

# Treatment strategies for radiation-induced brain injury

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## ► Review article

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## ABSTRACT

Radiation-induced brain injury (RIBI) is a common complication in patients with head and neck tumors. RIBI usually occurs six months to three years after therapy and is often accompanied by cognitive dysfunction, epilepsy, and other neurological dysfunctions. In severe cases, RIBI can cause a wide range of cerebral edema and herniation. A systematic search was conducted through PubMed/Medline, EMBASE, and Cochrane library databases and articles with the keywords radiation-induced brain injury, pathogenesis and protective agents were collected. The commonly known pathogenesis of RIBI includes vascular injury, immune-inflammatory response, glial cell damage, and neuronal damage. Therapeutic agents, hyperbaric oxygen, surgery, and stem cells transplantation are the most common treatment for RIBI. Tamoxifen, curcumin, and quercetin can prevent glial cell activation, proliferation, and oxidative stress caused by irradiation. Over recent years, the RIBI remission rate has gradually increased; however, there are still no effective prevention and treatment methods. This review summarized recent progress in the treatment for RIBI, as well as the pathogenesis of RIBI, including vascular injury, glial cell injury, immune-inflammatory response, and neuronal damage.

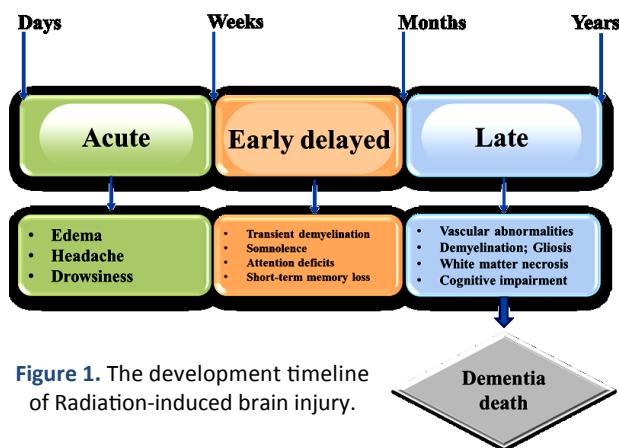
## INTRODUCTION

Radiotherapy is widely used to treat recurrent cancer, such as brain and breast carcinomas. Radiation exposure usually depends on the type of malignancy. Whole-brain radiotherapy (WBRT) is the treatment of choice for local recurrence after surgical resection of brain metastases. Yet, radiation to the brain may cause certain side effects. RIBI is a common complication caused by radiation treatment for head and neck tumors <sup>(1)</sup>. The longer the radiation exposure, the more malignant the disease. Acute injury and subsequent long-term damage often lead to multifocal hypometabolism and persistent neuroinflammation of the brain <sup>(2)</sup>.

According to clinical symptoms, RIBI can be classified into three stages: an acute stage, an early delayed stage, and a late delayed stage <sup>(3,4)</sup>. Acute RIBI often occurs days or weeks after irradiation <sup>(5)</sup>, mainly due to cerebral edema, increased intracranial pressure, and transient neurological impairment caused by increased blood-brain barrier (BBB) permeability. Its main clinical manifestations include headache, nausea, vomiting, increased body temperature, disturbance of consciousness, and convulsions, which are generally recoverable. Early delayed RIBI is usually a temporary and reversible white matter injury that occurs after a few weeks to 3 months after brain radiotherapy and is mainly

characterized by demyelinating lesions of oligodendrocytes with axonal edema. Its clinical manifestations include lethargy, nausea, and irritability, which can usually be cured after active treatment during this period. Late delayed RIBI complicated with abnormal vascular changes and demyelination <sup>(6)</sup>, and white matter necrosis often occurs 6 months after irradiation <sup>(7,8)</sup>; this stage is commonly irreversible and progressive (figure 1). According to the volume range of therapeutic radiation, late RIBI (3 months to several years) is accompanied by local nerve tissue abnormalities and increased intracranial pressure, and its diagnosis, which is based on the clinical manifestations alone, is difficult to establish. During this stage, low-density areas of white matter increase with irregular enhancement effects on the computed tomography (CT) images, accompanied by diffusing edema around the lesion and varying degrees of space-occupying effects <sup>(9)</sup>. Similar changes are shown on magnetic resonance imaging (MRI). Under MRI, RIBI is usually seen as peripheral enhancement accompanied by mild mass effect and peripheral edema. The important microscopic changes of RIBI include fibroid necrosis of vessels, coagulative necrosis, peripheral reactive gliosis, and vascular hyalinization with luminal stenosis <sup>(10)</sup>. The most obvious clinical features are personality changes, memory loss, decreased concentration, and dementia. The main

manifestations among children are growth delay and mental retardation, which eventually lead to severe dementia.



**Figure 1.** The development timeline of Radiation-induced brain injury.

Currently, the mechanism leading to RIBI is believed to involve vascular injury, glial cell injury, autoimmunity, inflammation, and nerve injury. The most conventional therapeutic protocols include steroid hormones, vasodilators, dehydrating agents, neuroprotective agents, hyperbaric oxygen therapy (HBO), and surgery.

In this review, we summarized recent progress in the treatment for RIBI (primarily focusing on the therapeutic agents) as well as the pathogenesis of RIBI, including vascular injury, glial cell injury, immune-inflammatory response, and neuronal damage.

## MATERIALS AND METHODS

A systematic search was conducted through PubMed/Medline, EMBASE, and Cochrane library databases about the articles with the keywords of radiation-induced brain injury, pathogenesis and protective agents.

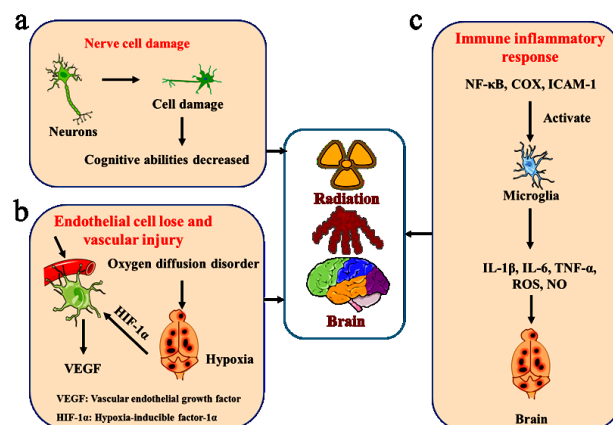
### RIBI pathogenesis

The current pathological changes of RIBI include vascular injury, immune-inflammatory response, and neuronal damage (figure 2).

### Vascular injury

Radiation causes vascular tissue damage and affects oxygen diffusion between the brain and blood vessels. Also, the expression of hypoxia-inducible factor (HIF)-1 $\alpha$  in the brain increases and then activates the astrocytes, which secrete the vascular endothelial growth factor (VEGF), thus promoting angiogenesis. These new blood vessels, which have high permeability, further promote the infiltration of surrounding tissue fluid and consequently lead to cerebral edema (figure 2b) <sup>(11)</sup>. Vascular injury is

represented by loss of endothelial cells and increased blood vessel permeability, which would lead to late delayed RIBI <sup>(12)</sup>. Compared with healthy individuals, patients who undergo radiotherapy suffer from more plaque formation, hemodynamic abnormalities, and common thickening of intima-media thickness <sup>(13)</sup>. Some studies suggested that RIBI is a multifocal cerebrovascular injury manifested as perivascular edema and abnormal angiogenesis <sup>(14)</sup>. In a mouse model of RIBI, established using a single large dose of radiation, the number of vascular endothelial cells was significantly reduced in the early stage after irradiation <sup>(15)</sup>. The number of endothelial cells and density of blood vessels were found to decrease in a time- and dose-dependent manner <sup>(15, 16)</sup>. Previous studies have suggested that vascular endothelial cells lose collagen connectivity after radiation, which affects the smoothness of the endothelium, and even results in endothelial defects <sup>(17)</sup>. Moreover, radiation can also cause DNA damage. The p53-dependent apoptosis mechanism in the mitochondria and the death receptor pathways regulated by neuroamide often lead to the death of endothelial cells <sup>(18)</sup>.



**Figure 2.** Illustration schemes of Radiation-induced brain injury.

### Radiation induces an immune and inflammatory reaction in the brain

An inflammatory response occurs in the damaged tissues when the whole brain is irradiated. Nerve cells mainly include myelin-producing glial cells, astrocytes, and microglia. Microglia are important immune cells of the CNS <sup>(19)</sup>. In the healthy brain, healthy neurons express and secrete molecules (CD47, CD55, CD20, and CX3CL1), maintaining adjacent microglial cell stationery. Cerebral vascular endothelial cells are also in a quiescent state, allowing a continuous flow of blood lymphocytes (figure 3).

After radiation, neurons and microglia are directly affected (cellular damage and activation). Damaged neurons secrete pro-inflammatory cytokines activating microglia (figure 2c). The brain's immune and inflammatory responses may be activated in different ways, which are explained in the following paragraphs (figure 4).

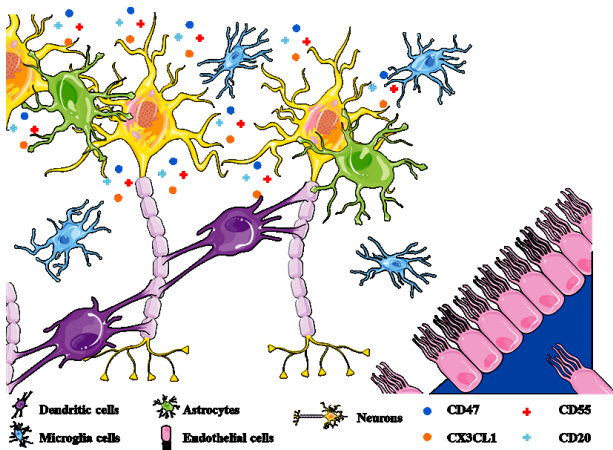


Figure 3. Cells in the healthy brain.

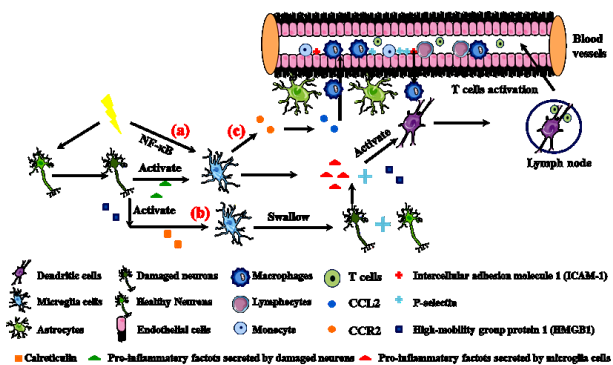


Figure 4. The immune and inflammatory reaction in brain induced by radiation.

Microglia are activated through the NF- $\kappa$ B pathway (figure 4a), which then activate MHC molecules. At the same time, microglial cells secrete pro-inflammatory cytokines (COX, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) (20, 21), chemokines (CX3, CL1, CCL3), which activate antigen-presenting cells (APCs) in the brain (22, 23).

Damaged neurons secrete the high-mobility group protein 1 (HMGB1), which then activates microglia that swallow damaged and healthy neurons (figure 4b). Moreover, pro-inflammatory signals emitted by microglia and HMGB1 activate dendritic cells, which migrate to regional lymph nodes due to increased BBB permeability and induce immune activation in the brain. The most commonly activated immune cells are regulatory T cells (24, 25), which produce IL-10 and TGF- $\beta$ .

CCL2 could induce peripheral macrophages to express CCR2, which penetrate the BBB. Activated microglia also increase CCL2 and CCR2 expression (figure 4c). At the same time, radiation upregulates the adhesion markers (ICAM-1, P-selectin), which allows peripheral lymphocytes and monocytes to adhere to endothelial cells and migrate through the microvessel wall (26).

Immune and inflammatory reaction induced by radiation is a complicated process that involves various cellular components and the surrounding immune system (27). The extent of radiation-induced injury, such as inflammation or immune response, is

determined by the radiation type, dose, delivery method, and total cumulative dose (28).

### Neuronal damage and cognition dysfunction

One of the severe outcomes in patients with fractionated partial brain irradiation is significant cognitive impairment at > 6 months after irradiation (29), which significantly affects the quality of patients' life. Cognitive deficits usually include a decrease in memory. Studies on memory of RIBI animals evaluated using Morris water maze (30-33) showed increased average escape latency and decreased number of crossing platforms compared to control animals, which suggested that the learning and memory ability of animals is decreased.

It is well known that radiotherapy can prolong survival in patients with brain tumors; yet, previous studies have also suggested that 50 - 90% of adult patients with brain tumors usually present cognitive impairment (decreased memory ability (learn, verbal, and work) even dementia) after fractionated irradiation lasting six months (18,34). Once the patient receives radiotherapy, the hippocampus and temporal lobes damage lead to a cognitive function decrease (35). Therefore, selectively avoiding critical brain areas for irradiation may be essential to preserving cognitive function.

Damage to neurons is well known to cause reduced memory function. After brain inflammation, inducible NO synthase (iNOS) expressed in macrophages, neutrophils, and microglia increase NO levels in the brain. Radiation oxidizes water, which in turn produces hydroxyl radicals (36). Hydroxyl radicals are also indirectly produced by forming secondary partial active oxygen, including superoxide, hydroxyl, and NO radicals (figure 2a and figure 5). Several reports suggested that free radicals lead to the loss of neurons (37). Spatial memory and learning deficits have also been correlated with hippocampal neurons damaged (38-40). Neurons are known to underlie endogenous synapses and control cognitive behavior. The impaired neuronal function can cause mental retardation, memory loss, dementia, and ataxia. *In vivo* and *in vitro* studies have shown that radiation induces changes in hippocampal cell activity, synaptic efficiency, synaptic production, and neuronal gene expression (3). Yet, the acute effects of radiation on synaptic function on neurons are still not well understood.

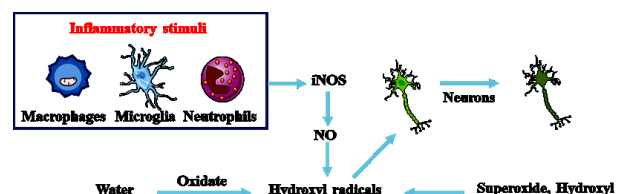


Figure 5. The relationship between apoptosis in hippocampal neurons and oxidative stress.

### Therapeutic protocols of RIBI

The occurrence and extent of RIBI are related to



the radiation dose, exposure volume range, age, time, physical condition, etc. Hyperbaric oxygen (HBO), glucocorticoids, nerve growth factor, bevacizumab, and craniotomy are common treatments used for RIBI. A craniotomy is a highly invasive and risky procedure that is usually only considered when extensive cerebral edema and space-occupation are detected. In addition to surgery, the therapeutic protocols of RIBI include the therapeutic agents, HBO, and stem cells transplantation. Therapeutic agents are those used to decrease apoptosis, inhibit immune responses, improve microcirculation, and eliminate reactive oxygen<sup>(41)</sup>. However, RIBI patients with increased intracranial pressure need long-term dependence on dehydrating agents and hormone maintenance therapy.

### Therapeutic agents

#### Glucocorticoids (GC)

The main clinical manifestations of RIBI are increased intracranial pressure caused by cerebral edema and localized symptoms or signs caused by necrotic brain tissue. Moreover, an inflammatory response occurs in the damaged tissues when CNS is irradiated<sup>(42)</sup>. Dehydration combined with immunosuppressive agents (such as GC) is a common treatment for RIBI<sup>(43-45)</sup>. GC is a steroid hormone with strong immunosuppressive and anti-inflammatory that has an important role in regulating the immune system and is the endocrine basis of inflammatory diseases. GC binds to the GC receptor (GR) in the cytoplasm and then moves through the nuclear pore (NP) to the nucleus. The complex then binds to GC-responsive elements (GRE) and activates gene transcription (figure 6). The expression of anti-inflammatory proteins is then upregulated, and the expression of pro-inflammatory proteins in the cytosol is suppressed<sup>(46)</sup>.

Some studies have found that GC could reduce the permeability of BBB in mouse vascular brain endothelial cells<sup>(47, 48)</sup>. However, this relief is temporary and cannot reverse or inhibit the clinical progress of RIBI, and its effective rate is only about 20%<sup>(49)</sup>. Long-term use of hormones can also cause complications, such as infection, ulcers, high blood pressure, osteoporosis, and muscle atrophy. There is still a controversy as to whether select a high-dose attack regimen or low dose maintenance.

#### Bevacizumab

Bevacizumab is a humanized monoclonal antibody targeting VEGF, which has been used to treat RIBI by reducing vascular injury and permeability brain edema<sup>(50,51)</sup>. In addition, bevacizumab has a long half-life (approximately three weeks)<sup>(52,53)</sup>, and a good therapeutic effect for patients with RIBI with poor hormone effects<sup>(54)</sup>. Neuroimaging studies demonstrated that bevacizumab could alleviate brain radiation necrosis<sup>(55,56)</sup>. A recent study included 17 RIBI patients with

head and neck tumors treated with bevacizumab. Except for one case that had no obvious therapeutic effect, the brain injury lesions of the other patients showed significant improvement in imaging<sup>(57)</sup>. The bevacizumab application after radiotherapy could significantly prolong the survival of RIBI patients, improve clinical effects and cognitive function, and finally reduce the RIBI incidence<sup>(58)</sup>. Yet, considering that necrotic brain tissue has no blood vessels, bevacizumab has been shown ineffective in RIBI patients with necrotic brain tissue<sup>(11)</sup>.

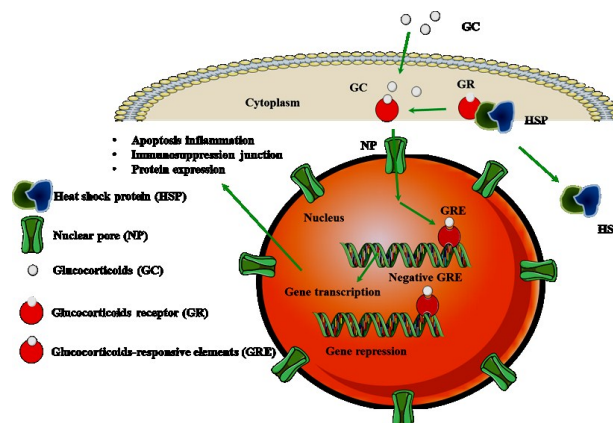


Figure 6. Mechanisms of glucocorticoid (GC) action.

#### Edaravone

There is a relationship between apoptosis in hippocampal neurons and oxidative stress. Edaravone, a new free radical scavenger, positively affects the pro-inflammatory response, nitric oxide production, and apoptotic cell death<sup>(59, 60)</sup>. The neurological symptoms of nasopharyngeal carcinoma were significantly improved after radiotherapy with edaravone treatment. The brain edema and brain necrosis volume of patients significantly decreased<sup>(61)</sup>. Recently, it has been found that cognitive dysfunction after brain radiation therapy may be related to hippocampal neurogenesis damage caused by oxidative stress. This damage is induced by proliferating neural stem cells (NSCs) or progenitor cells<sup>(62)</sup>. Edaravone can protect NSCs from cell death and restore differentiation after irradiation, while edaravone has no obvious protective effect on human brain tumor cells<sup>(63)</sup>.

#### Cyclooxygenase-2 (COX-2) inhibitor

Cyclooxygenases are the main mediators of inflammation, which act by catalyzing the metabolism of arachidonic acid and prostaglandin synthesis<sup>(64,65)</sup>. A previous study found that radiation induced an increase in the expression of COX-2 protein after brain irradiation in male C57/BL6 mice, as well as the increase in prostaglandin E(2) and thromboxane A(2)<sup>(66)</sup>. Furthermore, it showed that NS-398, a selective COX-2 inhibitor, could reduce prostaglandin induction and edema formation against RIBI. The production of prostaglandin E2, which is a COX-2 biological product, was reduced by 75% in irradiated

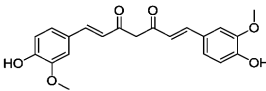
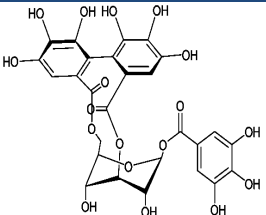
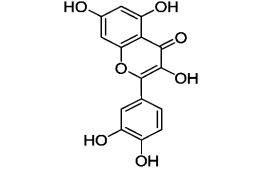
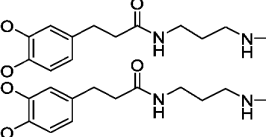
brains after giving meloxicam <sup>(67, 68)</sup>. Celecoxib is a paradigm-selective inhibitor of cyclooxygenase-2, which can reduce the damage of BBB and brain edema after radiotherapy. By inhibiting the expressions of NF- $\kappa$ B and vascular endothelial growth factors, the level of radiation inflammation and cerebrovascular damage could be alleviated <sup>(69)</sup>.

**Table 1.** Commercial drugs for the treatment of RIBI.

Drugs	Company	Formulations	Mechanisms
Edaravone	Nanjing Xiansheng Dongyuan Pharmaceutical Co., Ltd.	Injection	Reduce cerebral edema <sup>(61)</sup> . Protect ischemic neurons <sup>(63)</sup> Promote the recovery of nerve function <sup>(63)</sup>
Bevacizumab	Qilu Pharmaceutical Co., Ltd.	Injection	Reduce cerebral edema <sup>(50,51)</sup> Reduce vascular injury <sup>(50,51)</sup>
Celecoxib	Pfizer Pharmaceuticals LLC	Capsules	Reduce the damage of brain edema and BBB <sup>(69)</sup>

Chinese medicine has also attracted much attention due to its advantages of multiple targets and low toxicity (table 2, <https://m.chemicalbook.com/>).

**Table 2.** Chinese medicine for the treatment of RIBI.

Main ingredients	Chemical formula	Mechanism of treating RIBI
Curcumin		Reduce cerebral edema <sup>(70)</sup> Neuroregeneration <sup>(71)</sup>
Corilagin		Enhance angiogenesis <sup>(72)</sup> Anti-inflammatory <sup>(73,74)</sup>
Quercetin		Anti-oxidation <sup>(75)</sup> Anti-inflammatory <sup>(76)</sup>
Kukoamine A		Neuroprotection <sup>(77)</sup> Anti-inflammation <sup>(78)</sup>

### Curcumin

Curcumin is a natural ingredient in turmeric rhizomes with anti-oxidation, anti-inflammation, inhibition of angiogenesis, and antitumor properties. Curcumin can restrain NF- $\kappa$ B and i $\kappa$ B kinase, inhibiting proliferation and inducing cell apoptosis <sup>(79,80)</sup>. It can also effectively reduce cerebral edema in rats with intracerebral hemorrhage by inhibiting the

NF- $\kappa$ B pathway and subsequent aquaporin expression <sup>(70)</sup>. *In vitro* showed that curcumin can stimulate neurogenesis, synaptogenesis, and cell migration of brain-derived adult neural stem cells, thus could be used as a suitable drug candidate for radiation-induced neuropathic applications <sup>(71)</sup>. Curcumin could also significantly ameliorate the BBB damage in the brain to treat RIBI, which is mainly manifested in the decreased expression of glial fibrillary acidic protein and the increased expression of cyclic nucleotide 3' phosphohydrolase in the hippocampus <sup>(81)</sup>.

### Corilagin

Corilagin is a type of tannin family with anti-inflammatory activities that can enhance angiogenesis and reduce oxidative stress by regulating the Nrf2 signaling pathway against cerebral ischemic injury <sup>(72)</sup>. Another study showed that corilagin mitigated the cognitive impairment in RIBI mice and partially protected the BBB integrity from RIBI. Corilagin could inhibit the activation of microglia by the NF- $\kappa$ B pathway and reduce the expression of inflammatory cytokines against RIBI <sup>(73, 74)</sup>.

### Quercetin

Quercetin has strong antioxidant activity. Histopathological data showed that the degradation and infiltration of cells were significantly reduced with quercetin, which demonstrated its obvious neuroprotective effects <sup>(82)</sup>. The administration of quercetin before radiation could significantly increase the cytoskeletal protein Tuj1 and the neurotrophin brain-derived neurotrophic factor in the neuron, suggesting its neuroprotective effect on the brain against radiation-induced inflammatory responses <sup>(83)</sup>. Quercetin can also effectively protect oligodendrocyte precursor cells from radiation injury by oxygen-glucose deprivation *in vitro*, and this mechanism may be related to the activation of the phosphatidylinositol-3-kinase/alanine aminotransferase assay signaling pathway <sup>(75)</sup>. It could repair brain injury by inhibiting inflammation and apoptosis, thus promoting recovery of nerve function <sup>(76)</sup>.

### Kukoamine A

Kukoamine A (KuA) is a natural bioactive alkaloid found in wolfberry root bark, which has diverse therapeutic effects, including anti-oxidation, neuroprotection, and anti-inflammation. KuA can reduce malondialdehyde levels, increase glutathione and superoxide dismutase levels by regulating the expressions of caspase-3, cytochrome C, Bax, and Bcl2 catalase, and inhibit the apoptosis of neuron cells after whole-brain irradiation <sup>(77)</sup>. In addition, KuA can reduce the activation of hippocampal microglia in rats <sup>(78)</sup>. Therefore, KuA can serve as a neuroprotective agent on RIBI by inhibiting neuronal

oxidative stress and cell apoptosis.

### Other drugs

There are some other reported effective drugs for RIBI treatment. (1) Magnesium can exert protective effects against RIBI by reducing calcium overloading, improving oxidation-reduction, and inhibiting apoptosis<sup>(84)</sup>. In addition, it can significantly reduce the protein or mRNA levels of NF- $\kappa$ B and intercellular adhesion molecule-1<sup>(85)</sup>. (2) Valproic acid can inhibit the generation of reactive oxygen species by regulating the nuclear factor erythroid-2-related factor 2/heme oxygenase-1, which may improve cognitive behavior following RIBI<sup>(86)</sup>. It could also improve the effectiveness of glioma radiotherapy by protecting normal hippocampal neurons<sup>(87)</sup>. (3) Tamoxifen is a selective estrogen receptor modulator approved by FDA for its diverse neuroprotective properties. It can regulate antioxidants, anti-inflammatory and anti-glial hyperplastic responses<sup>(88)</sup>. Tamoxifen can significantly reduce the activation of astrocytes and neuronal apoptosis after radiation therapy, which is conducive to the structural reconstruction and functional recovery of the brain<sup>(89)</sup>. (4) Chinese medicine Shenqi Fuzheng injection could effectively reduce RIBI by inhibiting the NF- $\kappa$ B signal pathway and microglial activation<sup>(90, 91)</sup>. Tanshinone IIA has also been found to restore RIBI by reducing apoptosis and brain edema<sup>(92)</sup>. *Acanthopanax senticosus* (AS) is a widely used Chinese herbal medicine rich in phenolic compounds with antioxidant and anti-inflammatory properties<sup>(93)</sup>. It can maintain the normal activity of the nervous system of rats by regulating various signaling pathways, which has a positive effect on the movement, fission, structure, adhesion, and phagocytosis of nerve cells<sup>(94, 95)</sup>.

### HBO

During HBO therapy, the patient inhales 100% oxygen at a pressure of at least 1.5 atmospheres absolute (150 kPa)<sup>(96)</sup>. HBO can be used as a radiosensitizer to enhance the effect of radiation or as a therapeutic agent to reduce delayed radiation damage<sup>(96-99)</sup>. It helps oxygen dissolve in plasma and reach the brain independent of hemoglobin. In addition, HBO could promote the formation of new blood vessels in areas where the partial pressure of oxygen is reduced due to vascular damage, which can restore radiation-induced damage.

Combined with HBO, radiotherapy can destroy tumor cells and control the growth of tumor cells and reduce the incidence of RIBI, as well as prolong the survival time<sup>(100, 101)</sup>. A clinical trial involving 505 patients with various cancers studied the effects of HBO on radiotherapy. Compared with patients only receiving radiotherapy, patients with cervical or bronchial cancer receiving maximum-dose radiotherapy and hyperbaric oxygen showed higher survival<sup>(102, 103)</sup>.

HBO is a non-invasive treatment that promotes tissue repair and accelerates the recovery of the nervous system<sup>(104, 105)</sup>. Small retrospective studies have shown that the stability or improvement rate is higher in 70-80% of the patients receiving treatment<sup>(106-108)</sup>. Also, data from patients with symptomatic brain radiation necrosis treated with HBO between 2008 and 2018 showed that HBO could improve clinical and radiologic effects in most cases<sup>(109)</sup>. The prophylactic effect of HBO therapy for RIBI patients with brain metastasis was evaluated. The rate of white matter damage in the HBO group (2%) was lower than that in the non-HBO group (36%)<sup>(110)</sup>.

Many patients receiving radiotherapy can reduce the dose of hormonal drugs during or after HBO therapy. Despite common complications, HBO is considered relatively safe with tolerable toxicity. Clinically, it is also often combined with other interventions (such as bevacizumab) to treat RIBI. Endostar® (a commercial recombinant human endostatin injection) combined with short-term HBO therapy reduces the necrosis area of the radiated brain with non-recurrence<sup>(111)</sup>.

### Stem cells transplantation

Stem cell transplantation is a promising treatment protocol for CNS damage. Stem cells are pluripotent cells that can differentiate into cells with different functions and structures. Mesenchymal stromal cells (MSCs) can potentially alleviate radiation-induced fever by inhibiting activation of the related domain<sup>(112)</sup>. A combination of MSCs and nimodipine has a good therapeutic effect in RIBI mice, which was mainly reflected by improved exercise and cognitive ability, and decreased percentage of necrotic neurons and astrocytes in mice. Combination therapy with other methods is more effective than MSC alone. After receiving treatment, the expression of pro-apoptotic indicators (p53, Bax) and anti-apoptotic indicator Bcl-2 increases, thus protecting brain cells from further injury. The therapeutic effects of the combination of MSCs and nimodipine may be related to the inhibition of cell apoptosis and the promotion of mesenchymal stem cells to move to damaged brain sites<sup>(113)</sup>.

In addition, stem cells powered by electric vehicles can effectively treat brain injuries, including cognitive deficits caused by radiation<sup>(114)</sup>. Adult stem cells can also restore cognitive function in mice with neurodegenerative diseases and brain damage by reducing oxidative stress and promoting hippocampal neurogenesis<sup>(115)</sup>. After neural stem cells were transplanted into the brain of rats exposed to radiation, the cognitive dysfunction of these rats was restored, and the defects of hippocampal function induced by radiation were improved, suggesting that stem cell transplantation is feasible for the treatment of RIBI<sup>(116)</sup>.

It should be noted that there may be safety concerns about grafting foreign stem cells into the

brain. Therefore, cell-free alternatives are necessary. Stem cell-derived extracellular vesicles are nano-sized lipid-bound vesicles that could easily pass through BBB<sup>(117)</sup>. They may be effective in treating RIBI, especially radiation-induced cognitive deficits.

## DISCUSSION

Radiotherapy is an important treatment strategy for head and neck tumors. However, the related RIBI cannot be ignored. Many long-term studies have been conducted on the diagnosis, mechanism and treatment of RIBI. Yet, so far, no fully effective treatment method for RIBI has been developed, which is mainly attributed to the complexity of the CNS. Due to the complex structure of the brain and the indivisible human body, the mechanism that causes RIBI is not associated with a single factor. The above mechanisms may have a hierarchical relationship or different pathogenesis and vary from patient to patient. For RIBI, prevention may be more important than treatment due to the complicated injury mechanism. On the one hand, precise localized radiation and a detailed dose fractionation regimen are necessary<sup>(118-120)</sup>. On the other hand, efficient radiation protectants are needed to treat or prevent RIBI by eradicating free radicals, anti-inflammation or neuron restoration. Due to the complex damage mechanism of RIBI, traditional Chinese medicine may be more effective and superior to the treatment of RIBI than the use of single drugs due to its multiple targets.

Currently, the diagnosis of RIBI relies heavily on magnetic resonance imaging (MRI)<sup>(9, 121)</sup>. However, its diagnostic value is limited because white matter edema and demyelination commonly reveal diseases at a later stage. A radiodiagnosis approach can also help address microstructural changes in the temporal lobe that are not visible to human eyes, enabling precise prediction of RIBI, especially at early stages. Preclinical studies have shown that white matter lesions are the earliest form of radiation injury<sup>(122, 123)</sup>. The three radiodiagnosis models using T2-weighted images can help to better detect white matter lesions<sup>(121)</sup>. Contrast-enhanced T1-weighted images better indicate radiation-induced vascular changes. The combination of different MRI measures can therefore improve the predictive performance of RIBI. Recently, functional imaging techniques such as dynamic contrast enhancement (DCE), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) have been also used to provide functional and metabolic information<sup>(124-127)</sup>.

*In-vivo* experiments are conductive and important to study the pathogenesis, intervention, and optimization of the treatment strategies for RIBI. Many novel protocols are confirmed to effectively treat RIBI in various animal models. Rats and mice

remain the most commonly used RIBI models<sup>(128)</sup>. On this basis, neuronal regeneration, inflammatory mechanism, and glial cell function related to RIBI are evaluated, which is important to study the damage mechanism of RIBI. Nevertheless, the differences between rodents or cells and humans are substantial. Therefore, transforming RIBI treatment strategies from animal to clinical applications remains challenging. Preclinical studies can provide direction for the research on the pathogenesis of RIBI and provide reliable experimental, and theoretical support for the transformation from animal experiments to clinical experiments and applications. So, experiments are combined with actual clinical practice to find new targets or approaches for the treatment of RIBI.

## CONCLUSION

Thanks to the advancements in radiotherapy technology, radiation-induced brain injury has been gradually decreased. The mechanisms causing RIBI may have a hierarchical relationship or different pathogenesis. Traditional Chinese prescriptions may be more powerful and superior for the efficient treatment of RIBI due to their multiple targets. The next study emphasis should be focused on neuronal regeneration, inflammatory mechanism, glial cell function and so on, which could provide new targets or applicable approaches for the valid treatment of RIBI.

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