Neuro-Oncology
23(2), 179–181, 2021 | doi:10.1093/neuonc/noaa273 | Advance Access date 2 December 2020

Can proton therapy reduce radiation-related lymphopenia in glioblastoma?

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See the article by Mohan et al, pp. 284–294.

Immune checkpoint inhibitors against cytotoxicT-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) have demonstrated unprecedented success for numerous solid tumors, but the overall survival (OS) results in glioblastoma (GBM) to date have been disappointing.[1] GBM possess complex immune-suppressive properties, including multiple nonoverlapping mechanisms to evade antitumor immunity.[2] One of the consistent immune-suppressive observations regarding GBM is a varying but frequent degree of systemic lymphopenia. Importantly, significant and prolonged lymphopenia can occur after radiation therapy (RT) and temozolomide (TMZ) in approximately 30%–40% of GBM patients and is independently associated with poor OS.[3,4] Multiple factors appear to contribute to this lymphocytopenic environment, including tumor-induced bone marrow sequestration of lymphocytes, brain volume exposed to intermediate dose of RT, overall corticosteroid exposure, concurrent and adjuvant temozolomide, etc. (Fig. 1).[4–7] As the partial-brain radiation field for GBM does not include the active bone marrow or much of the lymphatic system, its association with systemic lymphopenia is not immediately intuitive. Investigators from Johns Hopkins University were among the early pioneers to recognize and describe the association between RT dose/volume and lymphopenia in GBM.[8] A small randomized trial from India of large versus smaller volume RT for GBM demonstrated superior OS in favor of smaller volume RT.[9] Our group previously demonstrated that the volume of brain exposed to intermediate radiation doses of 15–30 Gy ($BrainV_{15–30Gy}$) is associated with grade 3 or higher lymphopenia (G3 + L, absolute lymphocyte count [ALC] < 500/μL) during chemoradiotherapy and that the reduction of $BrainV_{25Gy}$ (the most significant dosimetric factor) using a limited-field RT approach can reduce G3 + L compared to standard-field RT.[4,10] These retrospective single-institutional observations are considered hypothesis-generating and require external validation.

In this issue of *Neuro-Oncology*, Mohan et al provide these external validation data. They report a secondary analysis of their randomized phase 2 study comparing proton versus photon therapy for newly diagnosed GBM.[11] Proton therapy, which decreases the dose to uninvolved brain, was associated with a lower incidence of G3 + L (14% vs 39%, an absolute and relative risk reduction of 25% and 64%; $P = .024$) and higher nadir of ALC (860 vs 690; $P = .018$). Notably, they showed that $BrainV_{20Gy}$ is the most significant dosimetric factor associated with G3 + L and that proton therapy yields a lower $BrainV_{20Gy}$ than photon therapy (37% vs 54%; $P < .001$). In part, the variation between our observation of $BrainV_{25Gy}$ versus the current study observation of $BrainV_{20Gy}$ might be accounted for by the fact that 33% of the patients in the randomized study received proton therapy, and the average relative biological effectiveness (RBE) of proton beam on lymphocytes might be higher than the conventionally accepted value of 1.1.[12] Furthermore, volumetric computation drives this dosimetric parameter, and previous retrospective studies have used brain minus brainstem instead the whole brain for their dosimetric analysis.[4,10] In spite of these small computational differences, this well-designed randomized study validates the previous hypothesis that radiation exposure of the brain is a causative factor for G3 + L. It also demonstrates that reduction of radiation exposure using advanced technology such as limited-field proton therapy can further reduce the risk of G3 + L compared to limited-field photon therapy.

Since this randomized phase 2 study was not powered to evaluate impact on OS, definitive conclusion cannot be drawn regarding whether reduction of lymphopenia using proton therapy can translate to a higher OS. The ongoing NRG BN001 (NCT02179086), a much larger randomized study comparing dose-escalated proton therapy versus standard-dose photon therapy for newly diagnosed GBM, will examine whether improved lymphocyte sparing resulting in a more enhanced immune effect ascribable to proton therapy might increase OS.

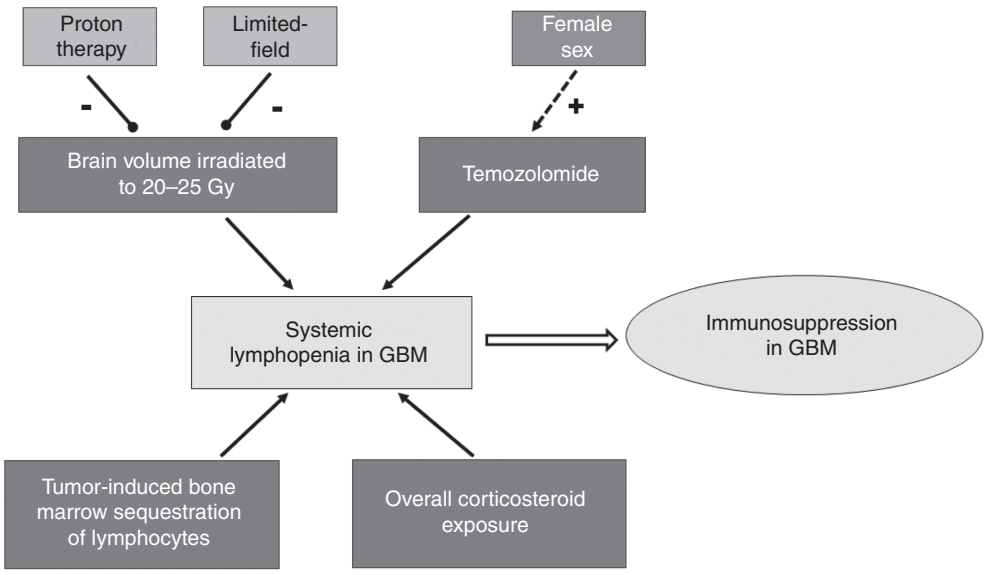

Fig. 1 Proposed causative factors that contribute to systemic lymphopenia in glioblastoma.

One additional implication from the current study is that proton therapy may be better suited to combine with immunotherapy. The potential synergy may be even more relevant once an active immunotherapy agent is discovered for GBM. In the meantime, the radiation oncology community should strive to optimize proton therapy with the development of intensity-modulated proton therapy and incorporate advanced imaging techniques to refine radiation field design. Overall, this study is the first to demonstrate that proton therapy can reduce treatment-related lymphopenia in GBM and adds valuable insights to our current understanding of the complex causes of systemic lymphopenia in GBM (Fig. 1). However, it also raises a few unanswered questions.

Although this study validates that radiation exposure to the brain directly contributes to G3 + L, the underlying mechanism remains unclear. Some proposed explanations include direct radiation killing of lymphocytes in the circulating blood or the brain lymphatics.[11] However, RT can also induce an indirect effect to cause systemic lymphopenia as extracorporeal irradiation of blood (without any radiation exposure to the body) can result in striking lymphopenia in dialysis patients.[13] Additional research is needed to elucidate the biological mechanism behind this indirect phenomenon.

Similar to previous retrospective studies,[4,6] this randomized study also observed that female sex is associated with a higher risk of G3 + L. One explanation may be different TMZ metabolism due to sex differences.[14] Detailed pharmacokinetic and pharmacodynamics studies of TMZ in male versus female patients may need to be conducted to optimize doses of TMZ. In the future, we may need to consider sex differences in the early stage of drug development and not uniformly assign the same maximum tolerated dose for both sexes.

Although this study did not find a correlation between G3 + L and OS, this could be a function of inadequate power. However, their intriguing observation that female sex had worse G3 + L but higher OS highlights the possibility that lymphopenia may be a confounding factor rather than a causative factor to drive worse OS in GBM. As an analogy, one may imagine that G3 + L may be the canary in a coal mine of the complex immunosuppressive environment created by GBM. Additional basic and translational research should be conducted to better understand the underlying mechanism, which may be the key to improve immunotherapy success for GBM in the future.

Acknowledgment

This editorial is the sole product of the author(s) and that no third party had input or gave support to its writing.

Conflict of interest statement. J.H. reports research support from Pfizer. M.M. reports consulting with Mevion, Karyopharm, Tocagen, Astra-Zeneca, and Blue Earth Diagnostics, and serves on the Board of Directors of Oncoceutics.

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