Editorial

Immunologic response of combined interleukin-2 and stereotactic body radiotherapy

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Introduction

Cytokine therapies have been available for the treatment of several cancers since the 1980s, with variable success. Since that time, the prevalence of metastatic disease has rapidly risen in the U.S. population as result of improvements in systemic and supportive therapies (1). In particular, there has been considerable advancement in targeted inhibitors of human ligands and receptors, which generally offer reduced toxicities compared to cytotoxic chemotherapy. Recently, this approach has been applied to the field of cancer immunotherapy, which aims to enhance the native immune system for the purpose of destroying malignant cells.

The greatest historical success of immunotherapy has been in the management of lymphomas and leukemias. Although these agents were initially cytokine therapies, the targeted CD20-inhibitor rituximab was developed and approved for the treatment of hematologic malignancies. More recently, targeted immunotherapies for the treatment of metastatic solid tumors have gained FDA approval, and may offer more favorable toxicity profiles (2). For patients with metastatic melanoma and renal cell carcinoma (RCC), targeted agents offer both progression-free and overall survival benefits over cytokines (2-4). Although these agents do not necessarily offer curative potential, their efficacy exceeds that of cytokine therapies with diminished or equivalent toxicity.

As systemic therapies improve, it is clear that the prevalence of metastatic disease will continue to increase. Accordingly, utilization of radiation therapy for palliation and local control of oligometastases will necessarily rise. As a result, a new role for radiation therapy as a sensitizer to systemic therapy is actively being explored. Unfortunately, scarce data exists describing the safety and efficacy of combined radiation and targeted therapies. Drawing from a breadth of preclinical data (5), many hypothesize that radiation therapy augments the response to immunotherapy. However, it is difficult to discern whether this increased response is solely attributable to these novel agents, or whether a synergistic effect is truly present.

In the June 2012 issue of *Science Translational Medicine*, Seung and co-authors report results from a phase I study investigating combination stereotactic body radiotherapy (SBRT) and interleukin-2 (IL-2) for the treatment of metastatic RCC and melanoma (6). Twelve treatment-naive patients were enrolled and assigned to one of three dose-escalated cohorts: (20–60 Gy in 1–3 fractions). Two cycles of high-dose IL-2 were administered after SBRT, with up to six total cycles for patients demonstrating an objective response. PET and CT imaging were used to assess response via modified RECIST guidelines (7). To assess for immunologic response, the authors collected peripheral T cells before SBRT and during IL-2 therapy. The frequencies of certain T cell subpopulations were predictive for response to therapy.

Seung *et al*. should be commended for their work, as it contributes valuable data to an area of great research interest. Although this is now an older paper, this study provided early data for SBRT in combination with

immunotherapy before the efficacy of newer agents had been established in randomized trials. As the utilization of both targeted therapies and SBRT increase, the safety and efficacy of combined therapy remains unclear. Many clinicians prefer to delay systemic therapy rather than administer concurrently with radiation therapy. However, many hypothesize that radiation-induced tumor antigen release augments immunogenic therapies, and thus concurrent therapy may offer an added benefit (8-10).

As a phase I trial, the principal objective of this investigation was to evaluate treatment-related toxicity and the feasibility of combined SBRT and IL-2. Although no dose-limiting adverse events attributable to SBRT occurred, several anticipated adverse events related to IL-2 were observed and resolved. Unfortunately, the overall incidence and grade of IL-2-related toxicities were not reported. As such, it is difficult to compare this series with historical toxicity rates, such as those reported by Atkins *et al*. (11). Late toxicities related to SBRT are certainly possible, and SBRT may have increased the rate of diarrhea, nausea, and transaminasemia attributed to IL-2, particularly among patients who underwent hepatic SBRT. Moreover, 60 Gy in 3 fractions (cohort 3) delivered peripherally or centrally is, at the least, associated with some degree of chest wall toxicity or fatigue. Of note, no patients in this cohort underwent SBRT to the hilum or mediastinum; larger samples may certainly demonstrate these toxicities.

It is unclear why the authors chose not to report more extensive toxicity data, as it would have strengthened their assertion that SBRT with IL-2 should be considered in this population. One must consider the relative risks and benefits of cytokine therapy over targeted therapy: grade ≥3 toxicities with IL-2 are very common, including hypotension (45%), oliguria (39%), vomiting (37%), diarrhea (32%), thrombocytopenia (17%), confusion (13%), infection (11%), pulmonary edema (9%), and hepatic dysfunction (9%) (11). In addition, the incidence of treatment-related fatal toxicity is approximately 2%. In contrast, the overall incidence of grade ≥3 toxicity with the use of nivolumab alone, ipilimumab alone, and combination nivolumab/ipilimumab for untreated melanoma are 16%, 27%, and 55%, respectively, with significantly greater efficacy (2).

Given the morbidity and cost associated with management of these toxicities, clinicians and patients must consider whether IL-2 should be considered over novel targeted immunotherapies. With recent encouraging phase III data, it is unclear whether patients treated with combination IL-2 and SBRT will achieve superior outcomes compared with CTLA-4 or PD-1 inhibitors alone or in combination with SBRT. Although most studies report minimal toxicities associated with SBRT and targeted therapies, there have been several reports of an increased risk of radiation necrosis (12) and bowel toxicity (13,14).

The authors predominantly focused upon objective response in their study, which exceeded recent data for combination nivolumab and ipilimumab (2). The overall response rate in the intent-to-treat analysis was 67%, and was higher among patients with melanoma (71%) compared with RCC (60%). The authors assert that this 71% response rate is statistically significantly greater than the historical response rate of IL-2 monotherapy for melanoma (16%) (11). As a phase I study, it is difficult to compare this response with historical IL-2 response rates (*Table 1*). In the frequently-cited historical standard, Atkins *et al*. included 270 patients with metastatic melanoma from eight clinical trials (11). The overall response rate was 16%, similar to that observed among patients with metastatic RCC (14–20%) (15). Accordingly, we are presented with a phase I study reporting response rates of 67% compared with historical response rates of 16%, with the difference attributed to SBRT. Although this may be a real effect, one must also consider the differences in study design. First, an older set of response guidelines was utilized in Atkins *et al*.: a partial response required at least 50% reduction in total tumor area with stable symptomatology and laboratory abnormalities on at least two separate instances. Just 4 of 12 (33%) patients in Seung *et al*. achieved a 50% reduction in maximal tumor diameter. In contrast, the more recent criteria used by Seung *et al*. required a decrease in total maximum lesion diameter of at least 30%. Second, Seung *et al*. included only treatment-naïve patients, while 46% of patients in Atkins *et al*. had progressed on a different systemic therapy. Therefore, it is unclear whether this 67% response would remain as robust if identical response evaluation and patient eligibility were used. To address this, the authors have initiated two accruing phase II randomized trials (SBRT + IL-2 *vs*. IL-2 alone), which include the requisite control group to assess the research hypothesis (NCT01416831, NCT02306954).

To further evaluate these results, we can explore whether available data support an immunologic basis for radiation as a sensitizer to immunotherapy (5,17,18). Total body irradiation (TBI), for example, has been demonstrated to increase the efficacy of IL-2 in mice (19). However, a phase II trial failed to replicate this effect, with an overall

Table 1 Efficacy and safety of immunotherapies with or without radiation therapy for advanced melanoma and renal cell carcinoma

Study	Population	Therapy	Objective response†	PFS‡ (month)	OS‡ (month)	Grade ≥3 toxicity
Atkins *et al*. (11) meta-analysis	Melanoma	IL-2 (n=270)	16%	NR	11	>45%
Klapper *et al*. (15) retrospective series	RCC	IL-2 (n=259)	20%	NR	19	>38%
Knisely *et al*. (16) retrospective series	Melanoma	SRS + ipilimumab (n=50)	NR	NR	21	NR
		SRS (n=27)	NR	NR	5	NR
Seung *et al*. (6) phase I	RCC/Melanoma	SBRT + IL-2 (n=12)	67%	NR	>16	NR
Larkin *et al*. (2) phase III	Melanoma	Nivolumab (n=316)	44%	7	NR	44%
		Ipilimumab (n=314)	19%	3	NR	56%
		Nivolumab + ipilimumab (n=314)	58%	12	NR	69%
Patel *et al*. (12) retrospective series	Melanoma	SRS + ipilimumab (n=20)	NR	NR	8	>30%
		SRS (n=34)	NR	NR	9	>12%

†, complete or partial response; ‡, median PFS and OS reported. PFS, progression-free survival; OS, overall survival; RCC, renal cell carcinoma; SBRT, stereotactic body radiotherapy; IL-2, interleukin-2; NR, not reported; SRS, stereotactic radiosurgery.

response rate of just 4% (20). Seung *et al*. assert that this poor response is due to bystander irradiation (lymphocyte depletion) or inadequate dose per fraction (poor immunogenicity) (21,22). Among patients with metastatic RCC and melanoma, there has been some evidence suggesting a benefit with the use of immunotherapies after SRS (23) or whole-brain radiotherapy (9). In addition, ipilimumab has been demonstrated to increase survival when combined with radiation in mice (24,25). However, a lack of prospective controlled data limits the ability to draw any meaningful conclusions (12,16,26).

In addition to distant control, one must also consider local control after SBRT. Melanoma and RCC are among the most common histologies treated with SBRT and stereotactic radiosurgery (SRS), with 12-month local control ranging from 70% to 95% (22,27-34). Given this high rate of local control, an ongoing cooperative group trial (NRG-BR001) is exploring the feasibility of irradiating multiple lung, colon, or breast oligometastases over a 1–3 weeks period. If the primary endpoint of acceptable toxicity is met, this may lead to future trials exploring SBRT in the management of oligometastases. Of note, Seung *et al*. reported no local failures among irradiated lesions despite significant variation in dose among the three cohorts. With larger samples, one would expect to see greater durability in cohorts 2 and 3. Although the sample size was small and radiographic follow-up was not reported, this control rate is impressive and may support a synergistic local relationship between SBRT and IL-2.

Although the utilization of IL-2 has decreased given the development of targeted therapies, the results presented by Seung *et al*. are provocative given the 67% objective response rate. In comparison, the recent Larkin *et al*. phase III trial for untreated melanoma reported a 58% response with the use of combined nivolumab and ipilimumab, with a grade ≥3 toxicity rate of 55%. It is unknown whether either regimen is associated with a survival benefit, or whether SBRT truly augments the efficacy of immunotherapy. Several ongoing trials are exploring immunotherapies alone and in combination with SBRT. Beyond the aforementioned trials designed by Seung *et al*., ipilimumab is being combined with SBRT (phase I, NCT01557114; phase I/II, NCT01497808; phase II, NCT01565837) and whole brain radiotherapy (phase I, NCT01703507).

Conclusions

Seung *et al*. have provided early results describing favorable safety and efficacy with combination immunotherapy and SBRT. In select situations, the available preclinical and clinical data suggest an additive benefit of SBRT without substantially increased toxicities. However, newer targeted therapies may offer similar efficacy and toxicity without SBRT, and have been studied in randomized settings. Although IL-2 with SBRT may provide encouraging local control rates, it is difficult to favor this approach as upfront

therapy given the available phase III data demonstrating considerable efficacy with CTLA-4 and PD-1 inhibitors. To address this gap in the literature, currently accruing trials are exploring SBRT with these targeted agents to corroborate studies such as this paper. Given the encouraging preclinical and clinical results, we look forward to the results of such trials on whether SBRT can truly augment response rates.

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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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