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Review Article

The current research status of the mechanisms and treatment of radioactive brain injury

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Abstract: Radioactive brain injury, a severe complication ensuing from radiotherapy for head and neck malignancies, frequently manifests as cognitive impairment and substantially diminishes patients' quality of life. Despite its profound impact, the pathogenesis of this condition remains inadequately elucidated, and efficacious treatments are notably absent in clinical practice. Consequently, contemporary interventions predominantly focus on symptom alleviation rather than achieving a radical cure or reversing the injury process. This article provides a comprehensive review of the various pathogenic mechanisms and therapeutic strategies associated with radioactive brain injury, offering insights that may guide the development of novel therapeutic strategies.

Keywords: Radioactive brain injury, brain radiation necrosis, blood-brain barrier, inflammatory response, oxidative stress

Introduction

Radiotherapy constitutes a principal modality for the treatment of malignant tumors, demonstrating efficacy in the eradication of tumor cells; however, it unavoidably inflicts collateral damage on adjacent normal tissues [1]. Radioactive brain injury (RBI), a common complication subsequent to radiotherapy for head and neck malignancies, results in enduring cognitive deficits, significantly compromising patients' quality of life and overall survival [2]. Despite its high incidence, the underlying mechanisms of RBI are not well elucidated, and efficacious therapeutic interventions remain limited [3]. Therefore, elucidating the underlying mechanisms, preventive measures, and the development of diagnostic and therapeutic strategies for RBI is essential for improving the efficacy and prognosis of radiotherapy in patients with head and neck malignancies.

RBI was first documented by Fisher in 1930 [4], and subsequent research in this domain has shown considerable advancement. In the past two decades, investigations have predominantly focused on the molecular pathology and therapeutic strategies associated with RBI [5]. Clinically, RBI is characterized by a high incidence and often presents with severe cognitive impairments and compressive symptoms, such as dementia, depression, anxiety, headaches, and syncope, thereby significantly affecting the prognosis of patients undergoing radiotherapy [6]. Based on the timing of symptom onset, RBI is classified into acute, early delayed, and late delayed injury. Acute injury, manifesting within 48 hours to several weeks following radiotherapy, is predominantly attributed to brain edema resulting from disruption of the blood-brain barrier (BBB), and is characterized by symptoms such as headaches, lethargy, and memory loss [7]. Early delayed brain injury, which appears 1-4 months post-irradiation, encompasses brain edema, alterations in neuronal networks, organic damage to the nervous system, and transient demyelination [8], frequently presenting as fatigue and impaired concentration. Although these early injuries can be severe, they are reversible. In contrast, late delayed damage is irreversible and progressive [9], typically commencing 4-6 months following radiotherapy, central nervous system (CNS) radiation injury is histologically character-

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ized by gray matter damage, ataxia, vascular abnormalities, demyelination, and eventual white matter necrosis, with potential progression over subsequent years. In summary, vascular abnormalities and white matter demyelination are the predominant histopathological features of this condition [10].

RBI represents a complex pathological condition modulated by a multitude of factors, such as endothelial cell damage, neuroglial cell responses, oxidative stress, and autoimmune inflammatory reactions. Early intervention in RBI is associated with favorable prognoses for early-onset cases. Conversely, late-onset RBI may progress to radiation necrosis (RN) or leukoencephalopathy, both of which are predominantly irreversible and present significant therapeutic challenges [11]. A variety of treatment modalities are available for RBI, predominantly pharmacological, with varying degrees of efficacy. Corticosteroids are considered a first-line therapy and can significantly alleviate symptoms [12]. Additionally, Pentoxifylline and hyperbaric oxygen therapy are frequently utilized. Anti-VEGF antibodies, such as bevacizumab, have also been employed in the management of radiation-induced brain necrosis [13]. For patients who do not respond to or cannot tolerate pharmacological treatments, surgical intervention is recommended. Alternatively, when surgery is contraindicated, Laser Interstitial Thermal Therapy (LITT) is regarded as a viable salvage option. Furthermore, numerous novel therapeutic drugs and methods are currently under investigation.

The incidence of progressive and disabling cognitive impairment among survivors who have received radiotherapy for craniocerebral tumors ranges from 50% to 90% [14]. Given the current limited understanding of RBI, optimizing the therapeutic benefits of radiotherapy remains challenging. This article aims to elucidate the mechanisms underlying RBI and to review existing treatment modalities, thereby contributing to the development of novel therapeutic strategies.

Mechanism of radiation-induced brain injury

Despite extensive research over the past few decades, the complete pathogenic mechanism of RBI remains incompletely understood. Previous studies by Serduc et al. have investigated RBI in relation to the brain vascular system, neuroglial cells, and hypoxia, with findings validated in rodent models [15]. To date, the precise mechanisms underlying RBI continue to be elucidated and are generally considered to involve a dynamic and complex cascade of processes. Several principles have been proposed to elucidate its pathogenesis, encompassing radiation-induced direct damage [16], immune inflammatory responses [17], oxidative stress [18], neuroglial cell reactions, and impairment of the brain vascular system [19] (**Figure 1**).

Direct radiation-induced damage

Radiation has the potential to directly damage brain tissue. Exposure to radiation often results in the disruption of DNA within brain cells, which subsequently impairs protein synthesis. In the event of irreversible DNA damage, DNA repair mechanisms are activated, leading to cell cycle arrest and apoptosis [20]. Furthermore, radiation can harm endothelial cells, instigating neuroamide-mediated apoptosis and eliciting inflammatory responses. These processes ultimately contribute to the disruption of the BBB and the development of brain edema [21].

Radiation has the potential to modulate various signaling pathways, thereby impacting cellular processes such as growth, proliferation, and apoptosis, which collectively contribute to the progression of radiation-induced brain injury. Notably, the PI3K/AKT signaling pathway is known for its robust neuroprotective properties and its capacity to mediate brain repair through multiple mechanisms. According to research conducted by Ji et al., radiation exposure can inhibit the PI3K/AKT signaling pathway within brain tissue [22], leading to the attenuation of synaptic connections, substantial neuronal loss, and heightened neuronal apoptosis [23]. Radiation additionally disrupts the ERK1/ERK2 (extracellular signal-regulated kinase) signaling pathway, which impacts post-irradiation neuronal survival and activates cell cycle checkpoints associated with elevated levels of Trp53 and p21 proteins [24]. Moreover, radiation enhances the expression of cytokines, including tumor necrosis factor-α (TNF-α) and transforming

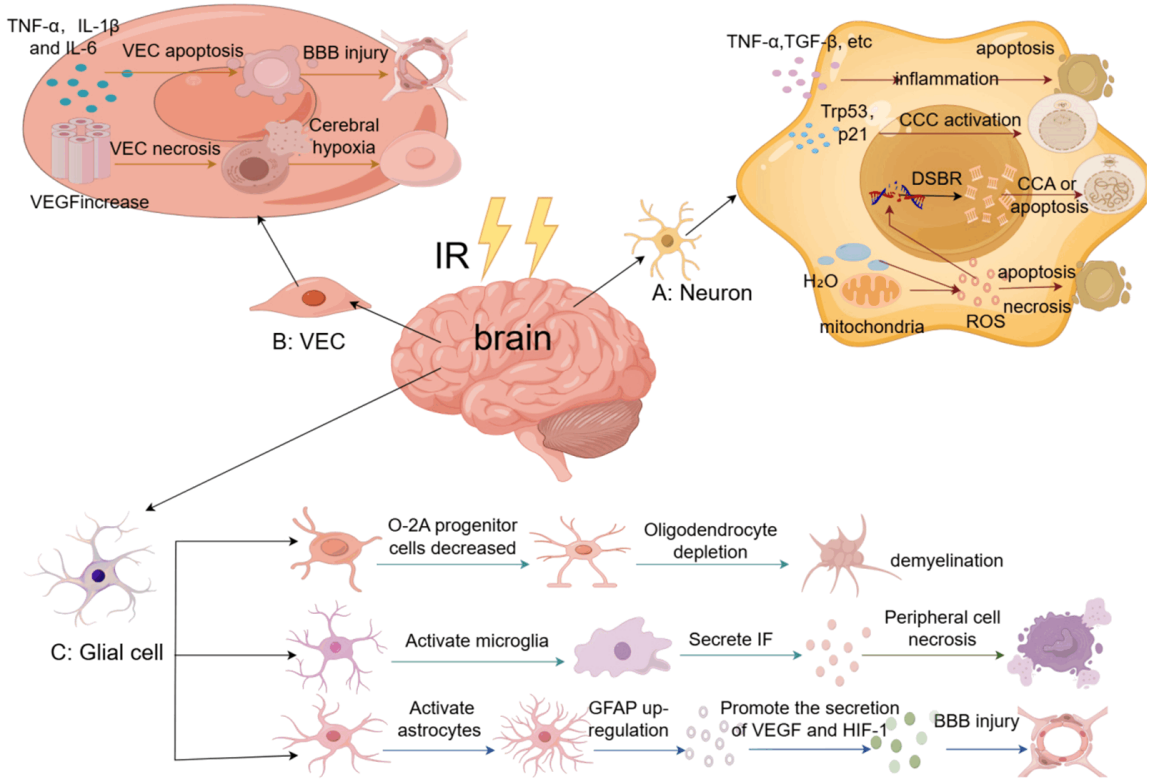

Figure 1. Radiation exposure to the brain initiates a complex cascade of reactions involving neurons, vascular endothelial cells, and neuroglial cells, which collectively mediate the onset and progression of radiation-induced brain injury. Specifically, neuronal response to radiation includes the upregulation of inflammatory factors such as TNF-α and TGF-β, which activate inflammatory pathways contributing to brain injury. Additionally, radiation exposure induces the increased expression of Trp53 and P21, resulting in the activation of cell cycle checkpoints. Additionally, radiation induces DNA double-strand breaks, thereby activating DNA damage repair mechanisms which can lead to cell cycle arrest or apoptosis. Furthermore, reactive oxygen species (ROS) generated by the interaction of radiation with water molecules and mitochondria not only inflict DNA damage but also facilitate neuronal apoptosis. In terms of endothelial cell response, radiation enhances the expression of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 in vascular endothelial cells (VECs), thereby promoting apoptosis and increasing the permeability of the BBB. Concurrently, the upregulation of vascular endothelial growth factor (VEGF) results in the aberrant proliferation of VEGF enhancing vascular permeability and compromising the integrity of the BBB. Regarding the glial cell response, radiation exposure detrimentally affects O-2A progenitor cells, leading to a reduction in oligodendrocyte production and subsequent demyelination. Additionally, radiation induces the expression of TNF-α and IL-6, which activate microglia to secrete substantial amounts of pro-inflammatory factors, facilitating the infiltration of macrophages into the BBB. Subsequent to neuronal injury, activated astrocytes undergo proliferation and hypertrophy, leading to the upregulation of glial fibrillary acidic protein (GFAP) and the enhanced expression of VEGF and HIF-1, thereby exacerbating the compromise of the BBB. Abbreviations: BBB, Blood-brain barrier; VEGF, Vascular endothelial growth factor; VEC, Vascular Endothelial Cell; IR, Ionizing Radiation; TNF-α, Tumor necrosis factor-α; TGF-β, Transforming growth factor-β; CCC, Cell Cycle Checkpoint; DSBR, DNA Double-Strand Break Repair; CCA, Cell Cycle Arrest; ROS, Reactive Oxygen Species; IF, Inflammatory Factors; GFAP, glial fibrillary acidic protein; HIF-1, Hypoxia-inducible factor-1.

growth factor-β1 (TGF-β1), as well as various transcription factors [25]. These molecular alterations promote inflammatory responses and contribute to the pathogenesis of RBI.

Numerous preclinical investigations have elucidated that the apoptotic response of brain cells to radiation is dose-dependent, manifesting within hours post-treatment. For instance, administration of a single large dose (2-10 Gy) of whole-brain irradiation has been shown to precipitate a marked increase in apoptosis within the dentate gyrus (DG) of the hippocampus within 3-6 hours post-irradiation, subsequently leading to significant short-term cognitive deficits [26]. In summary, radiation can inflict direct damage on brain tissue through multiple pathways, playing a pivotal role, particularly in the

early stages of radiation-induced brain injury [27].

Immune inflammatory responses

Inflammation is pivotal in the pathogenesis of radiation-induced brain injury. Exposure to radiation can inflict varying degrees of damage on brain cells, thereby initiating neuroinflammatory processes. Moreover, radiation has the capacity to induce both acute and chronic inflammatory responses by modulating immune cell activity. Excessive inflammatory reactions can further aggravate brain injury. Post-radiation exposure, there is a marked increase in the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), as well as in the synthesis of prostaglandin E2 (PGE2) within the brain, which collectively promote inflammation in the CNS [28]. Furthermore, radiotherapy induces the upregulation of numerous pro-inflammatory mediators within the CNS, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and matrix metalloproteinase-9 (MMP-9) [29]. These mediators contribute to endothelial cell apoptosis, increased permeability of the BBB, and activation of the nuclear factor-kappa B (NF-κB) signaling pathway, ultimately disrupting claudin-5 and precipitating early BBB breakdown [30].

In the initial phases post-radiotherapy, the secretion of various pro-inflammatory cytokines has the potential to induce neurotoxicity in neurons, neural stem cells, and glial cells, thereby accelerating neuronal apoptosis, inhibiting synaptic plasticity, and exacerbating cerebral injury. Interleukin-6 (IL-6) and other inflammatory mediators may be activated during brain injury, facilitating the release of oxygen free radicals [31]. Conversely, anti-inflammatory factors released during the later stages of inflammation, such as Interleukin-10 (IL-10), can attenuate the inflammatory response, promote neural tissue repair, and enhance neuronal survival. Therefore, anti-inflammatory therapy has the potential to mitigate cerebral damage and promote functional recovery [32]. Consequently, inflammation is increasingly acknowledged as a critical factor in the onset and progression of radiation-induced brain injury. Targeting inflammatory pathways for both prevention and treatment presents a promising avenue for therapeutic intervention.

Oxidative stress

For an extended period, oxidative stress has been identified as a significant contributor to both acute and chronic radiation-induced injuries. Oxidative stress arises from an increase in intracellular reactive oxygen species (ROS), resulting in the damage of lipids, proteins, and DNA [33]. The CNS is especially susceptible to oxidative damage due to its high content of polyunsaturated fatty acids, substantial oxygen consumption, and limited antioxidant defenses [34]. Research conducted by Marlon et al. demonstrates that exposure to low-dose irradiation (0-5 Gy) results in a significant elevation of ROS levels within brain tissue, thereby inducing prolonged oxidative stress and aggravating neuronal damage [35]. Moreover, this sustained oxidative stress has the potential to impede the self-repair mechanisms of compromised neurons, ultimately contributing to cognitive dysfunction [36].

Radiation exposure to water molecules results in the generation of ROS and an overproduction of free radicals due to mitochondrial damage. Consequently, this induces DNA and cell membrane damage, thereby activating multiple signaling pathways that influence cell growth, apoptosis, and autophagy [37]. Within the cell nucleus, ROS can induce DNA damage, whereas in the cytoplasm, ROS can compromise cell membranes and proteins, leading to impaired cellular function or apoptosis. The release of oxygen free radicals precipitates neuronal death and facilitates the adhesion, migration, and activation of neutrophils, thereby exacerbating inflammation and resulting in further brain tissue damage [38]. The generation of ROS is regarded as the principal cause of radiation-induced tissue damage [39]. Furthermore, the inflammatory response elicited during brain injury also contributes to the release of oxygen free radicals. Consequently, the development of antioxidant or anti-inflammatory therapeutic strategies for the treatment of radiation-induced brain injury is of considerable importance.

Neuroglial cell reactions

Glial cells are integral to the pathogenesis and progression of radiation-induced brain injury. These supportive cells, encompassing astrocytes, oligodendrocytes, and microgliap [40],

are involved in guiding neuronal migration, repairing the nervous system, stimulating immune responses, and forming myelin sheaths and the BBB. Demyelination is a characteristic pathological alteration observed in radiation-induced brain injury [35]. Mature oligodendrocytes are critical for the formation of myelin sheaths, while O-2A progenitor cells, the precursors to oligodendrocytes, exhibit high sensitivity to radiation. Radiotherapy can result in the depletion of O-2A progenitor cells, thereby hindering the replenishment of mature oligodendrocytes and culminating in demyelination [41]. Additionally, radiation has the capacity to directly induce the death of oligodendrocytes, further contributing to demyelination. For instance, in regions such as the hippocampus and temporal lobe, radiation inflicts direct damage on oligodendrocytes, leading to abnormal cell proliferation and subsequent peripheral or central demyelination. This pathological process manifests clinically as acute encephalomyelitis and various neurological disorders [42].

Microglia, as pivotal immune cells within the CNS, undergo significant activation in response to whole-brain radiotherapy, thereby eliciting pro-inflammatory responses [43]. Radiation-induced brain injury triggers microglial activation through various mechanisms, including the presence of inflammatory neurotransmitters, toxins, and the lack of inhibitory signals within the CNS [44]. Upon activation, microglia adopt an amoeboid morphology, exhibit enhanced phagocytic activity, secrete substantial quantities of pro-inflammatory mediators, and facilitate the infiltration of peripheral macrophages into the CNS via the BBB [45]. Microglial activation exhibits heterogeneity and can be categorized into M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes [46]. M1 microglia are characterized by the induction of inducible nitric oxide synthase (iNOS) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways, leading to the release of various pro-inflammatory mediators that can inflict damage on surrounding tissues. In contrast, M2 microglia facilitate extracellular matrix (ECM) reconstruction and tissue repair by promoting the phagocytosis of cellular debris and misfolded proteins, and by secreting abundant neurotrophic factors that support neuronal survival [47]. Following radiotherapy, microglia predominantly exhibit an M1 phenotype, which induces both acute and chronic inflammatory responses that are critical in the pathogenesis of radiation-induced brain injury [48]. Persistent activation of microglia is recognized as a significant contributor to radiation-induced cognitive impairment, and pharmacological interventions targeting microglial activity have demonstrated efficacy in ameliorating these deficits in preclinical models [49].

Astrocytes, which serve as supportive cells within the CNS, play a crucial role in maintaining the structural and functional integrity of neurons. In response to CNS injury, astrocytes can undergo proliferation and hypertrophy, leading to an upregulation of the activation marker GFAP [50]. Research conducted by Moravan et al. demonstrated that GFAP levels increase within a timeframe of 4 hours to 1 year following head radiotherapy, suggesting prolonged astrocyte activation post-radiation [51]. Activated astrocytes contribute to radiation-induced brain injury by secreting cytokines such as VEGF and HIF-1. Astrocytes can be categorized into A1 and A2 phenotypes based on their response characteristics. A1-type astrocytes, which are induced under inflammatory conditions, have been shown to inhibit axon regeneration and cause neuronal damage. Conversely, under ischemic or hypoxic conditions, astrocytes transition into the A2 phenotype, which involves the secretion of various neurotrophic factors that promote synaptic formation and exert protective and reparative effects [52]. Research indicates that the neurotrophic factors secreted by activated astrocytes are directly associated with neuronal function and the integrity of the BBB [53]. Therefore, further investigation into the underlying mechanisms is warranted.

Brain vascular system damage

The disruption of the BBB is a well-documented pathogenic mechanism underlying radiation-induced brain injury. This condition initially presents as cerebrovascular damage, typically manifesting within 24 hours post-radiotherapy, and subsequently progresses to parenchymal brain injury [54]. The damage to the BBB and the resultant increase in its permeability are pivotal aspects of vascular injury following radiotherapy [55]. Radiation exposure can induce

the overexpression of vascular endothelial growth factor (VEGF), which contributes to the increased permeability of endothelial cells and a reduction in microvascular density within brain tissue [56]. Research has demonstrated that radiation-induced pericellular senescence can result in the production of the senescence-associated secretory phenotype (SASP), including cytokines such as IL-6, TNF-α, and IL-1β. These factors adversely impact the integrity of the BBB and contribute to the disruption of endothelial cell tight junctions [57].

Radiation-induced vascular damage predominantly impacts endothelial cells, initially manifesting as abnormal proliferation, migration of smooth muscle cells, and platelet aggregation. This pathological process results in the formation of scar tissue, thickening of the vessel wall, and subsequent luminal narrowing or obstruction, ultimately leading to cerebral tissue ischemia and hypoxia-induced necrosis [58]. Secondary cerebral edema and ischemic brain necrosis, consequent to vascular damage, are the primary contributors to radiation-induced brain injury. Moreover, the modification of microvasculature is a critical determinant in the manifestation of both acute and chronic cognitive side effects in healthy brain tissue subsequent to radiotherapy. The early identification of radiation-induced microvascular alterations is imperative to mitigate the detrimental effects of radiation on patients [59].

Treatment of radiation-induced brain injury

In the context of preventing RBI, it is crucial to improve the therapeutic ratio of radiotherapy. Presently, a growing array of precise radiotherapy techniques with enhanced efficacy are being employed to mitigate damage to normal brain tissue. However, due to the ambiguous mechanisms underlying RBI, standardized treatment protocols for this condition remain insufficiently developed. Numerous treatment modalities have been proposed historically for the management of RBI, encompassing corticosteroids, surgery, hyperbaric oxygen, heparin, pentoxifylline, and vitamin E [60], each demonstrating varying degrees of efficacy. Despite the advent of several novel approaches for addressing RBI, conclusive evidence substantiating their effectiveness remains elusive. Consequently, the pursuit of effective treatments for RBI continues to be beset by substantial challenges and responsibilities (**Table 1**).

Corticosteroids

Corticosteroids, including dexamethasone, have historically been considered the gold standard for the treatment of radiation-induced brain injury. These pharmacological agents exhibit significant anti-inflammatory properties and are capable of mitigating BBB permeability [61]. For patients presenting with symptomatic brain injury, corticosteroids are the primary therapeutic intervention. They effectively attenuate the pro-inflammatory response associated with radiation-induced brain injury and enhance the integrity of the BBB, thereby alleviating the severity of cerebral edema. Dexamethasone, in particular, is commonly administered due to its pronounced immunomodulatory effects. Pulse corticosteroid therapy has been shown to rapidly alleviate symptoms of cerebral RN in the short term [62]. However, the therapeutic benefits of corticosteroids are transient and primarily supportive rather than curative. While corticosteroids can provide significant benefits with a relatively low incidence of adverse reactions when administered over a limited duration, their discontinuation or prolonged use without appropriate caution may result in serious side effects [63]. Some patients with chronic conditions necessitate prolonged corticosteroid therapy, which can result in numerous concomitant toxicities, rendering this approach unsustainable in the long term [64].

In the context of immunotherapy, a novel concern has arisen regarding the potential for corticosteroids' immunosuppressive properties to attenuate the effectiveness of immunotherapeutic or targeted interventions [65]. Clinically, corticosteroids are frequently administered to manage inflammation and provide rapid symptom relief in cases of brain injury. Empirical evidence suggests that the concomitant use of corticosteroids and hyperbaric oxygen therapy results in superior outcomes compared to corticosteroid monotherapy [66]. Furthermore, corticosteroids may be administered in conjunction with agents such as mannitol and hypertonic saline to enhance the reduction of cerebral edema. Nonetheless, the efficacy of

Table 1. Common treatments for RBI

Treatment method	Principle	Advantage	Disadvantage	Clinical trial
Corticosteroids [61-64]	Anti-inflammatory, improve BBB	Rapid and obvious	Ephemeral and supportive	Yes
Anti-VEGF therapy [67-70]	Anti-inflammatory, anti-angiogenesis	Obvious effect and can reduce steroid use	risk of hypertension and renal insufficiency	Yes
Laser interstitial hyperthermia [76-78]	Ablation of tissue by radiating heat	Minimally invasive, can reduce drug use, do a biopsy	High application requirements, less data	No
Hyperbaric oxygen Therapy [80-82]	Increase dissolved oxygen in the brain	Suitable for acute phase, reduce neuronal necrosis	Barotrauma risk	No
Surgery [84, 85, 87]	Direct resection of lesion	Relieve the occupying effect, do a biopsy, obvious effect	Big damage, high risk	No
Stem cell therapy [89, 90]	Reduce oxidative stress, regulate inflammation	Can protect neurons, low side effects	Low selectivity, immature technology	No
Targeted microglia therapy [95-98]	Decreased microglia activation and secretion	Strong pertinence, low side reaction	Lack of evidence support and experimental verification	No

corticosteroids is predominantly observed during the initial stages of onset or for short-term relief, providing limited advantages for patients necessitating long-term or late-stage therapeutic interventions.

Anti-VEGF therapy

Bevacizumab, a humanized monoclonal antibody, inhibits the biological activity of vascular endothelial growth factor (VEGF) by binding to it, thereby attenuating the inflammatory cascade and effectively treating edema [67]. Additionally, it reduces endothelial cell proliferation and neovascularization, consequently decreasing vascular permeability [68]. A clinical study conducted by Xu et al. evaluated the efficacy of bevacizumab in comparison to traditional steroid therapy for the treatment of radiation-induced brain injury. The study revealed that 62.1% of patients in the bevacizumab group exhibited significant symptom improvement, a proportion notably higher than the 42.6% observed in the steroid therapy group. Consequently, bevacizumab is postulated to mitigate the symptoms of radiation-induced brain injury and enhance patient prognosis [69]. Additionally, it is recognized as an efficacious agent in inhibiting the progression of brain RN [70], and it remains the sole therapy demonstrated to be effective for this condition in randomized controlled trials (RCTs). Bevacizumab antagonizes the effects of vascular endothelial growth factor (VEGF) on brain RN and diminishes the necessity for steroid administration. Nevertheless, given the irreversible nature of brain necrosis, cessation of bevacizumab treatment may precipitate the recurrence of brain RN [71]. In summary, while bevacizumab therapy for RBI shows promising results, it lacks sufficient evidence support.

Apatinib is a small molecule inhibitor of multiple receptor tyrosine kinases, with a high selectivity for VEGFR2 [72]. During the investigation of RBI, Owen et al. identified VEGF as a critical factor contributing to increased BBB permeability and abnormal vascularization [73]. Apatinib exerts its effects by inhibiting the VEGF-mediated signal transduction pathway and preventing the phosphorylation of VEGFR2. Research conducted by Xiong et al. demonstrated that apatinib could mitigate brain edema and BBB damage in rats following RBI, reduce neuroinflammation, and inhibit astrocyte activation [74]. In murine models, administration of apatinib was observed to downregulate astrocyte activation, ameliorate brain hypoxia, mitigate brain edema, and significantly alleviate the adverse effects associated with acute RBI [75]. These findings indicate that apatinib holds potential as a novel therapeutic candidate for RBI. However, further investigation is necessary to validate its neuroprotective effects and elucidate the underlying mechanisms of action.

Laser interstitial hyperthermia (LITT)

LITT is a minimally invasive procedure that entails the insertion of a laser probe under stereotactic guidance to generate heat and ablate targeted tissue. LITT has demonstrated efficacy in the ablation therapy of radiation-induced brain injury [76]. It is particularly utilized in patients whose brain injuries have not responded to pharmacological treatments, especially in cases of steroid-resistant or steroid-dependent conditions, or for lesions situated in surgically inaccessible regions or in patients with a history of multiple surgeries that pose high surgical risks [77]. Research indicates that LITT can facilitate the successful discontinuation of steroid use in the majority of patients, with complete regression of lesions generally observed within weeks post-procedure. A meta-analysis conducted by Palmisciano et al. demonstrated symptomatic improvement in 61% of patients following LITT treatment, with 44% of patients achieving cessation of steroid use [71]. In a comparative study conducted by Sankey et al., examining LITT versus pharmacological treatment for brain RN, it was found that patients undergoing LITT were more likely to discontinue steroid use at a median of 37 days (84% compared to 53%) and exhibited a lower likelihood of radiographic progression (5% compared to 27%) [78].

Another advantage of LITT is its capability to perform biopsies, which can inform decisions regarding adjuvant therapy if tumor recurrence is confirmed histologically. Given its minimally invasive nature, LITT should be considered early in the course of lesion recurrence to optimize local control outcomes. Despite its numerous advantages, there is a paucity of direct comparative data for LITT, with only a limited

number of patients having undergone this treatment, and the technology is not yet widely accessible [79]. Consequently, LITT remains a potential treatment strategy at present.

Hyperbaric oxygen therapy (HBOT)

Radiation exposure can induce vascular fibrosis and thrombosis, which subsequently diminishes blood and oxygen supply to the brain, culminating in brain injury. Hyperbaric oxygen therapy (HBOT) is frequently employed in the treatment of radiation-induced brain injury, particularly in patients during the acute phase, as it enhances cerebral oxygenation. Additionally, HBOT has been shown to reduce capillary permeability, decrease tissue fluid extravasation, and ameliorate cerebral edema. The effectiveness of hyperbaric oxygen therapy (HBOT) in the treatment of radiation-induced brain injury has been substantiated through numerous studies. Bennett et al., in a comprehensive meta-analysis, demonstrated that the prognosis for most patients with radiation-induced brain injury is favorable following HBOT, significantly decreasing the risk of neuronal necrosis during the course of treatment [80].

Hyperbaric oxygen therapy (HBOT) has been reported to ameliorate both radiographic and symptomatic manifestations of radiation-induced brain necrosis [81]. A study by Cihan et al. indicates that administering 20 sessions of HBOT one week following stereotactic radiosurgery (SRS) can decrease the incidence of brain RN from 20% to 11% [82]. However, the evidence remains predominantly confined to case reports, with a scarcity of randomized controlled trials available for corroboration [83]. Furthermore, numerous reported cases indicate that hyperbaric oxygen therapy (HBOT) is frequently administered in conjunction with dexamethasone or bevacizumab. This concurrent administration complicates the ability to isolate and evaluate the independent effects of HBOT. Consequently, while HBOT has the potential to exert therapeutic effects on tissues and vessels through enhanced oxygenation, additional research is necessary to determine the optimal dosage, timing, and application methods to achieve the most favorable outcomes.

Surgery

Craniotomy is linked to considerable trauma and elevated risk, and therefore, it is typically not favored as the initial treatment modality for radiation-induced brain injury. Nonetheless, in cases where patients present with progressive intracranial pressure elevation, prolonged dependence on diuretics and steroids for maintenance therapy, or radiographic findings suggestive of significant brain edema and mass effect, surgical intervention may be warranted [84]. Surgical resection is the standard treatment for rapidly progressing, symptomatic radiation-induced brain necrosis, contingent upon the lesion's anatomical location. Furthermore, cases of brain RN that are refractory to pharmacological interventions may require surgical intervention to mitigate the mass effect.

Following surgical resection, the resolution of edema surrounding the necrotic lesion may necessitate several weeks, thereby requiring meticulous monitoring [85]. Additionally, surgical intervention facilitates tissue diagnosis, allowing for biopsy to exclude potential tumor progression that might have been previously undetected. In instances where radiation-induced brain necrosis coexists with residual tumor cells, surgical procedures may contribute to reducing the overall burden of central nervous system (CNS) tumors. However, in cases of glioblastoma multiforme (GBM), if RN is characterized exclusively by necrosis, overall survival rates following surgical intervention or combined treatment with bevacizumab are comparable to those observed in groups with residual tumor cells [86]. Given the objective of optimizing the quality of life for patients with tumors, addressing distressing symptoms such as seizures or headaches offers a justifiable rationale for surgical intervention [87].

Stem cell therapy

Mesenchymal stem cells (MSCs) exhibit the capacity to repair damaged tissues and demonstrate significant immunomodulatory, anti-apoptotic, and angiogenic properties [88]. The application of MSCs has been shown to mitigate oxidative stress and modulate inflammatory responses [89]. Nonetheless, the efficiency of MSCs in homing to target sites remains suboptimal, with only a minor proportion of administered cells reaching the intended tissue following systemic delivery [90], thereby considerably constraining their clinical utility.

Wang et al. demonstrated that umbilical cord mesenchymal stem cells (UC-MSCs) can inhibit

the secretion of the pro-inflammatory cytokines TNF-α and IL-6, while promoting the release of the anti-inflammatory cytokine IL-10, thereby exerting neuroprotective effects against radiation-induced brain injury [91]. Furthermore, Soria et al. reported that intranasal administration of human bone marrow mesenchymal stromal cells (hMSCs) facilitates the repair of radiation-induced brain injury and enhances neurological function [92]. Endothelial progenitor cells (EPCs), which serve as precursors to endothelial cells, are integral to the process of angiogenesis. Transplantation of EPCs has demonstrated potential in ameliorating damage induced by radiotherapy to the BBB, tight junctions, and brain capillaries [93]. Consequently, leveraging the multifunctional properties of stem cells for the treatment of radiation-induced brain injury may constitute a promising therapeutic approach.

Targeted microglia therapy

Following radiation exposure to brain tissue, microglial cells swiftly adopt a pro-inflammatory phenotype, characterized by the secretion of substantial quantities of inflammatory mediators and a concomitant reduction in the release of neurotrophic factors [94]. This phenotypic shift is pivotal in the pathogenesis and progression of radiation-induced brain injury. Consequently, therapeutic strategies aimed at modulating microglial cell activity may hold significant promise for the treatment of this condition. For instance, Pregabalin has been shown to attenuate the activation of microglial cells and the expression of inflammatory cytokines by directly inhibiting the cytoplasmic translocation of high mobility group box 1 (HMGB1). The study conducted by Zhang et al. demonstrated that Pregabalin can ameliorate radiation-induced brain injury by targeting the HMGB1-TLR2/TLR4/RAGE signaling pathway in microglial cells [95]. Another compound, ShK-170, serves as a specific inhibitor of the voltage-gated potassium (Kv)1.3 channel and has demonstrated efficacy in protecting mice from radiation-induced brain injury. The pharmacological blockade of Kv1.3, achieved through either specific short interfering RNA or ShK-170, has been shown to inhibit the production of pro-inflammatory factors and mitigate radiation-induced neurotoxicity in microglial cells, thereby alleviating RBI [96].

Furthermore, Fractalkine (FKN) serves as a critical mediator in the regulation of microglial cell activity. By binding to the CX3CR1 receptor on microglial cells, FKN can induce polarization towards the M2 phenotype, which may mitigate the effects of radiation-induced brain injury. Consequently, the promotion of the FKN/CX3CR1 axis represents a potentially promising therapeutic strategy for addressing RBI [97]. Additionally, elevated levels of extracellular ATP (eATP) in the cerebrospinal fluid (CSF) of RBI patients have been correlated with the severity of the disease. The P2X7 receptor (P2X7R) is an ion-selective purinergic receptor involved in microglial cell activation and paracrine signaling. Xu et al.'s study revealed the critical role of the ATP-P2X7R axis in RBI and suggested that inhibiting this axis may be a potential method for treating RBI patients [98].

In conclusion, the microglial cell response to RBI involves a complex interplay of various biochemical substances, receptors, and signaling pathways. Modulation of these pathways, through either inhibition or activation, holds promise as a potential therapeutic strategy for managing RBI. Nevertheless, despite the encouraging preliminary findings, there remains a significant paucity of experimental data and empirical support. Consequently, these therapeutic approaches are not yet ready for clinical application.

Discussion

Research indicates that 70% of cancer patients necessitate radiation therapy at various stages of their disease progression [99]. While radiation therapy is efficacious in reducing tumor growth, it is also associated with the potential for severe brain damage following head and neck irradiation [100]. This damage can manifest as cognitive impairments, including deficits in learning and memory, secondary epilepsy, and progressive dementia [101]. The prevalence of radiation-induced brain injury consequently imposes a substantial burden on healthcare systems and society at large. Considering the advantages of timely diagnosis and early intervention for patients with RBI, it is imperative to enhance awareness and diagnostic rates of the condition. Concurrently, there is a critical need to develop more efficacious preventive and therapeutic strategies to improve

the prognosis of patients undergoing radiation therapy.

The pathogenesis of RBI is multifaceted, encompassing inflammation, oxidative stress, vascular damage, and additional contributing factors [102]. Studies utilizing animal models have demonstrated that radiation therapy can compromise the integrity of the BBB, resulting in cerebral edema [103]. Furthermore, radiation-induced cellular damage can trigger tissue inflammation and the infiltration of immune cells, thereby elevating the secretion of various inflammatory mediators [104]. This cascade perpetuates and exacerbates the inflammatory state, culminating in sustained damage to brain tissue [105].

At present, there are no well-defined guidelines for the diagnosis and treatment of RBI. The diagnosis of RBI predominantly depends on clinical assessment and imaging techniques, which frequently pose difficulties in differentiating RBI from tumor progression [106]. The therapeutic approaches commonly employed for RBI encompass corticosteroids, bevacizumab, LITT, hyperbaric oxygen therapy, and surgical intervention. Corticosteroids are considered the first-line treatment, especially for managing symptoms associated with cerebral edema, and typically result in rapid symptomatic improvement. Bevacizumab, whether administered as a monotherapy or in conjunction with other pharmacological agents, has demonstrated efficacy in mitigating radiation-induced brain injury [107]. Hyperbaric oxygen therapy has been shown to alleviate cerebral edema by enhancing oxygen concentration, thereby potentially reducing the reliance on corticosteroids [108]. Furthermore, numerous novel therapeutic approaches are currently undergoing development and clinical evaluation, thereby expanding the potential treatment landscape for radiation-induced brain injury. In conclusion, the early detection and treatment of RBI are essential for effective management. Nevertheless, existing diagnostic techniques for RBI are constrained and frequently indistinguishable from tumor progression [109]. Consequently, the development of novel diagnostic strategies or criteria, such as the application of biomarkers in patient plasma [110], may significantly enhance the prognosis for patients with RBI.

Despite the existence of multiple treatment modalities for RBI, their overall efficacy remains ambiguous and is not adequately substantiated by empirical evidence. Therefore, the prevention of RBI is of utmost importance. Advanced radiotherapy techniques, such as Stereotactic Ablative Radiotherapy (SAS), have demonstrated the capability to minimize radiation exposure to adjacent normal tissues [111]. Furthermore, the administration of neuroprotective agents prior to radiotherapy has been shown to mitigate the risk of RBI. For example, the pre-radiotherapy administration of erythropoietin (EPO) has been found to prevent impairments in hippocampal-dependent learning and memory [112]. Furthermore, research conducted by Zhou et al. indicates that pre-radiotherapy intranasal administration of a miR-122-5 antagonist and a miR-741-3p inhibitor can mitigate radiation-induced cognitive dysfunction and neuronal apoptosis [113]. However, the current body of research on the prevention of radiation-induced brain injury is limited, presenting significant opportunities for further investigation. The feasibility of these interventions remains to be validated through additional studies.

In summary, despite extensive research on RBI over the past few decades, numerous critical issues remain to be addressed. These include elucidating the comprehensive mechanisms underlying RBI, developing effective preventive strategies, improving early detection rates, refining treatment methodologies, and enhancing the efficacy of radiotherapy. These challenges persist as significant obstacles within this field.

Disclosure of conflict of interest

None.

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