Clinical Neurology and Neurosurgery 184 (2019) 105444

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Viable treatment options for patients with symptomatic radiation necrosis treated with stereotactic radiosurgery and immunotherapy

Dear Editor,

We have read, with great interest, the recently published article by Weingarten et al. entitled, "Symptomatic radiation necrosis in brain metastasis patients treated with stereotactic radiosurgery and immunotherapy" [1]. Immune checkpoint inhibitors (ICIs) have demonstrated clinical benefit in phase III trials and have become first- or second-line therapy for many cancers that metastasize to the brain (e.g., lung, melanoma, and renal cell carcinoma) [2,3]. With the increase in usage of ICIs, several retrospective studies have demonstrated an increased rate of development of radiation necrosis (RN) in patients treated with stereotactic radiosurgery (SRS) and an ICI compared with SRS alone [4,5]. As the first paper to establish the incidence of symptomatic RN with histopathologic confirmation, Weingarten et al. [6] present useful insight into the association of symptomatic RN with SRS and ICIs in patients with brain metastases. In this retrospective cohort of 57 patients with brain metastases treated with both SRS and an ICI, 7% developed symptomatic RN, comparable to the 7–10% rate of RN in patients treated with SRS alone. There is some equipoise in the limited data at hand, and more data will be required to determine whether treatment with SRS and ICI confers a higher incidence of symptomatic RN. Nevertheless, given that a growing number of patients with brain cancer treated with SRS will also receive an ICI, it is important for treating physicians to be aware of all of the treatment modalities available for RN.

Corticosteroids are considered first-line treatment in patients with RN who present with cerebral edema and worsening symptoms [7]. For example, Shaw et al. [8] demonstrated improved neurologic symptoms in a patient with RN when treated with corticosteroids. It is believed that corticosteroids have the potential to reduce edema, deleterious cytokine response, and permeability of the blood–brain barrier [8]. Although efficacious, prolonged corticosteroid use is associated with known complications such as myopathy, Cushing syndrome, osteopenia, hypertension, and glucose intolerance; this has resulted in the medical community identifying other approaches to treating RN [7].

VEGF inhibitors such as bevacizumab (BVZ), an anti-VEGF monoclonal antibody, have demonstrated therapeutic promise. VEGF plays a role in edema and breakdown of the blood–brain barrier after damage from radiation. To that end, BVZ has been shown to be an effective therapeutic agent. Wang et al. [9] reported on 17 patients with RN refractory to corticosteroids who were subsequently treated with BVZ. These patients demonstrated a 48.4% decrease in T2 signal on magnetic resonance imaging scans, reduction in corticosteroid usage by 4 weeks, and clinical improvement in 16 of 17 patients. Corroborating these findings, a multi-centered randomized controlled trial by Xu et al. [10] analyzed 112 patients with RN treated with either BVZ or corticosteroids. The authors found that the patients treated with BVZ demonstrated better radiographic and clinical improvement compared with the corticosteroid group. Although the cost and incomplete side-effect profile may be deterrents to its use, there are more than 40 published studies demonstrating the effectiveness of BVZ, and it should be considered when talking to patients about treatment options [7].

In addition to VEGF inhibitors, there has been literature reporting the efficacy of hyperbaric oxygen therapy (HBOT) in treating RN. In theory, increasing brain oxygen aids in angiogenesis and increases blood supply that is damaged by radiation. Aghajan et al. [11] demonstrated that 4 of 5 pediatric patients with RN who were treated with HBOT had both radiographic and clinical improvement. The median number of HBOT treatments in this cohort was 40. Furthermore, Ohguri et al. [12] published a retrospective cohort of 78 patients with RN and demonstrated that prophylactic usage of HBOT after SRS decreased the rate of RN by 9% when compared with the control group that did not undergo HBOT. In 2017, the European Consensus Conference classified HBOT for RN as type 3 and level C evidence, indicating that this evidence was derived from well-designed studies without randomization. Although there is insufficient evidence to definitively rule for or against the proposed treatment, it would be reasonable to consider for treating patients [13]. The prescribing provider should be aware that more data are needed to accredit this form of therapy because most published literature involves small sample sizes and patients taking steroids concurrently.

Resection may be considered when RN is causing substantial mass effect, is in noneloquent regions, or is refractory to medical treatment [14], but there is a high risk of complications. McPherson et al. [15] demonstrated a surgical morbidity rate of 54% in 11 patients who underwent resection of RN. Because of the morbidity and unclear survival benefits, the authors stated that surgery should be reserved for cases that are refractory to medical management. Grossman et al. [16] reported on 159 patients who underwent surgery for presumed tumor recurrence, of whom 18 patients were found to have RN rather than recurrence. When comparing the patients with actual tumor recurrence and those with RN, surgical removal carried no survival advantage. The main advantage offered by surgery is confirmation of the diagnosis by histopathological analysis.

In cases not amenable to resection, laser interstitial thermal therapy (LITT) is a new form of therapy showing therapeutic promise. LITT is used for laser-guided ablation of target lesions. A laser probe is centered in the lesion to produce thermal damage, thereby creating an area of coagulative necrosis. Rahmathulla et al. [17] published a case report of a 74-year-old patient with RN that was refractory to corticosteroids, was in a location not amenable to resection, and had many comorbidities that obviated surgery. The patient received LITT and was discharged 48 h postoperatively; imaging at his 7-week follow-up showed significant resolution of the mass effect. Corroborating these findings, Hong et al. [18] analyzed outcomes in a retrospective cohort of patients with RN treated with LITT versus resection. Although only 33 patients

https://doi.org/10.1016/j.clineuro.2019.105444
Received 22 May 2019
Available online 14 July 2019
0303-8467/

with RN were analyzed, the authors found comparable results in neurologic outcome and ability to taper off steroids. LITT appears to demonstrate therapeutic promise, but further studies using larger, prospective trials are needed.

We applaud the authors Weingarten et al. on their paper analyzing the association of SRS and ICIs with symptomatic RN in brain metastases patients. Given that a growing number of patients with metastatic brain cancer treated with SRS will also receive an ICI, it is important for treating physicians to be aware of all of the treatment modalities available for RN. Although corticosteroids are the first-line therapy, there may be some therapeutic benefit with VEGF inhibitors, LITT, and HBOT. In cases refractory to medical therapy, surgery is still an option. We hope that this review of treatment options will help providers discuss the potential risks and benefits associated with the various treatment options with their patients and thus help guide treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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