patients, another PPARγ agonist, rosiglitazone, was tested in a double-blind, placebo-controlled pilot study in patients with mild Alzheimer's disease or amnestic mild

Table 1. Pharmacologic agents for treatment of cognitive dysfunction.

Drug	Mechanism of action	Study population	Outcome	Ref.
PPAR agonists[†]				
Pioglitazone	PPARγ agonist	Rats undergoing 40 Gy fWBI	Prevented cognitive impairment	[52]
Fenofibrate	PPARα agonist	WT mice undergoing 10 Gy WBI	Prevented decrease in newborn hippocampal neurons and decreased microglial activation	[53]
Rosiglitazone	PPARγ agonist	Adults with Alzheimer's disease	Better delayed recall and selective attention	[54]
Renin–angiotensin system blockers[‡]				
Ramipril	ACE inhibitor	Studied in rats undergoing 40 Gy fWBI	Decreased changes in cognitive function and decreased microglial activation	[58]
ARB L-158, 809	ARB	Rats undergoing 40 Gy fWBI	Prevented cognitive impairment at 5, 26 and 52 weeks	[59]
CNS stimulants[§]				
Methylphenidate	Mixed dopaminergic noradrenergic agonist	Prior treatment for malignant gliomas	Significant cognitive improvement	[62]
		Long-term survivors of childhood ALL	Reduced attention deficits and improved social functioning	[63]
		Childhood cancer survivors with learning impairments	Improvement in attention, cognitive flexibility and processing speed	[64]
Modafinil	Unknown mechanism of action	Adults with brain tumors undergoing surgery, radiation, and/or chemotherapy	Improvement in cognition, mood and fatigue	[65,66]
Acetylcholinesterase inhibitors[¶]				
Donepezil	Reversible acetylcholinesterase inhibitor	Adults receiving brain radiation	Improvement in cognitive function, mood and quality of life	[68]

[†]PPAR regulates inflammatory signaling. Agonists inhibit inflammatory response by preventing activation of AP-1 and NF-κB.
[‡]The brain renin–angiotensin system helps modulate the blood–brain barrier, stress, memory and cognition.
[§]Unknown specific mechanism of action.
[¶]Mechanism to reduce plaque formation/collagen deposition
ALL: Acute lymphoblastic leukemia; ARB: Angiotensin receptor blocker; fWBI: Fractionated whole-brain radiation; WBI: Whole-brain radiation; WT: Wild-type.

cognitive impairment [54]. A total of 30 patients were randomized to placebo or rosiglitazone for 6 months. The experimental group had better delayed recall at 4 and 6 months and selective attention at 6 months.

Renin–angiotensin system blockers

The brain renin–angiotensin system (RAS) is involved in the modulation of the blood–brain barrier, stress, memory and cognition [55]. Beneficial effects of RAS blockade on cognitive function have been observed in patients taking losartan [56], which suggests RAS may play a role in normal cognitive function and, therefore, may be used as a potential treatment for radiation-induced cognitive dysfunction [57].

Rat experiments have shown benefit to RAS blockade. In one study, rats were given ramipril (an ACE inhibitor) for 3 days prior to 40 Gy of fWBI, during RT and after RT [58]. Rats that received the drug were found to have decreased radiation-induced changes in perirhinal cortex-dependent cognitive function as well as microglial activation in the dentate gyrus. In another rat study, the angiotensin receptor blocker, L-158, 809 was given to rats 3 days prior to 40 Gy fWBI, during RT and after RT for 28 or 54 weeks [59]. The researchers found that drug administration prevented radiation-induced cognitive impairment at 26 and 52 weeks following radiation treatment. Additionally, they found administering the drug for only 5 weeks postradiation provided the same cognitive protection as 28 weeks of administration.

CNS stimulants

Stimulants, such as methylphenidate (MPH), have been used in treating concentration difficulties, psychomotor retardation, fatigue and depression in patients who have undergone brain irradiation [60].

MPH hydrochloride (methyl-α-phenyl-2-piperidineacetate hydrochloride) is a mixed dopaminergic noradrenergic agonist similar to amphetamines in its pharmacological properties [61]. Numerous studies have evaluated efficacy of MPH in treatment-related cognitive dysfunction.

Meyers and colleagues published results from a trial showing a significant cognitive improvement in patients with malignant gliomas who receive 10 mg of MPH twice daily following treatment with minimal side effects [62]. In 2004, Mulhern and colleagues showed long-term survivors of childhood brain tumors or acute lymphoblastic leukemia that were randomized to MPH versus placebo for 3 weeks had reduced attention deficits and improved social functioning according to parent and teacher reports [63]. This was followed in 2007 by fellow St Jude Children's Research Hospital (TN, USA) researcher, Heather Conklin, who showed an acute neurocognitive response to MPH in childhood cancer survivors with learning impairments after just 2 days of MPH versus placebo [64]. Significant improvement was seen in attention, cognitive flexibility and processing speed within the experimental group.

The precise mechanism of action is unknown in modafinil, but is believed to act in a similar manner to MPH. A pilot study of adult patients with cerebral tumors who underwent surgery, radiation and/or chemotherapy were randomized to placebo or modafinil for 3 weeks [65]. Assessment at 8 weeks showed improvement in cognition, mood and fatigue. This was followed by a randomized, open-label, pilot study in which patients received modafinil, immediate-release MPH or sustained-release MPH for 4 weeks [66]. There was no difference between the groups; however, 40% of patients in all arms reported subjective improvement in fatigue and quality of life.

Donepezil

Donepezil is a reversible AChE inhibitor that is approved for the treatment of Alzheimer's-type dementia. Mouse models have shown ionizing radiation decreases both ChAT and acetylcholine levels in irradiated mice, similar to the changes seen in Alzheimer's dementia [67]. This led researchers to study the effect of donepezil in patients who have undergone brain radiation. A Phase II study performed at Wake Forest University (NC, USA) in 35 patients who received 5 mg of donepezil for 6 weeks followed by 10 mg for 18 weeks showed a dramatic effect on cognitive function, mood and quality of life compared with baseline measurements [68]. This led to a Phase III study that included adult patients with primary or metastatic brain tumors having received at least 30 Gy of whole- or partial-brain RT at least 6 months prior to randomization. Patients were randomized to placebo versus 5 mg of donepezil for 6 weeks followed by 10 mg daily for 18 weeks. End points included cognitive function, fatigue, quality of life and toxicity. Results are pending and will be presented at American Society for Radiation Oncology and Society for Neuro-Oncology in 2013 [69].

Glucocorticoids

Glucocorticoids are often used acutely in patients with brain tumors to decrease vasogenic edema. Treatment of vasogenic edema can temporarily reduce cognitive changes associated with the tumor edema. In general, they are not used to treat chronic or treatment-related cognitive dysfunction as they may exacerbate inhibition of neurogenesis via increasing microglial inflammation [70].

Prevention

Although the treatments for radiation-induced cognitive dysfunction have promising results, ideally long-term cognitive dysfunction should be preserved through prevention of injury. This can be accomplished through radiation technique as well as through preventative pharmacologic intervention.

■ Radiation technique

Risk of deficit after cranial RT is associated with high radiation dose, large fraction size, larger field size, use of concurrent chemotherapy and extremes of age at time of treatment [4]. Avoiding concurrent neurotoxic chemotherapy (i.e., methotrexate) and delaying radiation in infants and young children when possible [71] have been effective in reducing risk of severe cognitive dysfunction in these populations. Daily fraction sizes <3 Gy are associated with reduced risk of cognitive injury as are total doses <60 Gy. Newer radiation techniques including intensity-modulated radiation therapy and proton beam therapy have allowed radiation oncologists to maintain appropriate tumor dose while reducing dose to and volume of the normal, uninvolved

brain receiving radiation [72]. Current techniques make it possible to preferentially spare brain structures believed to be important in learning and memory, such as the temporal lobes and hippocampus [73]. Results of a Phase II hippocampal avoidance study in patients receiving fWBI for brain metastases have just been presented and show a significantly improved degree of neurocognitive decline compared with historic controls (7 vs 30% decline at 4 months; p = 0.0003) [74].

■ Pharmacological intervention

NSAIDs

NSAIDs are thought to help with cognitive dysfunction after RT by modulating inflammatory response to RT. In a study performed in rats, indomethacin was administered twice daily in the presence of neural inflammation (injection of lipopolysaccharide that causes production of the inflammatory cytokines IL-1β, TNF-α, IFN-γ and IL-6) and also in the presence of RT starting 2 days prior to treatment, during treatment and continuing for 2 months following completion of treatment. Rats that were treated with indomethacin had a 35% decrease in activated microglia in the dentate gyrus and significantly more newborn hippocampal neurons than those who received radiation alone. Despite this, the radiation plus indomethacin rats had only 20–25% of the neurogenesis of a normal rat who had not been irradiated (Table 2) [32].

Lithium

The mechanism of action of lithium includes activation of antiapoptotic cell signaling pathway PI3K/AKT, which leads to inhibition of GSK-3β [75]. This inhibition prevents GSK-3β from inhibiting critical transcription factors that promote cell survival and proliferation (HSF-1, AP-1, MYC, NF-κB, NFAT and CREB) [76]. GSK-3β also decreases proapoptotic proteins p53 and Bax while increasing levels of prosurvival protein Bcl-2 [77]. In animal models, lithium acts as a protector of neuronal precursor cells in the subgranular zone of the dentate gyrus [78].

Armodafinil

Armodafinil is a CNS stimulant thought to have a mechanism of action similar to MPH. Edward Shaw headed a trial randomizing patients receiving WBI or partial-brain radiation therapy to a dose >45 Gy to either armodafinil or placebo during and for 4 weeks following radiation treatment. End points of the trial included fatigue, quality of life, cognitive function and toxicity. Results have been recently reported in abstract form and suggest an improvement in fatigue, as merited by the brief fatigue inventory, during and up to 4 weeks after RT, although the results were of borderline significance (p = 0.056) [69].

Memantine

Glutamate is the principle excitatory amino acid neurotransmitter in cortical and hippocampal neurons [79]. The *N*-methyl-D-aspartate (NMDA) receptor is activated by glutamate and is associated with learning and memory [80]. Excessive NMDA activation leads to excitotoxicity of the neuron. Recent reports suggest NMDA receptor antagonists, such as memantine, can protect against further damage in patients with vascular dementia by preventing this excitotoxicity [81]. In a rat model of stroke, memantine given as long as 2 h after an ischemic event reduces the amount of neuronal injury by 50% [82,83]. In addition, excitotoxicity is believed to play a role in apoptotic neuroglial cell death with the hippocampus being particularly sensitive to excitotoxic injury. Given the hypothesized role in mediating both vascular and neuroglial effects of radiation-induced cognitive toxicity, NMDA receptor antagonists have been evaluated as a potential preventative agent. In preclinical models, serial injections of MK 801, a NDMA receptor antagonist, reduced both behavioral changes and hippocampal granular zone hypoplasia in neonatal rats receiving WBI [84]. Although preclinical studies suggesting benefit have been available for decades, NMDA receptor antagonists, which include drugs in the ketamine family and the recreational drug phencyclidine, have not been selective enough to be safely utilized in humans.

Memantine is a unique competitive antagonist to the NMDA receptor that selectively binds to the receptor in excitotoxic states but has little binding affinity during normal learning or memory. Memantine was found to improve cognitive performance in patients with mild-to-moderate vascular and Alzheimer's dementia and is US FDA approved for those indications. Based on the hypothesized mechanism of action, memantine was recently utilized in a Phase III placebo-controlled trial randomizing patients undergoing whole-brain RT to 37.5 Gy for metastatic disease to 20 mg of memantine daily versus placebo during radiation and for 24 weeks following treatment. Results have been presented in abstract form [85]. The trial

Table 2. Pharmacologic agents for prevention of neurocognitive decline.

Drug	Mechanism of action	Study population	Outcome	Ref.
Indomethacin	NSAID: modulation of inflammatory radiation response	Studied in rats with neuroinflammation after injection of LPS and after RT	Decreased activated microglia and increased number of newborn hippocampal neurons compared with those who received radiation alone	[32]
Lithium	Indirect inhibition of GSK-3β to promote cell survival and proliferation transcription factors	Studied in irradiated mice	Acts as a protector of neuronal precursor cells in subgranular zone of the dentate gyrus	[78]
Armodafinil	CNS stimulant thought to work similarly to methylphenidate	Studied in adults receiving whole- or partial-brain RT to at least 45 Gy	Reduced fatigue during and 4 weeks after RT	[69]
Memantine	*N*-methyl-D-aspartate receptor antagonist prevents excitotoxicity of the neuron	Studied in rats after undergoing an ischemic event	Reduced amount of neuronal injury by half	[82,83]
		Phase III study in adults undergoing WBI to 37.5 Gy	Decreased reduction in several cognitive domains and increased time to cognitive decline	[85]

LPS: Lipopolysacharride; RT: Radiotherapy; WBI: Whole-brain radiation.

did not meet the predetermined end point for success owing to poorer than expected patient survival ($p = 0.059$) for improvement in the Hopkins Verbal Learning Test-Revised, a measure of short-term memory. However, the study results suggested a 17% reduction in relative risk of cognitive decline ($p = 0.01$), which was maintained even after memantine was discontinued, suggesting memantine was not solely acting as a treatment of cognitive dysfunction but also may prevent cognitive dysfunction in this population. In addition, memantine delayed time to cognitive decline ($p = 0.01$), reduced decline in memory ($p = 0.015$), cognitive, executive and global function, as well as processing speed ($p < 0.01$) [85].

Conclusion & future perspective

Based on the above suspected mechanisms of injury and preliminary and preclinical results, current studies are underway to further evaluate potential preventative and treatment strategies for radiation-induced cognitive dysfunction.

Pioglitazone is currently being evaluated in an open Phase I/II trial evaluating two different doses of orally administered pioglitazone in patients undergoing radiation treatment for brain tumors [101]. A current Phase III trial looking at improving quality of life in children is randomizing childhood cancer survivors to modafinil versus placebo for 6 weeks. The primary end point is improvement in neurocognitive function as defined by parent report of inattention or working memory deficits or by direct assessment of attention, working memory or processing speed. The trial is currently recruiting [102]. Finally, a current Phase III trial is randomizing patients with glioblastoma to placebo versus armodafinil for 8 weeks at two different dose levels looking at fatigue as a primary end point [103].

RT is a necessary component in most primary brain tumors and metastatic brain disease. With increasing technology, radiation techniques have improved, however, patients are still experiencing long-term cognitive dysfunction, which has become more apparent as improvements in surgery and systemic therapies have improved survival. As cancer treatments continue to prolong life, the combination of improved radiation technique, behavioral modification and pharmacological agents targeting treatment, as well as prevention of cognitive dysfunction, are beginning

to show promise towards the goal of maintaining the highest quality of life and cognitive function for these long-term survivors.

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