Radiation-induced cognitive impairment

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Radiation-induced cognitive impairment is one of the late adverse effects of cranial radiation therapy (CRT) for cancer patients with primary and metastatic brain tumors, head and neck cancers etc. It affects approximately 40-50% patients who survive for >6 months and severely reduces the quality of survivors' life. With the advancement of radiation therapy technology, the survival of brain tumor patients is significantly improved, thus understanding the etiology of CRT-induced cognitive impairment and developing the potential strategies of the management of this side-effect have become more important than ever. Some valuable insights have been obtained through extensive preclinical studies. It is suggested that radiation-induced cognitive impairment is due to the dysfunctions of hippocampus-dependent learning, memory and spatial information processing after radiation exposure. Until now, research results have shown that radiation-induced cognitive impairment and neurodegenerative disorders such as Alzheimer disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and aging-related cognitive decline, share some similar pathogenic factors, including chronic oxidative stress and inflammation, impairment in neurogenesis and angiogenesis. Blockade of these factors by antioxidants, anti-inflammatory drugs, transplant of neural stem cells, systemic hypoxia etc. can significantly ameliorate cognitive decline in cranially irradiated experimental animals. These studies shed the light on the pathogenesis of radiation-induced cognitive impairment and may have important implication in developing novel therapeutic interventions for surviving cancer patients who suffer from cognitive decline after CRT.

Keywords: Cranial radiation therapy; Cognitive impairment; Oxidative stress; Inflammation; Neurogenesis; Angiogenesis

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vomiting, alopecia, headaches, somnolence syndrome, intellectual impairment, memory loss and dementia etc. While early complications tend to be reversible, late side effects such as cognitive impairment are often irreversible and progressive [8], thus significantly decreasing the quality of patients' life. Due to the fast improved radiation therapy techniques and systemic therapies, brain tumor patients especially children patients can survive long enough to experience late complications including cognitive impairment. Survivors with this complication displayed declined verbal memory, spatial memory, attention and novel problem-solving ability [9,10]. From the point view of the outcomes of clinical practice on cancer patients, quality of life after therapy has been regarded as the second most important factor only after survival [11]. Therefore, it is critical to understand the mechanisms underlying radiation-induced cognitive impairment and to develop the strategies and interventions to prevent or ameliorate this side effect. In this article, we are going to review the studies that have been performed in humans and animals so far, and discuss the proposed mechanisms and strategies.

Clinical facts

Cranial radiation therapy for acute lymphocytic leukemia

Central Nervous System (CNS) radiation therapy may be used to treat acute lymphocytic leukemia (ALL). However, the studies on the neuropsychologic functions of long-term survivors of childhood leukemia have shown a significant decline in their full-scale IQ and verbal IQ scores, mathematics skills, constructional skills, and memory for spatial material [12-14]. It has been found that gender and age of patients and treatment modality affects the neuropsychological outcome, more specifically, children in early age, especially girls are more vulnerable to radiation-induced neurotoxicity, increased radiation dose are associated with impairment of verbal memory and coding, and increased dose intensity of intravenous methotrexate may result in lower IQ [15,16]. Moreover, a study [17] assessed cognitive function of ALL survivors treated with cranial radiation therapy during extended intervals into adulthood, and found that the survivors' verbal intelligence impairment but not performance intelligence impairment also progressed with age, indicating long-term adverse effects of CRT on survivors’ quality of life. Thus CNS radiation therapy is currently recommended to be avoided in the treatment of childhood ALL and is replaced by intrathecal (IT) chemotherapy [17,18].

Prophylactic cranial irradiation (PCI) for lung cancer

The use of PCI in patients with limited-staged lung cancer can be a double-blade sword. On one hand, it significantly decreases the risk of brain metastases [19] and improve the survival [20,21]. On the other hand, it may cause cognitive impairment [22,23]. While some studies show either no significant adverse effects of PCI [20,24], or no statistic evidence for additional neurotoxicity from PCI [19,25] shortly after therapy (5 months-2 years), it has been reported that some patients with brain metastases from non-small-cell lung cancer who were aggressively treated with surgical resection followed by cranial radiotherapy survived 10 or more years with disease free, but developed cognitive impairment about 8 years post therapy [21]. Therefore, although the existing data do not support the omission of PCI in the treatment plan of lung cancer patients only on the basis of possible neurotoxicity [26], fears of radiation-induced cognitive impairment still deter both physicians and patients from using PCI.

Radiation therapy for brain tumors and head and neck cancers

As an important treatment modality for primary and metastatic brain tumors and head and neck cancers, whole brain radiation therapy (WBRT) causes damage to normal brain tissue besides to cancer cells. Cognitive impairment is one of the consequence of the brain damage [7,27-30]. It appears that WBRT for brain tumors caused more serious cognitive decline in younger children patients than in older children patients, suggesting the age-dependence of radiation-induced cognitive impairment, although it was difficult to ascribe the decline to the true impairment process induced by WBRT [31]. Incapability of acquiring new cognitive skills like their normal peers might play a role [34]. Thus it has been proposed that cranial radiation therapy for children patients should be delayed or postponed when possible to reduce their neurocognitive dysfunction and improve their quality of life after treatment [32]. However, WBRT is also related to cognitive decline even in adult patients (< 60 years old) [27]. As a matter of fact, almost all cancer patients survived from brain tumors or head and neck cancers have some risk for developing cognitive decline, but those treated with CRT display the most severe impairment [33]. And this adverse effect affects about 50% of adults and almost all of children who survive longer than 6 months after CRT for brain tumors [34,35].

Pathogenesis of radiation-induced cognitive impairment

To understand the pathogenesis of radiation-induced cognitive impairment, animal models have been developed [36,37]. Up to now, the preclinical studies using animal models have provided very important insights into potential...
The pathogenesis of radiation-induced cognitive impairment. It is believed that the cognitive impairment post-radiation is caused by radiation-induced impairment in the hippocampus-dependent functions involved in learning, memory, and spatial information processing [38-41]. Since the vasculature and the oligodendrocyte lineage were usually believed to be the major radiation targets in central nervous system (CNS), it was hypothesized that radiation-induced cognitive impairment might be ascribed to the DNA damage in vascular endothelial and brain glial cells, thus resulting in irreversible proliferation inhibition of these cells [42,43]. However, this hypothesis was indeed oversimple, more and more study results have revealed that the mechanisms underlying cognitive decline after CRT are more complicated than previously thought. It has been proposed that radiation-induced late effects in normal tissues including brain are partially caused by chronic oxidative stress and inflammation [44]. And these effects involve multiple cell types, in the case of brain damage including cognitive impairment, astrocytes, endothelial cells, neurons, microglia and oligodendrocytes all contribute to this adverse effect [45].

**Chronic oxidative stress**

Redox homeostasis is critical to cells, including the cells in CNS. Oxidative stress, e.g. increased levels of reactive oxygen species (ROS) play a very important role in the pathogenesis of many neurodegenerative disorders such as Alzheimer disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Lafora disease (LD) etc [45-48], which are characterized by memory loss, dementia and cognitive impairment.

As we know, ionizing radiation leads to a chronic and sustained oxidative stress [49], suggesting that the chronic oxidative stress in CNS induced by CRT may be involved in cognitive decline after therapy. A study [50] shows that in vitro rat neural precursor cells undergo a rapid dose-dependent apoptosis after exposure to X-rays, accompanied by a long-lasting (3-4 weeks) elevation of ROS levels. The in vitro results are coincident with the in vivo results about the reduction of proliferation of neural precursor cells within the hippocampal dentate subgranular zone (SGZ) and the number of their progeny. This suggests that oxidative stress may explain radiation-caused neurogenesis inhibition in cognitive decline. Other study supports the same hypothesis that oxidative stress inhibits hippocampal neurogenesis. It has been found that EC-SOD knockout mice exhibit decreased neurogenesis compared with wild type mice [51]. In addition, using some antioxidants can prevent radiation-induced cognitive impairment. For example, administration of melatonin followed by acute radiation exposure ameliorates radiation-induced protein oxidation and lipid peroxidation in brain tissue and inhibits radiation-induced decline in learning ability [52]. Another antioxidant, alpha-lipoic acid significantly protects against radiation-induced DNA damage, lipid peroxidation and protein carbonyls in mice cerebellum, and attenuates radiation-induced memory dysfunction [53]. All these studies have demonstrated that the oxidative stress in CNS contribute to radiation-induced cognitive impairment.

**Chronic inflammation**

As a self-defensive response against pathogens, inflammation may be harmful when it persists. Indeed increasing evidence has demonstrated that a number of neurodegenerative disorders including AD and PD are associated with chronic neuroinflammation [54]. Thus inflammatory molecules are proposed to be used as potential diagnosis biomarkers and therapeutic intervention targets for these neurodegenerative disorders [55].

Ionizing radiation leads to inflammatory responses by activating transcription factors such as NF-kappaB, STAT-3, and HIF-1etc [56]. Expression of inflammatory genes is one of the initial responses of the brain to irradiation. Most of the inflammatory responses in brains occur rapidly post-irradiation [57]. In addition, whole brain irradiation results in pro-inflammatory environments in some specific regions. Cytokines were found to be elevated in different extent in hippocampal and cortical regions, for example, elevation of TNF-alpha in cortex was 57% greater than in hippocampus, but elevation of IL-1beta in hippocampus was 126% greater than in cortex [58]. And radiation-induced acute inflammatory responses may segue into chronic inflammation. A robust inflammatory reaction in the mouse dentate subgranular zone (SGZ) was observed 9 months after exposure to heavy-ion radiation [59]. A quick and persistent activated microglia (brain macrophages) in both the granule cell layer and the hilus following cranial radiation exposure also contribute to a chronic inflammation [60]. While activation of immune system by radiation therapy can facilitate tumor cell killing, radiation-induced chronic inflammation can cause adverse effects. It has been demonstrated that neuroinflammation alone inhibits neurogenesis in rodents, and indomethacin, a nonsteroidal anti-inflammatory drug can restore neurogenesis following endotoxin-induced inflammation and ameliorate neurogenesis inhibition after cranial irradiation [61]. Furthermore, Blockers of the renin-angiotensin system (RAS) and peroxisomal proliferator-activated receptor gamma (PPARgamma) agonist pioglitazone (Pio) have been found to inhibit radiation-induced cognitive impairment through their anti-inflammatory function [62,63]. These results indicate that chronic neuroinflammation after irradiation plays a crucial role in radiation-induced cognitive
impairment.

Neurogenesis

In adults, new neurons are produced from the neural stem cells and progenitor cells predominantly exist in the hippocampus and the subventricular zone (SVZ) via a process called adult neurogenesis. Neurogenesis is critical for physiological brain functions such as certain forms of learning and memory, since new hippocampal neurons are recruited into the hippocampal neuronal circuits that are crucial to spatial learning [64]. Aging-related cognitive deficits is closely related to a significant reduction in adult neurogenesis [65]. Declined or failing neurogenesis may also lead to the development of a variety of progressive degenerative disorders such as AD, PD, HD etc [66-68]. Even though how altered adult neurogenesis contributes to these neurodegenerative diseases is not fully understood, the research results have shown that physical exercise can be an effective preventive and therapeutic intervention for age-related neurodegenerative conditions [64,69]. Animal studies showed that physical running improved the cognitive function accompanied by increased hippocampal neurogenesis, suggesting that increased neurogenesis may underlie this beneficial effects of exercise [70,71]. Impairment of hippocampal neurogenesis is proposed to be one of the important factors for CRT-induced cognitive decline, prominently memory loss [72,73]. Our previous results have shown that forced running after cranial irradiation can ameliorate the impairment of hippocampal neurogenesis and significantly prevent radiation-induced cognitive decline in rats [74]. And it is believed that radiation-induced cell killing in neural progenitor populations makes major contribution to the neurogenesis impairment [75]. Indeed these cells are extremely sensitive to radiation. Radiation has been reported to inhibit neurogenesis in mice at clinically relevant doses, i.e. 2-5 Gy. The progenitor cells in SGZ and their progeny, immature neurons, were decreased significantly 48 h post-irradiation due to radiation-induced apoptosis and differentiation inhibition, and the reduction last for at least 2-3 months [72,76]. The mechanistic studies showed that radiation causes apoptosis and inhibits neuronal differentiation in neural progenitor cells through activation of JNK, leading to neurogenesis inhibition. This suggests that JNK inhibition may be a strategy of protecting NSCs from radiation-induced damage [77]. The alteration of neurogenesis was associated with a significant inflammatory response and oxidative stress [59,76,78]. Thus blockade of neuroinflammation using anti-inflammatory drugs such as indomethacin, the peroxisomal proliferator-activated receptor (PPAR) alpha agonist fenofibrate etc [60,61], or blockade of oxidative stress using free radical scavengers such as edaravone and melatonin etc. [52,79] can protect neural progenitor cells from radiation-induced damage and preserve neurogenesis after irradiation.

But interestingly, our study also found that minocycline, a common antibiotic, significantly inhibits cranial irradiation-induced neuron apoptosis and improves the cognitive function of irradiated rats without any protection on radiation-induced neurogenesis impairment [80]. These results agree with the report from Allen et al. showing that difluoromethylornithine treatment prevents radiation-induced cognitive decline in a way that is not associated with neurogenesis [81]. Thus neurogenesis is probably just one of the mechanisms underlying radiation-induced cognitive impairment.

Angiogenesis

New blood vessels can be formed from pre-existing vessels through a process called angiogenesis. Since capillary density is closely associated with regional blood flow delivering oxygen, nutrients, and trophic factors, adequately organized capillary networks in brain are crucial to its normal function. Vascular perturbation is believed to be involved in the pathogenesis of neurodegenerative diseases such as AD. In AD patients, the accumulation of amyloid beta in cerebral vasculature has been found to be closely related to cognitive decline, suggesting that interventions promoting angiogenesis may have beneficial effects on AD patients [82].

As a vascular basis for AD and aging-related cognitive decline, neuroangiogenesis may be also important in radiation-induced cognitive impairment [35,83]. Radiation-induced damage in microvasculature is one of the most important components of the damage in normal tissues caused by irradiation [84-86]. Cranial irradiation has been reported to reduce endothelial cell number in rat brains within 1 day of radiation with doses of 5-200 Gy, and the early dose-independent loss in cell number last for up to 1 month post-radiation followed by a slow dose-independent decrease in cell number for 6 months post-radiation [87]. Ionizing radiation causes apoptosis [88] and abnormal proliferation of endothelial cells resulting in capillaries with abnormal diameter and shape [89]. Moreover, radiation induces adverse effects on the structure and function of microvasculatures such as decrease in vessel diameter and capillary surface area, and reduction of local blood flow [85,86]. Additionally, it has also been shown that vessel density and length are substantially decreased in rat brains at 10 weeks after 40 Gy of fractionated whole-brain irradiation, and the decrease lasts for up to 52 weeks, suggesting that radiation-induced cognitive impairment is probably one kind of vascular dementia [90,91]. Recent studies from Warrington et al. further confirmed that cerebrovascular rarefaction...
caused by WBRT is a key mechanism of cognitive impairment, a systemic hypoxia post irradiation can reverse angiogenesis capability of hippocampal microvasculature, thus restore cognitive function [92,93].

Summary

While cranial radiation therapy significantly improves survival in patients with brain tumors, head and neck cancers etc., its late adverse effects including radiation-induced cognitive dysfunction seriously affect the quality of life of the patients who survive for >6 month. Therefore the underlying mechanisms and the potential strategies have been actively investigated. Although so far, the etiology of CRT-induced cognitive impairment remains unclear, extensive preclinical studies have shown that the onset of radiation-induced impairment involves the same factors in neurodegenerative diseases and aging-related cognitive decline such as chronic oxidative stress, chronic inflammation, inhibited neurogenesis, and decreased angiogenesis etc. And blockade of these factors can improve the cognitive performance of irradiated experimental animals.

Our previous studies have demonstrated that minocycline has protective effect on cognition in whole-brain-irradiated -rats. But the underlying mechanisms remain elucidated. Although minocycline inhibits WBI-induced apoptosis in immature neurons shortly after irradiation, it is difficult to ascribe the long-term protective effects of minocycline to its short-term effect on apoptosis at this time. The studies on whether minocycline affects astrocytic activation and angiogenesis in irradiated rats are still in process in our laboratory. These study results may have implications in the management of cancer patients who suffer from significant cognitive impairment after CRT.

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Conflict of Interest

The authors declare that they have no competing interests.

Authors' contributions

Drs. Zhang L and Yang H wrote the manuscript; Dr. Tian Y provided intellectual input and helped with manuscript writing.

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