Editorial Commentary

Is there a role for stereotactic body radiation before immune checkpoint inhibitor therapy for advanced hepatocellular carcinoma?

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Comment on: Juloori A, Katipally RR, Lemons JM, *et al*. Phase 1 Randomized Trial of Stereotactic Body Radiation Therapy Followed by Nivolumab plus Ipilimumab or Nivolumab Alone in Advanced/Unresectable Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2023;115:202-13.

Keywords: Hepatoma; checkpoint inhibitors; radiation

Submitted Mar 21, 2023. Accepted for publication Jul 10, 2023. Published online Jul 25, 2023.
doi: 10.21037/tcr-23-488
View this article at: https://dx.doi.org/10.21037/tcr-23-488

Hepatocellular carcinoma (HCC) usually arises from a background of cirrhosis and has emerged as one of the most common cancer-related death worldwide (1). For eligible patients, liver transplantation or resection is definitive treatment but most patients are not candidates for a variety of reasons such as comorbidities, lack of insurance or advanced HCC (aHCC) (2). Since the introduction of tyrosine kinase inhibitors more than a decade ago and the more recent approval of immune checkpoint inhibitors, the management of aHCC has evolved in parallel whereby clinicians, guided by the appropriate clinical trials, are now incorporating these medications with or without loco-regional therapies (3,4).

Juloori *et al.* report the results of the first randomized trial of stereotactic body radiation therapy (SBRT) at a dose of 40 Gy in five fractions (at least 40 hours apart) followed by nivolumab plus ipilimumab versus nivolumab alone in 14 patients with aHCC (5). Of note, the primary end-point was drug or dose-limiting toxicity (DLT) for which the study was powered whereas secondary end points were overall response rate, progression free survival, overall survival (OS), distant disease control and local control of the irradiated tumor. At a median follow-up of 42.7 months, DLT within 6 months occurred in 1 of 6 patients (16.7%) in the nivolumab arm and 1 of 7 in the combined arm (14.3%) with grade 3 adverse events and hepatotoxicity occurring more frequently in the combined *vs.* nivolumab arm. (Unfortunately, 1 patient in the combination arm treated with SBRT passed away from progressive disease before receiving immunotherapy). Secondary endpoints also favored combination therapy *vs.* nivolumab alone.

Although the authors acknowledge the limitations of their phase I study, they did recommend additional studies to evaluate SBRT with immunotherapy. It remains unclear, however, why a randomized study was performed to evaluate drug toxicity in such patients versus a pilot or cohort study. The authors also did not explain why patient recruiting was difficult despite being a multi-center study leading to premature study termination. One possibility for the latter may have been the approval of other immunotherapeutic agents during the study period with patients preferring to be treated with an approved regimen *vs.* participating in a clinical trial. Another reason for poor patient recruitment may have been the exclusion of patients who were human immunodeficiency virus (HIV) positive. Since HIV positive patients with decompensated cirrhosis are eligible for liver transplantation (in addition to other organ transplants with acceptable 5-year outcomes), they should not have been excluded from the study based on their HIV positivity alone and additional information would be helpful (6).

The authors state secondary endpoints were driven more by the presence of extrahepatic disease than hepatic progression. However, it appears hepatic imaging studies were not standardized with parenteral contrast

recommended but not required -for patients who did not receive contrast, diagnostic computerized tomography or magnetic resonance imaging were performed prior to SRBT. For those patients with multiple target lesions or gross tumor volumes >100 cc, the target lesion chosen was up to investigator indiscretion as was the type of radiation (intensity modulated *vs.* 3-dimensional conformal radiotherapy) which could have introduced selection bias.

The investigators may have also, viz a viz, study design selected patients with worse tumor biology. For example, two patients had prior systemic therapy and two others had received prior loco-regional therapy which could have increased their risks of toxicity and OS *vs.* patients who were naïve to pre-study therapy. However, the investigators stated grade 3 hepatotoxicity was not associated with radiation therapy to the uninvolved liver. In addition, 4 patients had tumor thrombosis and median tumor size greater than reported in other studies evaluating radiation-based treatment and 1 patient in the combined arm passed away before receiving immunotherapy. Of note, all patients eventually died of disease progression and not from drug toxicity with long-term survival favoring the combined arm.

It would seem prudent to conduct additional randomized studies of SBRT followed by immunotherapy as drug toxicity was manageable. However, to obtain more compelling data on outcomes, inclusion/exclusion criteria would require some modifications. I would suggest patients with prior treatment (systemic treatment or prior loco-regional therapy to any intrahepatic tumor) should be excluded. Although it may seem odd to also exclude patients receiving radiofrequency ablation or transarterial chemoembolization to lesions distinct from the SBRT lesion, prior interventions may still affect clinical endpoints due to the abscopal effects of radiation (7). Although recent studies on predictive biomarkers have been promising, there are still no reliable biomarkers for patients with aHCC underscoring the importance of careful patient selection (8,9). Unless severely immune compromised, HIV positive patients on antiviral therapy should also be eligible for the study-they may not account for a large number of patients but are a vulnerable group and should not be excluded from the study based on HIV status alone (10). These changes alone may be sufficient to redesign a multicenter study which may not only help with patient recruitment but provide data applicable to other patients suffering from this lethal disease in parallel with ongoing efforts to identify predictive biomarkers.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-488/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-488/coif). 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: Mukherjee S. Is there a role for stereotactic body radiation before immune checkpoint inhibitor therapy for advanced hepatocellular carcinoma? Transl Cancer Res 2023;12(8):2229-2231. doi: 10.21037/tcr-23-488

