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In Regard to Smart et al

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I first wish to congratulate Smart and colleagues for providing an excellent report that adds to the dearth of literature focused on mucosal melanoma.[1] Combination therapy, especially with immunotherapy, is undoubtedly a central topic at the frontier of our expanding novel radiotherapeutic armamentarium. This is especially true in disease such as mucosal melanoma that does not display good clinical response to immune checkpoint inhibitors (ICIs). Tantalizing fundamental biologic questions also emerge from such work.

In the report by Smart and colleagues, 37 patients received immunotherapy, either cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (8%), programmed cell death protein 1 (PD-1/PD-L1) (51%), or a combination of both (41%). Immunotherapy was provided before radiation therapy (RT) for 5 patients (14%), concomitantly with RT for 9 patients (24%), after RT for 5 patients (14%), and at recurrence or metastasis in 18 patients (49%).[1] There was frank heterogeneity in the timing of immunotherapy use, which is coherent with reports from other groups. The authors have done a great job of trying to unveil associations between outcomes and treatment variables. However, although implicitly of limited validity, further dissecting the timing of ICI use with RT could be of interest, especially in melanoma.

The work of Karras and colleagues has shown that distinct cellular populations display specific cell fate in melanoma.[2] Cells poised to grow rapidly do not possess the intrinsic phenotypic competency of metastatic dissemination, an ability that appears circumscribed to another subpopulation. These authors also suggest that these capabilities can be dynamically altered, contingent upon the immune microenvironment within which cells are embedded.

It would be interesting to determine whether ICI timing (pre-, post- or intratreatment) could modify local control or alter tumoral ability to disseminate systemically through selective inhibitory pressure on a subpopulation of melanoma cells. Alternatively, perhaps the immunomodulatory effects of ICI could, depending on their timing with RT, promulgate this dynamic regulation of a melanoma subcellular population's phenotypical switch. This could alter systemic response to RT (abscopal) in these lesions. For example, concomitant PD-1 blockade has been suggested to potentiate the abscopal effect, specifically in melanoma,[3] and RT could potentiate ipilimumab in patients with non-small cell lung cancer, possibly in an abscopal-dependent way.[4] Contrarily, phenotypical switching to mesenchymal-like cells with heightened metastatic potential and reduced proliferative capabilities could hinder RT response,[5] which could drive differences in local as well as distant recurrences.

More work is needed to uncover the nuanced and intricate interplay between microenvironment, ICIs, melanoma cells, and radiotherapeutic effects. Such improved understanding could benefit patients by improving local control or preventing systemic recurrence.

Disclosures

The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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