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Research Article

Progress in the Pathogenesis and Treatment of Radiation-Induced Brain Injury

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Abstract: Malignant tumors are one of the serious public health problems that threaten the survival time of human beings. They are prone to metastasis to distant organs and the central nervous system is one of the common target organs. As it is difficult for chemotherapeutics, targeted drugs and other macromolecules to pass through the blood brain barrier (BBB), local radiation therapy is often used for treating intracranial primary or metastatic tumors. However, whether it is whole brain radiation therapy (WBRT) or stereotactic body radiation therapy (SBRT), the choice of radiation dose is limited by the side effects of radiation therapy on the surrounding normal brain tissues. Radiation-induced brain injury (RBI) can further develop into radiation necrosis (RN) in the late stage. Bevacizumab is often effective against RBI by antagonizing vascular endothelial growth factor (VEGF), but it still cannot completely reverse RN. Emerging treatment options such as human pluripotent stem-cell transplantation have made it possible to reverse the process of RN.

Keywords: radiation brain injury; radiation necrosis; VEGF; stem cell transplantation

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Currently, a variety of radiotherapy modalities have been applied to the treatment of nasopharyngeal carcinoma, high-grade intracranial primary tumors (such as glioma) or metastases, as well as the treatment of epilepsy and refractory pain[1]. It is considered to be the most effective treatment besides surgical procedures. Although radiotherapy can significantly improve the symptoms of the central nervous system, it inevitably leads to the occurrence of radiation-induced brain injury (RBI) as the irradiation area covers part of the normal brain tissue, which not only results in tissue and organ dysfunctions, but also limits the dose selection of radiotherapy[2]. There are different opinions on the exact pathogenesis of radiation-induced brain injury. This paper will comprehensively describe the pathological mechanism, clinical manifestations, and latest progress in the diagnosis and treatment of RBI.

1 Pathogenesis

The occurrence of RBI is the result of multiple factors. The exact pathogenesis of RBI is still inconclusive. The following pathogenic mechanisms are widely recognized.

1.1 Vascular Injuries

A large number of previous experiments have studied the histological characteristics of microcirculation damage caused by radiation, including the destruction of endothelial cells, the loss of tight junctions between cells, the formation of thrombus in microvessels, and the decrease in blood vessel density[3-6]. The most important factor leading to these pathological changes is the pathological up-regulation of vascular endothelial growth factor (VEGF), resulting in the increase of the blood brain barrier (BBB) permeability, microcirculation disorders, and brain edema. It is also positively

correlated to the dose of radiotherapy. If it is not intervened in time, the late stage may cause brain parenchymal necrosis due to cerebral ischemia and hypoxia[7]. Nordal et al.[8] studied the mechanism of radiation damage to the central nervous system by constructing a rat radiation spinal cord injury model. The study believes that poor recovery of central nervous system symptoms (such as cerebral edema, cerebral hypoxia, paralysis, etc.) after radiotherapy is not caused by a single factor of VEGF. Astrocyte activation, VEGF, hypoxia-inducible factor-1 (Hypoxia-inducible factor-1, HIF-1) overexpression and other pathological characteristics altogether lead to central nervous system damage in the rats after radiotherapy. And the immunofluorescence double staining method further confirmed the interactions between the three, that is, activated astrocytes secreted HIF and VEGF in the hypoxic area of the brain after irradiation. By comparing VEGF wild-type mice and VEGF transgenic mice, Zhou et al[9]. proved that even without radiotherapy, the increase in BBB permeability and the angiopoietin-2 (angiopoietin-2, The high expression of Ang-2) and the low expression of cytoplasmic tight junction protein-1 (zonula occludens-1, Zo-1) can still be observed in the latter. As Ang-2 and Zo-1 are considered to be involved in maintaining the integrity of the BBB, it was thought that VEGF overexpression is an independent factor leading to microcirculation disorders. Nonoguchi et al[10]. believed that the secretion of VEGF by activated astrocytes is not only limited to the acute phase of RBI, but it is also a common cause of late radiation necrosis (RN) and peripheral angiogenesis.

1.2 Glial cell damage

Astrocytes, microglia, and oligodendrocytes are the most common glial cells in the central nervous system. They are all sensitive to radiation. The activation of glial cells can be observed as early as the acute phase of RBI, and it occurs throughout all stages of RBI. The podocytes of astrocytes participate in the formation of BBB. The direct damage of radiation to astrocytes further destroys BBB, and at the same time promotes its secretion of HIF-1, VEGF and other cytokines to further aggravate brain edema after radiation, causing brain parenchymal hypoxia and exacerbates the damages[11-13]. Microglias are the main immune defense cells of the central nervous system and they are involved in the maintenance of homeostasis. They have also been shown to be the main cells of the neuroinflammatory response after radiation[14-16]. Xu et al.[17] irradiated microglias in vitro and found that nuclear factor-KBm (NF-KB) signal transduction pathway can be observed after 3 hours of irradiation to stimulate microglia to secrete multiple inflammatory cytokines, and it was dose-dependent. The demyelination of white matter oligodendrocytes is an important cause of long-term cognitive dysfunctions, emotional disorders and memory loss[18, 19]. Many studies have confirmed that the damage of hippocampal neurons can cause varying degrees of loss in spatial memory and learning ability[20, 21], even fractional irradiation can still cause the hippocampus-dependent cognitive function to decrease, but it can reduce the activation level of microglia[22, 23].

1.3 Neuroinflammatory Response

Animal studies and clinical trials have shown that neuroinflammatory response is a non-specific response of the central nervous system to injuries, and it also plays an important role in RBI. Sharp et al.[24] believed that the migration and infiltration of inflammatory cells in the non-irradiated area is an important contributor to RBI in the irradiated area. A single exposure in vivo or in vitro can cause an increase in multiple inflammatory factors[25]. Michael et al.[11] further studied the relationship between the inflammatory response of the central nervous system and the radiation dose-time. The brain of C57BL/6 mice was irradiated with a dose greater than 15Gy, and the up-regulation of transcription levels of multiple inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-A (TNFA) and transforming growth factor B (TGFB), and the acute infiltration of neutrophils were observed after 4 hours, indicating that there are two-way or multiple inflammatory reactions in the central nervous system during the acute phase of RBI. The study also detected the accumulation of CD-11-positive T lymphocytes in the white matter of the brain during the delayed RBI period (after 1 month of irradiation).

2 Clinical Manifestations

According to different clinical manifestations, RBI can be divided into three stages: acute, delayed and late[26, 27]. The acute phase and the early delayed phase are mainly demyelinating diseases such as

lethargy, drowsiness, and symptoms of intracranial hypertension induced by cerebral edema, such as dizziness and headache. In severe cases, brain herniation may occur. Most of the lesions are reversible, and the symptoms can relieve by themselves[28]. Different from the acute phase and the delayed phase, late RBI mainly manifests as radiation necrosis (RN) caused by local or diffuse neuronal necrosis, mild to moderate cognitive dysfunctions, emotional disorders and memory loss. Both stages develop progressively and are irreversible. They are more pronounced in patients with extensive hippocampal damage, which severely affects the patient's recovery and quality of life[29-33].

3 Progress in Treatment

Traditional treatment methods include surgical treatment, dehydrating agents (mannitol), anticoagulants, steroid hormones, neuroprotective agents, and traditional Chinese medicine, etc., which have certain alleviating effects on acute RBI, but the efficacies are quite low. VEGF monoclonal antibody (bevacizumab) and emerging treatment options such as virizumab and human pluripotent stem cell transplantation have made it possible to reverse the RN process[10, 34-38]. It should be pointed out that the new quinolone antibiotic EHQA can reduce the activation level of IL-7 due to its anti-inflammatory and immunomodulatory effects. Its therapeutic effects on RBI remain to be further studied[39].

3.1 Anti-VEGF Treatment

Thrombosis and increased permeability in the microcirculation induced by overexpression of VEGF are important factors leading to cerebral edema in the acute phase of RBI. The specific receptor of VEGF is vascular endothelial growth factor receptor (VEGFR), which has three subtypes of VEGFR1, VEGFR2, and VEGFR3. VEGF mainly combines with VEGFR2 to exert its physiological effects[40]. Bevacizumab is a recombinant monoclonal antibody. Due to its highly antagonistic properties on VEGF, it can block the phosphorylation after the combination of VEGF and VEGFR and inhibit signal transduction. It has been widely used in treatment to relieve cerebral edema in the acute phase of RBI[41, 42]. A large number of in vivo and in vitro experiments have proved that the efficacy of bevacizumab for RBI is not limited to improving acute cerebral edema, but it also has considerable efficacy for advanced RN[31, 43]. Yonezawa et al.[44] used magnetic resonance imaging (MRI) and 11C-methionine positron emission tomography (MET-PET) to evaluate the clinical imaging changes and morphological changes of the application of bevacizumab in the treatment of advanced radiation brain necrosis. The reduction of lesion/normal tissue ratio (lesion/normal, L/N) after applying bevacizumab can be observed in all patients with RN confirmed by imaging studies. It can be seen from the above that the imaging evaluation of the microcirculation after radiation is being increasingly recognized as the most critical factor in predicting the recovery of the RBI acute phase.[45] Bevacizumab used in the treatment of RBI can not only repair BBB, reduce microvascular permeability, and improve the microvascular environment, but also inhibit immune response and inflammation. Emerging anti-angiogenic drugs are being released one after another, and whether they can relieve cerebral edema in the acute stage of RBI remains to be further explored.

3.2 Hyperbaric Oxygen Therapy

Currently, the most effective auxiliary modality for the treatment of acute RBI is hyperbaric oxygen treatment (HBOT), which improves the permeability of the microcirculation and relieves cerebral edema in the acute phase of RBI[46]. Synchronous combination of HBOT with drug therapy such as anticoagulant drugs, hormones, and vitamin E, etc., is also a widely used treatment method. As hormones reduce cerebral edema, they are often combined with HBOT, but the effects are not satisfactory[10, 47-49]. In summary, HBOT can improve the symptoms of RBI, but it still requires combination with drugs and is only recommended as an adjuvant therapy in the recovery period.

3.3 Stem-cell Transplantation Treatment

Stem cell transplantation therapy is currently an emerging field in the treatment of RBI. Previous experiments have found that when the tissue is damaged, stem cells can migrate to the damaged site, differentiate and repair the damaged tissue[50]. Depletion of neural stem cells and progenitor cells can inhibit neurogenesis, induce neuroinflammation, and cause serious consequences such as damage to neuronal structure[51-54]. Stem cell transplantation has benefited mice with cognitive impairment after radiotherapy and improved their neurodegeneration[55-59], but there is no unified

standard for the transplantation time window, resulting in different treatment effects. Through animal experiments, Acharya et al.[60] reported the beneficial effects of transplanting induced pluripotent stem cell-derived (iPSC-derived) human neural stem cells (hNSCs) into the brain of irradiated mice on cognitive functions. Experimental data shows that transplantation during the delay time after the initial injury is the most beneficial. The best transplantation time window is 1 month after injury. It also helps to reduce the host's brain graft rejection. Standardizing the transplantation time window and improving efficiency are still worthy of further study.

3.4 Nursing Care for Neurological Disorders

In clinical work, due to the long course of craniocerebral radiotherapy, patients will most likely experience the transition from acute to delayed or late stage of RBI, develop symptoms of intracranial hypertension caused by cerebral edema (such as vomiting, headache, optic nerve head edema and even brain herniation), changes in personality and cognition, and even brain necrosis. Due to the complex and changeable symptoms and a long time span, it is necessary for nursing staff to strengthen the care for the patient's consciousness, blood pressure, heart rate, and respiratory rate, pay attention to the patient's 24-hour fluid intake and output during the treatment process using mannitol and other dehydrating agents, and closely monitor the patient's urine properties to avoid urinary adverse events. Once there is an abnormal increase in blood creatinine, stop in time. Steroid hormones are one of the important treatment modalities to fight neuroinflammation in the delayed phase of RBI. As they can easily lead to an increase in blood sugar, they should be used with caution in patients with diabetes. For patients who have suffered from peptic ulcers in the past, we should pay close attention to the presence of black stools and bloody stools, which should be sent for regular stool examinations in time to avoid hypovolemic shock due to blood loss. As targeted drugs such as bevacizumab have partial cardiotoxicity, one-person-one-monitor policy should be strictly implemented during use. Meanwhile, pay attention to the management of skin and mucous membrane during radiotherapy by administrating appropriate combination of radiation protection agents to avoid skin and mucous membrane ulceration caused by the adverse reactions of radiotherapy. Pay attention to changes in the patient's blood routine. If there is a significant decrease in platelets, raise the level of care in time to prevent patient falling from bed. Do good jobs in patient psychological care, enhance communication, and assist patients in successfully completing the treatment process.

4 Conclusion

Microcirculation disorders, intravascular thrombosis, increased permeability of the blood-brain barrier, long-term cognitive dysfunctions, and radiation brain necrosis after radiotherapy are important factors leading to poor prognosis of RBI. Due to its toxic side effects that cannot be ignored, it is very crucial to seek effective prevention and treatment measures. Although the mechanism of RBI has not been accurately explained, it cannot be summed up by monism alone. It is the result of the interactions of multiple processes. Meanwhile, individual differences between patients, previous diagnosis and treatment processes are also factors that cannot be ignored. In general, the prevention of RBI is better than the treatment of RBI. At the same time, personalized treatment schemes should be developed for different patients.

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