Correspondence

Radiation, cytokines and T-cell checkpoints: can we cure metastatic cancer?

Brendan D. Curti

Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, USA.

Correspondence to: Brendan D. Curti. Earle A. Chiles Research Institute, Providence Cancer Center, 4805 NE Glisan Street, Suite 2N82, Portland, OR, 97213 USA. Email: Brendan.Curti@providence.org.

Response to: Miller JA, Chao ST, Stephans KL, *et al.* Immunologic response of combined interleukin-2 and stereotactic body radiotherapy. Transl Cancer Res 2016;5:89-93.

Submitted Apr 02, 2016. Accepted for publication Apr 19, 2016.
doi: 10.21037/tcr.2016.04.15
View this article at: http://dx.doi.org/10.21037/tcr.2016.04.15

Miller *et al.* discuss the clinical findings of a pilot study investigating the combination of stereotactic body radiation therapy (SBRT) and interleukin-2 (IL-2) in patients with advanced melanoma and renal cancer performed by our group (1). The authors discuss our work in the context of anti-tumor efficacy and toxicity of T-cell checkpoint antibodies including anti-CTLA-4 and anti-PD1. We treated our first patient with SBRT and IL-2 in 2009. There have been remarkable and practice-changing discoveries in cancer immunotherapy since that time summarized in *Table 1*, and many more are anticipated to follow in the near term.

One of the main points raised by Miller was that our report did not extensively discuss toxicity of the combination. The focus of our report was on the immunobiology of SBRT + IL-2 and also to describe the clinical responses, which were greater than anticipated. There was a general description of toxicity in our manuscript in which we make the points that there was not dose-limiting toxicity of radiation over the dose range and schedule explored and that the toxicity from IL-2 was not greater than anticipated. In a separate report from our group we reported on IL-2 toxicities in 500 patients treated in our biotherapy program (2). It is the practice of our biotherapy program to treat each patient to their individualized maximum tolerated dose of IL-2. This practice is based the biology of IL-2. The capillary leak, which is the main underlying cause of IL-2 toxicity, is related to the activity and trafficking of T cells, which in turn is related to the anti-tumor effect of this cytokine. All of the patients who participated in our SBRT + IL-2 clinical trial had hypotension requiring pressor support, acute kidney injury with serum creatinine peaking between 4–6 mg/dL and capillary leak with fluid retention resulting in weight gain of between 10–20 pounds. The side effects of IL-2 are indeed severe, but all of our patients recovered normal function after completing IL-2. In our report of 500 patients who had received IL-2, the incidence of death from IL-2 was less than 1% and no individuals died during the administration of SBRT + IL-2. It should also be noted that the side effects of combined T-cell checkpoint antibodies can be severe and are not always reversible. In the report by Larkin *et al.*, the probability of experiencing grade 3 or 4 toxicity with the combination of ipilimumab and nivolumab was 68.7% in patients with previously untreated melanoma (3).

As is pointed out by Miller and colleagues, the objective response of ipilimumab and nivolumab in patients with untreated melanoma is high and remarkably so compared to treatments used in the past. In the report by Larkin cited above, complete response was observed in 11.5%, partial response 46.2% and stable disease in 13.1% of patients. These findings are impressive, yet the median progression-free survival was 11.5 months. This implies that at least half the patients who receive ipilimumab and nivolumab will need a new therapy within a year. The reality for the majority of patients with melanoma and renal cancer is that they will die as a consequence of their malignancy, despite the advances that have been made in the immunotherapy of cancer in the last 5 years.

The goal for future cancer immunotherapy (or any cancer therapy) should be the cure of malignancy, and not just delayed progression. Of the 8 patients we describe in our pilot study who had regression of melanoma or renal cancer, 6 remain alive and free of malignancy, now

Table 1 Summary of T-cell checkpoint antibody approvals and indications

Agent	Year of FDA approval	Indications
Ipilimumab	2011	Advanced melanoma
Pembrolizumab	2014	Advanced melanoma, lung cancer
Nivolumab	2015	Advanced melanoma, lung cancer, renal cancer
Ipilimumab and nivolumab	2015	Advanced melanoma

greater than 6 years after SBRT + IL-2, and we believe that these patients are likely cured of their malignancy. Of the 2 initial responders who expired, one died from an unrelated pulmonary condition 7 years after SBRT + IL-2 and 1 died 3 years after treatment from melanoma brain metastases. New immunotherapy pathways or modalities with the potential to achieve cure include other T-cell checkpoints such as TIM-3 and LAG-3, T-cell costimulatory agents like OX40 and 4-1BB, bi-specific targeting antibodies, oncolytic viruses, engineered T cells and vaccines. There will almost certainly still be a role for cytokines like IL-2, in part because IL-2 monotherapy can still cure some individuals, but it will also be needed to provide a proliferation signal for engineered T cells and tumor infiltrating lymphocytes. Radiation will be needed not only for palliation, but also because of its ability to prime immune responses. There are still many unanswered questions about the best way to amplify the clinical effects of immunotherapy with radiation, but since our initial report of SBRT + IL-2, there are now at least 21 trials listed on the cancer.gov web site investigating the combination of high dose per fraction radiation and immunotherapy. These efforts will help us to better understand the immune mechanisms of radiation, but more importantly, will help us to guide us in curing more patients with advanced cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Hongcheng Zhu, MD, PhD (Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: The author has research finding and is on the speaker's bureau for Prometheus Pharmaceuticals.

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.

References

1. Seung SK, Curti BD, Crittenden M, *et al.* Phase 1 study of stereotactic body radiotherapy and interleukin-2--tumor and immunological responses. Sci Transl Med 2012;4:137ra74.
2. Payne R, Glenn L, Hoen H, *et al.* Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program. J Immunother Cancer 2014;2:13.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, *et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

Cite this article as: Curti BD. Radiation, cytokines and T-cell checkpoints: can we cure metastatic cancer? Transl Cancer Res 2016;5(S1):S149-S150. doi: 10.21037/tcr.2016.04.15

