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Review

Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis?

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ABSTRACT

Radiosurgery is an important non-invasive procedure for the treatment of tumors and vascular malformations. However, in addition to killing target tissues, cranial irradiation induces damage to adjacent healthy tissues leading to neurological deterioration in both pediatric and adult patients, which is poorly understood and insufficiently treatable. To minimize irradiation damage to healthy tissue, not the optimal therapeutic irradiation dose required to eliminate the target lesion is used but lower doses. Although the success rate of irradiation surgery is about 95%, 5% of patients suffer problems, most commonly neurological, that are thought to be a direct consequence of irradiation-induced inflammation. Although no direct correlation has been demonstrated, the appearance and disappearance of inflammation that develops following irradiation commonly parallel the appearance and disappearance of neurological side effects that are associated with the neurological function of the irradiated brain regions. These observations have led to the hypothesis that brain inflammation is causally related to the observed neurological side effects. Studies indicate that hyperbaric oxygen therapy (HBOT) applied after the appearance of irradiation-induced neurological side effects reduces the incidence and severity of those side effects. This may result from HBOT reducing inflammation, promoting angiogenesis, and influencing other cellular functions thereby suppressing events that cause the neurological side effects. However, it would be significantly better for the patient if rather than waiting for neurological side effects to become manifest they could be avoided. This review examines irradiation-induced neurological side effects, methods that minimize or resolve those side effects, and concludes with a discussion of whether HBOT applied following irradiation, but before manifestation of neurological side effects may prevent or reduce the appearance of irradiation-induced neurological side effects.

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Introduction

Since 1987, more than 500,000 patients in North America have undergone stereotactic radiosurgery, subsequently referred to as irradiation, for the management of a variety of brain disorders, including tumors, vascular malformations, pain, movement disorders and epilepsy. Irradiation is now considered a mainline intervention and is often used as an alternative to more conventional invasive neurosurgical procedures.

Irradiation-induced inflammation, tissue necrosis and neurological deficits

Whole brain radiation carries the serious risk of neurotoxicity in about 90% of patients, with the extent of tissue necrosis increasing with the increasing volume of radiated tissue. However, the extent of tissue necrosis and the severity and types of side effects induced by irradiation can be reduced by using focal irradiation such in stereotactic Gamma Knife surgery.

When following irradiation, the irradiated site is examined using T2-weighted magnetic resonance images (MRI), 36% of patients manifest an increased signal around the irradiation site (Mahadevan et al., 2011; Yen et al., 2010). Clinically this signal is generally interpreted as irradiation-induced brain inflammation changes associated with tissue swelling, neuron death and neurological losses (Son et al., 2001; Stancanello et al., 2009; Wanebo et al., 2009; Wu et al., 2009; Yen et al., 2010). The appearance and disappearance of inflammation seen in T2-weighted magnetic resonance images are frequently associated with the appearance and disappearance of necrosis (Stancanello et al., 2009; Yen et al., 2010). This observation led to the hypothesis that irradiation-induced inflammation underlies, or is causally related to, the appearance and disappearance of tissue necrosis and the manifestation of neurological deficits.

Depending on the tissue irradiated and the extent of tissue necrosis that develops, various side effects and neurological deficits may manifest including mental deterioration, progressive dementia, loss of memory, headache, fatigue, nausea and vomiting sleepiness, dry-mouth, altered sense of taste, blurry vision, loss of hearing and ataxia (Chan et al., 2003; Chin et al., 2000; Tuan et al., in press). However, when irradiation is used to destroy tumors, such as Schwannomas, intimately associated with nerves, such as the trigeminal, optic, occulomotor, olfactory or acoustic, the irradiation can lead to nerve demyelination and degeneration, fragmentation, or loss of axons (Vernimmen et al., 2009; Yeung et al., 2009). This nerve damage can result in even greater neurological deficits since the neurological functions of the damaged nerves are permanently lost causing deafness, loss of taste, blindness, and with trigeminal nerve damage, the loss of sensation in the face, and certain motor functions such as biting, chewing, and swallowing (Akamatsu et al., 2010; Arvold et al., 2009; Dea et al., 2010; Lesser et al., 2010; Petsuksiri et al., 2011; Vernimmen et al., 2009; Zakrzewska and Akram, 2011). The presence of necrosis can be documented by performing biopsies on the irradiated tissue areas (Chuba et al., 1997). Radiation-induced necrosis is generally considered irreversible (Delanian and Lefaix, 2004; Przybyszewska et al., 2011; Wang et al., 2009).

Following the manifestation of irradiation-induced necrosis, the major clinical interventions are steroid treatment, decompression, and hyperbaric oxygen therapy (Djalilian et al., 2007; Foroughi et al., 2010; Narozny et al., 2005; Spiegelberg et al., 2010). However, additional methods will also be discussed that can be used in attempts to slow or block the manifestations of inflammation and necrosis.

Presently there is no way of anticipating which irradiated patients will manifest irradiation-induced inflammation and neurological side effects (Wanebo et al., 2009). Therefore, clinically one is forced to wait and see which patients manifest inflammation, tissue necrosis and neurological deficits. Of brain irradiated patients who show edema, 33% are asymptomatic for clinical manifestations of neurological deficits (Geraci et al., 1993). However, even though irradiation induces significant peritumoral cerebral edema, or a worsening of a preexisting edema, reducing the edema results in a better quality of patient life, but not longer patient survival (Kosower et al., 1980).

Irradiation-induced inflammation and normal brain tissue necrosis are the main risk factors associated with brain irradiation, with the neurological side effects being more frequent and appearing earlier following higher total irradiation doses and at higher doses per fraction (Clavo et al., 2009). Irradiation-induced brain injury is a complex and dynamic process involving all cells in the brain, including endothelial and oligodendroglial cells, astrocytes, microglia, neurons, and neuronal stem cells. The symptoms of irradiation-induced brain injury may be acute, subacute, or chronic, occurring hours, days, weeks, months, and even years after irradiation exposure (Butler et al., 2006). Because of the increasing application of irradiation, and the fact that irradiated patients survive for many years following irradiation, its potential risks and benefits have become more widely known, especially for cases in which the damage is manifest only at long times, up to years, post irradiation. Therefore, rather than wait for irradiation-induced necrosis to become manifest, it is important to identify methods that can prevent, reduce or eliminate irradiation-induced triggers that lead to tissue damage and thereby prevent the development of necrosis.

Only a few techniques are currently used clinically for providing protection against irradiation-induced brain injury, and these involve a multidisciplinary approach using pharmacologic, behavioral, and rehabilitative therapies. However, given the prevalence of brain neoplasms and the high incidence of irradiation-induced negative symptoms, more clinical research is essential to address these important clinical problems.

This review starts with an examination of neurotoxic factors associated with irradiation, including cytokines, prostaglandins (PGs), and nitric oxide (NO) that lead to inflammation, neurotoxicity and neurological side effects. It then discusses methods that reduce irradiation-induced changes, and an examination of evidence indicating