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Radiation-induced cognitive impairment-from bench to bedside

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Approximately 100 000 patients per year in the United States with primary and metastatic brain tumor survive long enough (>6 months) to develop radiation-induced brain injury. Before 1970, the human brain was thought to be radioresistant; the acute central nervous system (CNS) syndrome occurs after single doses of ≥30 Gy, and white matter necrosis can occur at fractionated doses of ≥60 Gy. Although white matter necrosis is uncommon with modern radiation therapy techniques, functional deficits, including progressive impairments in memory, attention, and executive function have become increasingly important, having profound effects on quality of life. Preclinical studies have provided valuable insights into the pathogenic mechanisms involved in radiation-induced cognitive impairment. Although reductions in hippocampal neurogenesis and hippocampal-dependent cognitive function have been observed in rodent models, it is important to recognize that other brain regions are affected; non–hippocampal-dependent reductions in cognitive function occur. Neuroinflammation is viewed as playing a major role in radiation-induced cognitive impairment. During the past 5 years, several preclinical studies have demonstrated that interventional therapies aimed at modulating neuroinflammation can prevent/ameliorate radiation-induced cognitive impairment independent of changes in neurogenesis. Translating these exciting preclinical findings to the clinic offers the promise of improving the quality of life in patients with brain tumors who receive radiation therapy.

Keywords: inflammation, neurogenesis, peroxisomal proliferator-receptor agonist, radiation-induced cognitive impairment, renin-angiotensin system.

Radiation-Induced Cognitive Impairment

Our view of the radiation response of the brain has evolved considerably over the past few decades as preclinical and clinical knowledge has been acquired. Prior to 1970, the human brain was thought to be radioresistant, with acute central nervous system (CNS) syndrome occurring after single doses >30 Gy and white matter necrosis occurring at fractionated doses >60 Gy. During the 1980s–1990s, late radiation-induced brain injury, characterized by vascular abnormalities, demyelination, and ultimately white matter necrosis, was recognized as a dose-limiting morbidity evident >6 months after irradiation.[1] Extensive preclinical studies in rodents revealed dose-dependent changes in these histopathological lesions.[1,2] Classically, late radiation-induced brain injury was viewed as solely attributable to a reduction in the proliferative capacity of glial[3] or vascular endothelial[2] cells. Of importance, these late effects were viewed as progressive and irreversible. In recent years, there has been a growing appreciation that patients receiving fractionated partial or whole-brain irradiation (fWBI) can develop significant cognitive impairment at >6 months after irradiation, even in the absence of detectable anatomic abnormalities. Thus, current efforts investigating radiation-induced brain injury are focused on the functional consequences of brain irradiation.

Radiation-induced cognitive impairment in some series is reported to occur in up to 50%–90% of adult patients with brain tumor who survive >6 months after fWBI.[4–7] Moreover, because patients with brain tumor are surviving longer because of improved radiation therapy techniques and systemic therapies,[8,9] the patient population experiencing these significant late effects is growing rapidly. Radiation-induced cognitive impairment is marked by decreased verbal memory, spatial memory, attention, and novel problem-solving ability,[10–13] with incidence and severity increasing over time.[14] Rarely after focal radiotherapy and in up to 1.9%–5.1% of long-term survivors after whole-brain radiotherapy,[15] this cognitive impairment progresses to dementia, in which patients experience progressive memory loss, ataxia, and urinary incontinence.[16] As noted previously, all of these late sequelae can be seen in the absence of radiographic or clinical evidence of demyelination or white matter necrosis.[17,18]

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Radiation-induced cognitive impairment has significant effects on quality of life (QOL), and this diminished QOL has become an important and growing concern, being recognized as one of the most important measurements of brain tumor therapy outcomes, second only to survival in clinical trials.[19] Although short-term interventions have proved to be effective,[20] there are no proven successful long-term treatments or effective preventative strategies for radiation-induced cognitive impairment. Thus, the search for therapeutic strategies to prevent/ameliorate radiation-induced cognitive impairment has become very important.

Pathogenesis of Radiation-Induced Cognitive Impairment

Preclinical studies have provided valuable insights into the pathogenic mechanisms involved in radiation-induced cognitive impairment. Numerous studies conducted over the past ~20 years have clearly demonstrated that the classic dogma that radiation-induced late effects arise simply from mitotic cell death of particular target cell clonogens is no longer tenable. Radiation-induced late effects are now believed to reflect complex and dynamic interactions between multiple cell types within an organ.[21] In the brain, radiation-induced late effects, including cognitive impairment, are hypothesized to occur because of dynamic interactions between the multiple cell types within the brain,[22] including astrocytes, endothelial cells, microglia, neurons, and oligodendrocytes. An additional and important component of radiation injury to the brain is the relatively recent observation that irradiation can inhibit hippocampal neurogenesis.

Neurogenesis

In rodents, the hippocampus plays a major role in learning, consolidation, and retrieval of information.[23,24] Consequently, most rodent studies have focused on the hippocampus to investigate radiation-induced brain injury. The hippocampus consists of the dentate gyrus (DG), CA3, and CA1 regions; these regions have been implicated in both rodent and human cognition. In addition, the DG is 1 of the 2 sites of adult neurogenesis in the mammalian brain. Neuronal stem cells (NSCs) in the DG are capable of both self-renewal and generating neurons, astrocytes, and oligodendrocytes.[25–27] Neurogenesis depends on the presence of a specific neurogenic microenvironment in which endothelial cells and astrocytes can promote/regulate neurogenesis.[28,29] Irradiating the hippocampus has been shown to result in a dose-dependent loss of NSCs,[30] decreased proliferation of the surviving NSC, and decreased NSC differentiation into neurons.[31–33] Young adult rats irradiated with a single dose of 10 Gy, a dose that fails to cause demyelination or white matter necrosis, produced only 3% of the new hippocampal neurons formed in unirradiated rats.[32] In contrast to neurogenesis, gliogenesis appears to be preserved following irradiation.[33] Of interest, all these phenomena can be observed after doses of ≤2 Gy that fail to produce demyelination and/or white matter necrosis. Recent data from human patients indicate that radiation therapy for malignant brain tumors may also lead to a significant reduction in the number of neurogenic cells.[34]

These reductions in hippocampal neurogenesis have been implicated in radiation-induced cognitive impairment. Whole-brain irradiation (WBI) of the mouse and rat brain leads to a significant decrease in the number of newborn mature and immature neurons in the DG[32,35,36] and has been associated with impairments in hippocampal-dependent spatial learning and memory 3 months after WBI with a single 5 Gy dose in 21-day-old mice.[35] When young adult mice received 10 Gy of focal irradiation to the hippocampus, a significant decrease in neurogenesis and cell proliferation was detected 3 months after irradiation; this reduction correlated with a decline in cognitive function as assessed by the Barnes maze.[36] Similarly, both a reduction in neurogenesis and cognitive impairment has been observed in young adult rats after fWBI.[37–39] However, it should be noted that older rats fail to show a radiation-induced decrease in neurogenesis[40] but still exhibit cognitive impairment.[41]

It is important to recognize that the hippocampus is not the only domain that appears important in radiation-induced cognitive impairment. Using a recently characterized young adult rat model,[42] Robbins et al applied the perirhinal cortex-dependent novel object recognition task to assess recognition memory. As seen clinically, fWBI (40 Gy given in 5 Gy fractions, twice per week for 4 weeks to young adult male rats) leads to a chronic, progressive cognitive impairment that is statistically significant 6 months after fWBI and worsens over the next 6 months (Fig. 1).[43] Thus, fWBI leads to significant and progressive reductions in both

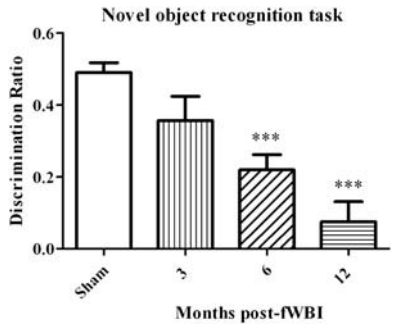

Fig. 1. Development of radiation-induced cognitive impairment as a function of time after young adult male Fischer 344 X Brown Norway rats were irradiated with a total 40 Gy dose of fractionated whole-brain irradiation (fWBI) delivered in 5 Gy fractions, twice/week for 4 weeks. Cognition was assessed using the novel object recognition (NOR) task. The sham-irradiated group value is the average of the NOR scores from unirradiated rats at all of the time points. In this rat model, cognitive impairment is both progressive and not significantly different from sham-irradiated rats until ~6 months after fWBI, similar to what is observed in the clinic. $***P < 0.001$.

hippocampal- and non–hippocampal-dependent cognitive function, indicating that that multiple regions of the brain, and not simply the hippocampus, are involved.

Neuroinflammation

In addition to the significant reductions in neurogenesis, previous studies have also shown a correlation with an increase in the number of activated microglia, the immune cells of the brain, following brain irradiation. Although microglial activation plays an important role in phagocytosis of dead cells, sustained activation is thought to contribute to a chronic inflammatory state in the brain.[44] Rodent studies and analysis of human brain tissue suggest that microglial activation may be associated with decreased hippocampal neurogenesis and decreased cognitive function.[32,34,36] Administration of the anti-inflammatory agent indomethacin reduced the number of activated microglia in the hippocampus and prevented radiation-induced cognitive impairment in rodents.[45]

Although the majority of preclinical studies have focused on the hippocampus and particularly the radiation-induced decrease in neurogenesis, it should be noted that multiple mechanisms are likely to be involved in radiation-induced cognitive impairment. Putative mechanisms include, (i) alterations in NMDA receptor subunit composition,[39] (ii) disrupted Arc expression in hippocampal neurons,[46] (iii) genetic risk factors,[36] and (iv) oxidative stress/neuroinflammation.[47] The latter appears to be particularly important.

A preponderance of evidence supports the hypothesis that late radiation-induced brain injury, including cognitive impairment, is driven by acute and chronic oxidative stress and inflammatory responses.[47,48] In general, ionizing radiation produces its biological effects by, either directly or indirectly, generating reactive oxygen species (ROS), leading to molecular changes; damage to DNA, lipids, and proteins; and activation of early response transcription factors and signal transduction pathways.[49] Activation of these pathways leads to the induction of reparative and restorative processes; changes in cytokine milieu; the activation/influx of inflammatory cells, particularly microglia; and the development of postirradiation complications. Evidence for a chronic inflammatory response to WBI and fWBI in rodent models include region-specific elevation of inflammatory and chemotactic cytokines in the mouse brain 6–9 months after irradiation[50–52] and persistent microglial activation in the rat brain up to 12 months after irradiation.[40,53]

Therapeutic Interventions for Radiation-Induced Cognitive Impairment

Stem Cell Therapies

There is a growing interest in the use of various stem cell therapies to restore the neurogenic niche and improve cognition. These studies are based on the rationale that radiation results in a dramatic reduction in hippocampal neurogenesis that has been linked to cognitive impairment.[35,36] Voluntary running has been shown to increase neurogenesis in the rodent hippocampus, with a concomitant improvement in spatial learning and memory after single WBI doses.[54,55] Direct injection of NSCs into rodent brains after WBI partially restores neurogenesis and hippocampal-dependent cognitive function.[56,57] However, these studies involved injecting NSCs into immunodeficient rats; previous studies by Monje et al.[32,45] noted that inflammation impairs the neurogenic environment, because transplanted syngeneic NSCs cannot produce neurons. Thus, the use of exercise or NSC transplantation to prevent/ameliorate radiation-induced cognitive impairment in humans will require considerably more research before it can be translated to the clinic.

Drug-Based Approaches

Although the exact mechanism(s) of radiation-induced brain injury, including cognitive impairment, is unclear, the relative wealth of experimental data supporting a major role for inflammation suggests that use of anti-inflammatory–based approaches would be of benefit. Rather than attempt to develop novel agents, a process that would likely take several years and ultimately prove to be unsuccessful, we have focused on using drugs that have already received US Food and Drug Administration approval and have been used successfully for a number of years in the clinic. These drugs include peroxisomal proliferator-activated receptor (PPAR) agonists and blockers of the renin-angiotensin system (RAS).

PPAR Agonists

PPARs are ligand-activated transcription factors that belong to the steroid/thyroid hormone superfamily of nuclear receptors.[58] To date, 3 PPAR isotypes have been identified: PPARα (NR1C1), PPARδ (NR1C2), and PPARγ (NR1C3). A growing body of evidence suggests that PPARs regulate inflammatory signaling and are neuroprotective in a variety of CNS diseases.[59–61] Initial studies focused on the PPARγ agonist pioglitazone, a member of the thiazolidinedione class of insulin-sensitizing drugs used for a number of years in the treatment of type II diabetes[62] and effective in the treatment of a variety of brain disorders.[63] Administering the PPARγ agonist, pioglitazone (120 ppm), in the diet of young adult male rats starting 3 days prior to, during, and for 54 weeks after the completion of a total 40 Gy dose of fWBI delivered twice a week for 4 weeks prevented the radiation-induced perirhinal cortex-dependent cognitive impairment measured 52 weeks after fWBI (Fig. 2A).[64] Administering pioglitazone before, during, and for only 4 weeks after fWBI similarly prevented the radiation-induced decrease in cognitive function, suggesting that continued administration of the drug during the 1-year follow-up period

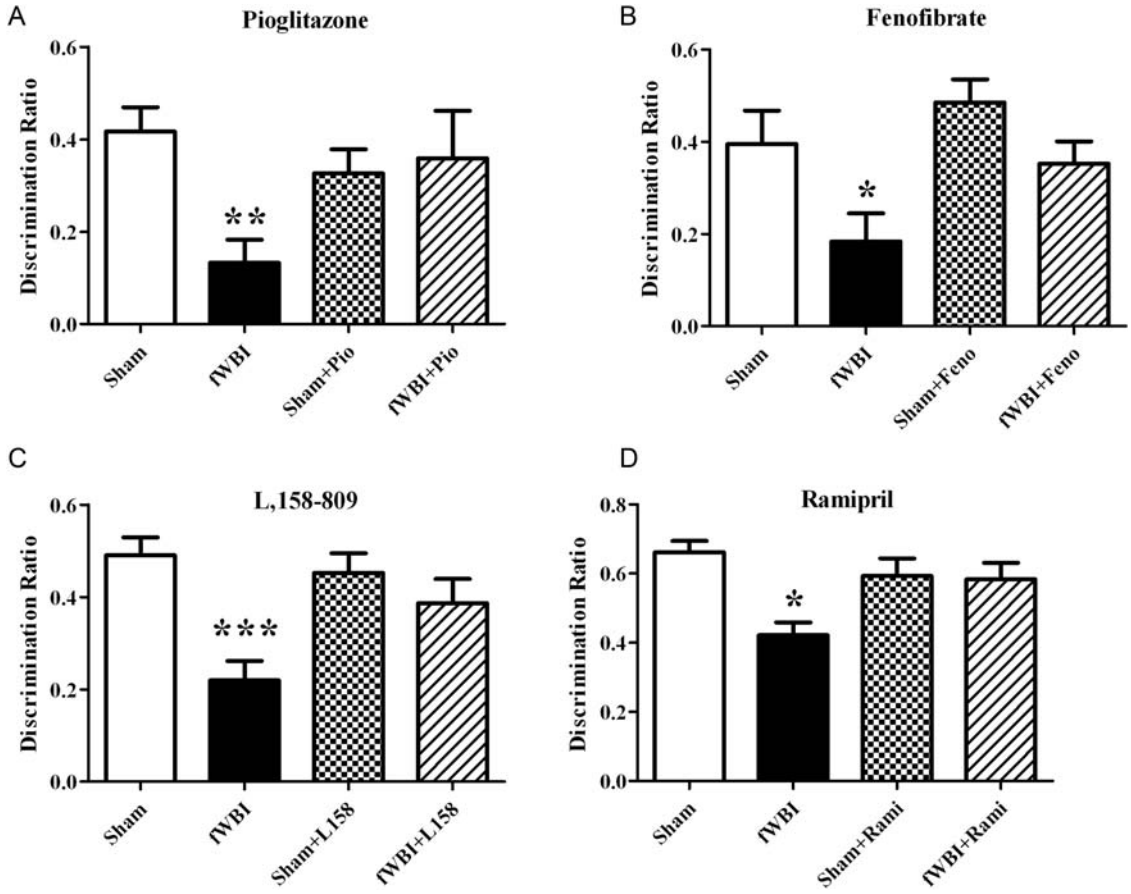

Fig. 2. Both PPAR agonists and RAS inhibitors prevent radiation-induced cognitive impairment in young adult male rats that received a total 40 Gy dose of fractionated whole-brain irradiation (fWBI) delivered in 5 Gy fractions, twice/week for 4 weeks, and then tested for cognition at 6–12 months postirradiation using the NOR task. Rats were administered, A, the PPARγ agonist, pioglitazone, before, during, and for 54 weeks post-fWBI; tested at 52 weeks; (B) the PPARα agonist, fenofibrate, before, during, and for 29 weeks post-fWBI; tested at 26 weeks; (C) the ARB, L158,809, before, during, and for 54 weeks post-fWBI; tested at 52 weeks; and (D) the ACEI, ramipril, before, during, and for 28 weeks post-fWBI; tested at 26 weeks. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ compared to sham-irradiated rats.

was not required.[64] Finally, administering pioglitazone starting the day after the completion of fWBI and for 54 weeks failed to prevent the radiation-induced decrease in cognitive function, suggesting that pioglitazone-mediated prevention of radiation-induced cognitive impairment depends on the drug being administered both during and after the fWBI regimen.[64] The need to administer the PPARγ agonist during fWBI raises concerns as whether the drug will also protect tumor cells against radiation damage. These concerns appear to be unfounded; PPARγ agonists, including pioglitazone, have been shown to induce anti-neoplastic signaling pathways in a variety of cancer cell lines, animal models, and human beings and are selectively cytotoxic to tumor cells.[65]

Additional studies have focused on the potential of PPARα agonists to modulate radiation-induced brain injury. PPARα has been shown to play a major role in regulating inflammatory processes. In vitro, PPARα agonists inhibit pro-inflammatory responses in a variety of cell types, including microglia and astrocytes,[66] and confer neuroprotection in several preclinical models, including stroke and Parkinson's disease.[63] Initial studies demonstrated that pretreating murine microglia (BV-2) cells with PPARα agonists prevented the radiation-induced pro-inflammatory response via negative regulation of NF-κB and AP-1 pathways.[67] Subsequent in vivo studies have used the selective PPARα agonist fenofibrate based on, (i) its ability to cross the blood-brain barrier (BBB), (ii) it is clinically approved for the treatment of hyperlipidemia,[68] and (iii) it is well tolerated. Administering fenofibrate (0.2% w/w) to the diet of young adult male mice receiving WBI (10 Gy single dose) both prevented the radiation-induced decrease in the number of newborn hippocampal neurons and inhibited microglial activation.[69] However, the 129Sv strain of mice used in these studies exhibit defects in the corpus callosum and perform poorly in cognitive function tasks, preventing assessment of radiation-induced cognitive impairment. The ability of fenofibrate to modulate radiation-induced cognitive impairment has been assessed in young adult male rats following fWBI (Greene-Schloesser, unpublished data). Young adult male rats received fenofibrate (0.2% w/w) in their diet starting 1 week prior to and

continuously until the end of the study at 30 weeks after fWBI. Fenofibrate prevented the reduction in perirhinal cortex-dependent cognitive function assessed 26 weeks after fWBI (Fig. 2B) and the increase in activated microglia determined 30 weeks after fWBI (Greene-Schloesser, unpublished data). This preservation of cognitive function was seen in the absence of any protection in terms of neurogenesis, further supporting the need to consider other regions than the hippocampus alone when studying radiation-induced cognitive impairment (Greene-Schloesser, unpublished data). Given that PPARα agonists, including fenofibrate, are increasingly recognized as potent antitumor agents,[70] they appear to be promising drugs in improving the QOL of patients with brain cancer who are receiving radiotherapy.

RAS Blockers

One of the most effective approaches in the prevention/amelioration of radiation-induced late effects has been blockade of the RAS. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) have proved to be highly effective in the treatment and prevention of experimental late effects in the kidney and lung.[71] The RAS has been classically viewed as a complex systemic hormonal system. More recently, several intra-organ RAS have been identified, including a brain RAS.[72] The brain RAS is involved in modulation of the BBB, stress, memory, and cognition.[73,74] Moreover, beneficial effects of RAS blockade on cognition have been observed; ACEI attenuate the age-related decline in cognitive function in spontaneously hypertensive and normotensive rats[75,76] and the ARB, losartan, improves cognitive function in hypertensive patients, independent of any reduction in blood flow.[77] These findings suggest an important role for the brain RAS in normal cognitive function and potential treatment of dysfunctional memory disease states.[78] On the basis of these findings, the use of RAS blockers in the treatment of radiation-induced brain injury, including cognitive impairment, appears to be logical.[79]

Using a recently established rat model of radiation-induced injury to the optic nerve, Kim et al were the first to demonstrate ACEI-mediated neuroprotection against late radiation-induced brain injury.[80] Chronic administration of the ACEI ramipril, which can cross the BBB, to young adult male rats 2 weeks after stereotactic irradiation of the rat brain with a single dose of 30 Gy was associated with a reduction in the severity of functional and histopathologic markers of optic neuropathy assessed 6 months after irradiation.[80] However, delaying the start of ramipril treatment to 4 weeks after irradiation resulted in a failure to reduce the severity of the radiation injury.[81] More recent findings do support a role for RAS blockers in protecting against radiation-induced cognitive impairment. Administration of the ARB L-158,809 (20 mg/L drinking water) to young adult male rats for 3 days before, during, and for 28 or 54 weeks after fWBI prevented the radiation-induced cognitive impairment observed 26 and 52 weeks after irradiation (Fig. 2C).[82] Continued RAS blockade may not be required. Giving L-158,809 before, during, and for only 5 weeks after irradiation prevented the cognitive impairment observed 26 weeks after irradiation.[82] Lee et al have extended these observations to show that RAS blockade using the ACEI ramipril can similarly prevent fWBI-induced cognitive impairment.[37] Administering ramipril (15 mg/L) in the drinking water starting 3 days before, during, and for 28 weeks after fWBI of young adult male rats prevented the radiation-induced decrease in cognitive function observed 26 weeks after irradiation (Fig. 2D).[37] Thus, RAS blockade with either ACEI or ARB appears to be effective at preventing radiation-induced cognitive impairment. However, the mechanisms involved remain unclear.

Conner et al tested whether the cognitive benefits of L-158,809 were associated with amelioration of the sustained neuroinflammation and changes in neurogenesis resulting from fWBI.[53] In rats examined at 28 and 54 weeks after fWBI, L-158,809 treatment did not alter the effects of radiation on the number and activation of microglia in the perirhinal cortex and hippocampus, nor did it prevent the radiation-induced decrease in proliferating cells and immature neurons in the hippocampus.[53] In contrast, analysis of radiation-induced changes in the number of total and activated microglia in the hippocampus of F344 rats treated with fWBI with or without ramipril indicate that the ramipril-mediated prevention of the radiation-induced cognitive impairment is associated with prevention of the radiation-induced activation of microglia 28 weeks after irradiation.[37] It is unclear whether this difference in the ability of L-158,809 and ramipril to modulate radiation-induced neuroinflammation represents differences in specific biological mechanisms and/or signaling pathways. Nevertheless, these findings clearly indicate that the development of radiation-induced cognitive impairment involves multiple brain regions, is not solely dependent on reductions in hippocampal neurogenesis and/or microglial activation, and can be modulated by RAS blockers.

As discussed with the PPAR agonists, the ability to translate these findings to the clinic is predicated by ensuring that the protective effect of RAS blockers on the normal brain is selective and not observed in tumor cells. A growing body of evidence suggests that ACEI and ARB exhibit antitumor effects, including inhibition of angiogenesis and proliferation,[83] and can enhance anticancer therapies.[84] Thus, given that RAS blockers are routinely prescribed for treatment of hypertension[85] and well-tolerated, they appear to be ideal drugs for translational clinical studies.

Translation of Therapeutics to the Clinic

Although the precise mechanisms involved in the development and progression of radiation-induced cognitive impairment remain ill-defined, it is clear that several agents, all of which are routinely used in the clinic for

a variety of chronic disorders, can prevent this late effect in preclinical models. Given that these agents are well-tolerated and have been shown to possess anti-tumor properties, they appear to be attractive translational agents. Indeed, a phase I/II trial of pioglitazone given to patients with brain tumor before, during, and after fWBI is currently under way at Wake Forest Baptist Medical Center, and phase I/II trials of the ACEI ramipril and also an ARB are being developed. A clinical trial of aerobic exercise to promote hippocampal neurogenesis after cranial irradiation is ongoing at University of Toronto/Sick Kids. Although it is simplistic to think that one approach or one pharmacological intervention will eliminate radiation-induced cognitive impairment for every patient whose brain is treated with ionizing radiation, it is highly likely that significant inroads will be made to prevent/ameliorate this increasingly important adverse effect of brain irradiation over the next decade.

Summary

Recent improvements in systemic treatments and radiation therapy techniques have resulted in >100 000 patients in the United States each year surviving long enough after fWBI to develop radiation-induced brain injury, including cognitive impairment that significantly affects their QOL. Although modern radiation therapy techniques have eliminated many cases of acute and early delayed brain injury and most late demyelination and white matter necrosis, functional deficits, including progressive impairments in memory, attention, and executive function have become important, having profound effects on QOL of most survivors.

Preclinical studies have provided valuable insights into the pathogenesis of radiation-induced brain injury, including cognitive impairment. Although reductions in hippocampal neurogenesis and hippocampal-dependent cognitive function have been observed in rodent models, it is important to recognize that other brain regions are affected; non–hippocampal-dependent reductions in cognitive function occur. Treatment using stem cell therapies suggest that the radiation-induced reduction in neurogenesis can be prevented. However, the use of stem cell–based therapies to prevent/ameliorate radiation-induced cognitive impairment in humans will require considerably more research before it can be translated to the clinic.

In contrast, preclinical studies using PPAR agonists and RAS blockers, clinically approved and well-tolerated agents used in the treatment of type II diabetes, hyperlipidemia, and hypertension, have demonstrated that these drugs can prevent/ameliorate radiation-induced cognitive impairment independent of changes in neurogenesis. Translating these exciting preclinical findings to the clinic offers the promise of significantly improving the QOL of patients with brain tumor who receive radiation therapy.

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