Editorial Commentary

Coming of age of bevacizumab in the management of radiation-induced cerebral necrosis

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Radiotherapy is an integral modality in the curative treatment of head and neck and nasopharynx cancers (NPCs) (1). Nonetheless, despite the advent of more conformal techniques of radiation delivery, head and neck cancer patients still suffer from late adverse events, which include potential debilitating neurological injury like cranial neuropathies and radiation-induced brain necrosis (RN). In particular for the management of the latter, protracted use of high dose corticosteroids has been the conventional treatment for RN, albeit with limited efficacy and significant side effects. Additionally, evidence surrounding other treatments such as hyperbaric oxygen and anticoagulation is scant and based on uncontrolled case series (2).

The past decade has seen an accumulation of evidence supporting the benefit of bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), in the treatment of RN. Examples include an observational study by Gonzalez and colleagues who reported 100% response rate to bevacizumab alone or in combination with other agents in eight patients with RN post-radiotherapy for malignant gliomas (3). Similarly, Wong *et al.* described the therapeutic effect of bevacizumab in an NPC patient who presented with symptomatic temporal lobe necrosis following definitive radiotherapy (4). Furthermore, in a placebo-controlled, double-blinded, randomised trial involving 14 patients performed by Levin *et al.*, all bevacizumab-treated patients experienced a marked durable improvement in patient-reported and physician-assessed symptoms (5). However, there remains considerable debate if bevacizumab is merely acting as a 'super steroid'. On this note, while the complex mechanisms of radiation-induced injury are not fully elucidated, the common understanding is that radiation necrosis stems from endothelial cell injury resulting in hypoxia and subsequently necrosis; this is followed by chemotaxis of inflammatory and immune cells accounting for the cerebral edema and imaging changes which are often associated with clinical neurological dysfunction. The onset of radiation necrosis is thus thought to be fundamentally driven by the upregulation of VEGF (6). As such, the use of bevacizumab in this setting should in theory, target the initiating mechanism and potentially reverse the course of RN as opposed to high dose steroids, which merely modulates the inflammatory process.

The randomised controlled trial by Xu and colleagues is therefore seminal given that it is the first head-to-head comparison between bevacizumab (5 mg/kg, once every two weeks and total of four cycles) and corticosteroids on the therapeutic effect for RN (7), thereby formally testing this scientific hypothesis. It is also the largest randomised controlled trial of its kind (N=112), and crucially, the study cohort is comprised of a homogeneous subgroup of NPC patient's post-radiotherapy who presented with symptomatic radionecrosis and no active intracranial cancer. This cohort avoided the diagnostic conundrum, which plagued the earlier studies that included patients with

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intracranial tumours; in these patients, there were often imaging uncertainty in distinguishing radiation necrosis from active tumour, and histological confirmations were not always feasible (8). The results showed that patients treated with bevacizumab demonstrated a significant improvement on radiology (assessed by both reduction of T2 flair and T1+ gadolinium signal intensities), as well as modest but significant improvements in cognitive function based on MoCA and SOMA than the control group treated with steroids alone. From a clinical standpoint, it also demonstrated the overall tolerability of bevacizumab and feasibility of omitting corticosteroids in bevacizumab-treated patients, thereby avoiding cumulative toxicities in the management of radionecrosis. This and other prior prospective studies thus provide good level I–IIa evidence to support the use of bevacizumab for the management of RN, and enhance our understanding to the pathogenesis of cerebral RN.

Nonetheless, there are still residual caveats on the clinical use of bevacizumab for RN. Foremost, the optimal dosing of bevacizumab still needs to be defined. In the historical studies, the common dosing that was reported to be efficacious ranged from 5–10 mg/kg every 2 to 4 weeks for at least 2 cycles (5,9), while the trial by Xu *et al.* applied a dose of 5 mg/kg every 2 weeks limited to a total of four cycles. As the overall reduction in T1-post gadolinium volume of 25.5% is lower compared to prior studies, it is not clear if there is a dose-response effect of bevacizumab on RN, and if better, more durable responses may be achieved with a higher dose and longer course of treatment. Furthermore, earlier studies were performed in the context of intracranial tumours and stereotactic radiosurgery, and it is possible that there are mechanistic differences underpinning the RN in these patients; the differences in radiological response to bevacizumab between the trial by Xu *et al.* and historical studies may be a reflection of that. In fact, from published reports, interpatient heterogeneity in bevacizumab radiological response for RN ranged from 25.5–63% (3,5,7,10,11) and a proportion of patients experienced a recurrence of their RN (5,7), suggesting that patient selection for this expensive targeted therapy needs to be optimally defined. On this note, the same group by Tang and colleagues investigated for potential clinical predictors of bevacizumab efficacy on RN (12). Using a random forests model, they found that maximum radiation dose of the temporal lobe and the interval between initial radiotherapy and bevacizumab administration were highly ranked predictors for therapeutic effect. This work is indeed a nice follow-up to their earlier trial result, which now affords clinicians the ability to better select patients for bevacizumab in the management of RT-induced cerebral RN.

In summary, while future work will entail addressing the queries pertaining to optimal dosing, and refining better models by exploiting novel methods like radiomics to improve on patient selection, we commend Tang and colleagues for these advances, which have further shaped the clinical management of patients with this potentially debilitating radiation-induced complication.

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Footnote

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