Letter to the Editor

Radiation-induced lymphopenia may negatively affect outcomes in patients receiving PD-1 directed immunotherapy

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We thank the editors for the invitation to contribute to *Therapeutic Radiology and Oncology* and Chen *et al.* for their excellent piece "Key immune system markers in immunotherapy: absolute lymphocyte count, neutrophil to lymphocyte ratio, and alternative immune system metrics" in which they discuss our recently published work, "The Impact of Radiation Therapy on Lymphocyte Count and Survival in Metastatic Cancer Patients Receiving PD-1 Immune Checkpoint Inhibitors" (1).

Indeed, it is becoming increasingly clear that the combination of CTLA-4- or PD-(L)1-directed immune checkpoint inhibitors (ICI) and radiation therapy (RT) is largely safe (2,3), and in the setting of the otherwise excellent systemic disease control that can be attained with these drugs in the setting of diseases such as NSCLC, renal cell carcinoma, and metastatic melanoma, definitive and/or ablative irradiation of gross disease may confer an overall survival benefit (4-6). Likewise, in preclinical models and limited clinical case series, it has been shown that the combination of RT and ICIs has the potential to yield so-called "abscopal responses" through neoantigen release, the diversification of the T cell receptor (TCR) repertoire, and both local and systemic effects on cytokine release (7-12). To date, clinical abscopal responses are uncommon, but we eagerly await the results of ongoing combination studies for evidence of increased activity as well as deeper and more informative translational correlate studies that might identify means by which to modulate these responses.

However, we and others have recently shown that RT also has the potential for harm in the setting of treatment with PD1-directed ICI (1,13). In our recently published study, we analyzed a cohort of 110 patients with metastatic NSCLC, melanoma, or renal cell carcinoma, who had received either of the approved PD-1 directed ICIs, nivolumab or pembrolizumab, as well as palliative RT as part of standard of care. We found that receipt of prolonged courses of extracranial RT was associated with the development of severe lymphopenia (<500 cells/μL), which often persisted for many months, and elevated neutrophil to lymphocyte ratio (NTL), and that this lymphopenic state at the time of initiation PD-1 directed ICI was associated with poor overall survival (1). As Chen *et al.* correctly point out, this work suggests that radiation-induced lymphopenia may impact oncologic outcomes in patients receiving PD-1 ICI. Limitations of this work include retrospective design, heterogeneous patient population, and lack of data on other endpoints such as progression free survival, cancer-specific survival or competing risks. In addition, we point out that the association of NTL with survival was weaker than the association of severe lymphopenia with survival, and that the former association was lost when a multivariable analysis was performed including other factors known to be associated with survival, such as performance status and albumin. We speculate that this difference may be due to the multitude of confounding causes for elevated neutrophil count, such as receipt of corticosteroids, infection, and systemic inflammation.

Mechanistically, RT-induced lymphopenia could affect

the efficacy of PD-1 directed ICI in several ways. Firstly, direct killing of CD8+ T effector cells, which are thought to be the primary mediators of tumor cell eradication could occur in the irradiated tumor microenvironment as well as in abutting normal tissues, lymph nodes, and circulating blood. Recent modeling studies have determined that the volume of irradiated blood pool could play an important role, and suggest that the total volume receiving low dose to be an important determinant of lymphopenia (14,15). Thus, RT to a tumor, although effectively eradicating cancer cells and releasing antigen for further T cell diversification, could also plausibly preferentially kill exhausted tumor-infiltrating lymphocytes that would be expected to exact cell mediated cytoxicity through disinhibition with a PD-(L)1 inhibitor. However, it should be noted that preclinical data to this point have suggested contradictory effects with potential activation of tumor resident T cells (16). Secondly, recent data suggests that T regulatory cells may be resistant to RT and could in fact be drawn to the site of irradiation via unclear mechanisms (17-19). Likewise, immunosuppressive myeloid-derived cells also appear to be relatively radioresistant, and thus could further push the balance towards immunosuppression (20,21). Thus, the culmination of these effect may result in a systemic deficit of cytotoxic T cells and an abundance of tumor specific T regulatory cells and myeloid-derived immunosuppressive cells, which could in sum abrogate any beneficial effects of RT on IO, or worse.

Ultimately, these results, though intriguing, are hypothesis-generating and warrant deeper evaluation through prospective study. We suggest that trials which include both radiation and ICI consider the inclusion of rigorous correlate studies to evaluate the potential positive and negative effects of radiotherapy on the lymphoid compartment and the resultant efficacy of ICIs.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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