



Dual angiogenesis and PD-1 blockade in hepatocellular carcinoma

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Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Comment on: Shigeta K, Datta M, Hato T, *et al.* Dual Programmed Death Receptor-1 and Vascular Endothelial Growth Factor Receptor-2 Blockade Promotes Vascular Normalization and Enhances Antitumor Immune Responses in Hepatocellular Carcinoma. *Hepatology* 2020;71:1247-61.

Submitted Oct 21, 2019. Accepted for publication Nov 28, 2019.

doi: 10.21037/hbsn.2019.10.37

View this article at: <http://dx.doi.org/10.21037/hbsn.2019.10.37>

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer related-death worldwide and its incidence is rising in most western countries (1). The majority of patients are unfortunately diagnosed with advanced disease not amenable to curative therapies such as surgical resection, percutaneous ablation or liver transplantation. The approved systemic therapies (including sorafenib, lenvatinib or regorafenib) have limited survival benefits and the identification of effective new drugs and/or combinations is critical (1).

Immunotherapy, widely recognized as a major breakthrough in oncology, has revolutionized the therapeutic strategies of various solid and hematological tumors, such as melanoma, lung adenocarcinoma or Hodgkin's lymphoma. We had high hopes in immunotherapy for the treatment of patient with advanced HCC, however clinical trials using immune checkpoint inhibitors did unfortunately not show significant benefits compared to standards of care. We must however point out that these trials were performed with all-comers designs, and the predictive factors (PD-L1 immunohistochemistry? Mutational burden? Genetic alterations or histological subtypes?) of response to immunomodulators remain to be identified. The next challenge is indeed to determine if immunotherapy can be beneficial for a particular subgroup of patients.

We may also hypothesize that the combination of immunotherapy with anti-tumor agents blocking other pro-tumorigenic biological pathways will yield improved efficacy. Agents targeting angiogenesis are drawing a

particular attention, as Ramucirumab, a monoclonal antibody that binds to VEGF-R2 and further prevents its activation, was recently shown to improve survival of a subset of patients previously treated by sorafenib (2).

In this line, several studies showed that angiogenesis is a key mediator of HCC aggressiveness. The macrotrabecular-massive subtype of HCC, a recently reported morphological variant characterised by increased rates of early relapse, is also associated with upregulation of VEGFA and ANGPT2, two of the most potent activators of angiogenesis (3,4). ESM1, a marker of endothelial tip cells, was also recently identified to be an accurate immunohistochemical marker of this subtype (5). The role of the vascular architecture is also underscored by the prognostic impact of a particular pattern designated as vessels that encapsulate tumor clusters and characterised by neoplastic cells aggregates completely surrounded by endothelial cells (6,7).

In a recent elegant study, Shigeta *et al.* investigated the effect of a dual VEGF-R2/PD-1 blockade on orthotopic mouse models of HCC (8). They first showed that the combination yields a significant increase in median overall survival compared to monotherapies, and further examined how the different treatment regimens impacted the immune microenvironment of the tumors. They observed that the combination was able to increase the proportion of M1 macrophages, which are known to promote anti-tumor immune responses (8). Using RNA sequencing, several pathways linked to B cells proliferation, differentiation and activation were shown to be upregulated after treatment (8).

Interestingly, the PD-1 blockade also showed an effect on tumor vasculature. Indeed, inhibition of the PD-L1/PD-1 immune checkpoint resulted in increased total and pericyte-covered microvessel densities, thus promoting vessel normalization (8). This effect was further demonstrated to rely on CD4⁺ T cells and the authors showed that a combination treatment associated with a depletion in CD4⁺ cells, compared to treatment with intact CD4⁺ cells, was associated with the downregulation of pathways related to blood vessel formation, maturation and normalization. These results are in line with previous works highlighting the interplay between angiogenesis and immunity (9). Indeed, the abnormal structure of tumor vessels (including inadequate covering by perivascular cells, tortuosity and irregular diameter) is known to limit immune cell proliferation and infiltration (9). It has been also showed, in various preclinical studies, that the normalization of the vasculature induced by anti-angiogenic agents was able to enhance the *in situ* anti-tumor immunity (9).

Interestingly, Tian and collaborators also reported another layer of interaction, where T cells reciprocally promote the normalization of tumor vessels (10). They investigated mammary cancers developed in various mouse models with CD4, CD8 or T cell receptor knock out, and showed that tumors exhibited less vessels covered by pericytes and increased vessel permeability (resulting in an increased number of circulating tumor cells) compared to those developed in wild type mice (10). Immune checkpoint blockade was able to induce tumor vessels normalization and pericyte coverage, and authors further showed that this effect on the vasculature relied interferon- γ secreting Th1 cells that were activated by the treatment.

In conclusion, the recent work by Shigeta and collaborators and the impressive reported response rates observed in preliminary studies of patients with advanced HCC treated by atezolizumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGF antibody) support the development of such combinations (11). A critical issue will also be to identify, by the histological, molecular and phenotypical analysis of pre-treatment biopsy samples, the patients who are more likely to benefit from these therapeutic strategies.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is 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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Cite this article as: Calderaro J. Dual angiogenesis and PD-1 blockade in hepatocellular carcinoma. *HepatoBiliary Surg Nutr* 2020;9(3):350-352. doi: 10.21037/hbsn.2019.10.37