Consolidating Radiotherapy with Immunotherapy

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SUMMARY

Radiotherapy and immunotherapy can be concomitantly or sequentially combined seeking synergistic effects in terms of control of irradiated tumors and abscopal effects on nonirradiated lesions. Clinical-trial testing of such combinations faces several obstacles to demonstrate efficacy and needs improvements in trial design, patient selection, evaluation of results and biomarker discovery.

See related article by Foster et al., p. 5510

In this issue of *Clinical Cancer Research*, Foster and colleagues (1) report on a phase I clinical trial in which stereotactic body radiotherapy (SBRT) is concomitantly given with a course of immunotherapy consisting of a combination of a standard regimen of nivolumab conforming doublets together with either tolerable doses of the anti-CD137 mAb (urelumab) or the anti-CSF-1R mAb (cabiralizumab). A very heterogeneous patient population bearing multiple types of metastatic solid malignances was enrolled. Treatment assignment was not randomized but chosen in accordance to the tumor type. Of 87 screened patients 27 failed to meet inclusion criteria or refused treatment. Dosimetry plans were individually adjusted according to the anatomical localization and organs at risk. The overall philosophy was to irradiate as much as possible observable malignant tissue, but permitting the presence of lesions that remained completely untreated and/or lesions that were only partially irradiated with low non-ablative doses.

This trial design makes it difficult to draw solid conclusions. But this clinical trial represents a major advance towards combining radiotherapy with novel immunotherapy agents in an attempt to show feasibility and explore potential improvements in clinical results.

Tolerability was reasonable even if 16% of patients experienced dose-limiting toxicities (DLT) at some point of time. Of great interest is the observation that combinations with urelumab resulted in no DLTs, while combinations encompassing cabiralizumab gave rise to DLTs in 30% of treated cases. Of note, the very low doses of 8 mg of urelumab come from the need to reduce its dose due to liver toxicity at higher doses.

From the point of view of clinical evidence in terms of RECIST criteria, activity was documented in terms of 55 irradiated lesions responding, as well as in 23 unirradiated lesions with evidence for objective response. It is difficult to conclude if actually the combination of radiotherapy and immunotherapy was responsible for such outcomes, or whether they would have also occurred in separate treatment schemes. However, a median OS of 17 months in this heavily pretreated population of advanced cancer patients seems encouraging. Importantly, those patients with high circulating concentrations of interleukin-8 did not respond to treatment, thus confirming reports on the negative biomarker value of the concentration of this chemokine in circulation for PD-(L)1 blockade (2).

Radiotherapy and immunotherapy strategies have resulted in evidence for synergistic efficacy in multiple preclinical mouse models. Because of this, radioimmunotherapy combinations have raised high expectations in the sense that efficacy would extend to lesions outside the irradiation fields (abscopal effects). However, evidence for radioimmunotherapy abscopal effects in clinical practice has been mostly anecdotal. By contrast, phase III clinical trial results suggest that PD-L1 checkpoint inhibitors consolidate the effects of chemoradiotherapy at least in locally advanced NSCLC (3). In this scenario of prolonged OS, immunotherapy probably controls distant micrometastatic disease. Ongoing research is trying to elucidate the beneficial interaction mechanisms of radiotherapy and immunotherapy that most likely include the induction of immunogenic tumor cell death.

Weicheselbaum and colleagues proposed and demonstrated (4) that in oligometastatic disease, defined as less than four detectable tumor lesions, patients benefited from approaches irradiating all the tumor lesions achieving overall survival advantage. Applying these concepts to other disease settings, radiotherapy can be given according, to "as much as feasible" paradigms. In this sense, if it is combined with radiotherapy, the role of immunotherapy would be to consolidate the direct local response to irradiation and also control the tumors left without ablative doses of irradiation. These concepts underline the report by Foster and colleagues (1) in which schemes of radiotherapy were prescribed that ablatively treated some lesions but irradiated only parts of other lesions. Actually, some metastases were left completely without irradiation. This concept is very attractive, albeit its clinical benefit becomes extremely difficult to prove in phase III randomized trials.

The choice of immunotherapy agents for combinations is complex aside from PD-L1 checkpoint inhibitors. Selection of urelumab (anti-CD137 agonist monoclonal antibody) and cabiralizumab (anti-CSF1R antagonist monoclonal antibody) makes sense. Preclinical mouse evidence for the efficacy anti-PD1+anti-CD137 in combination with radiotherapy is available (5). Although doses of urelumab could not be optimal due to liver toxicity, several tumor tissue-targeted CD137 agonists are under clinical development. Combinations with anti-CTLA4 checkpoint inhibitors are to be considered.

Contemplating the current status of radioimmunotherapy, the concept that immunotherapy can consolidate partial or complete responses to local SBRT is very attractive. Perhaps this approach could be focused on patients bearing oligometastatic disease. As

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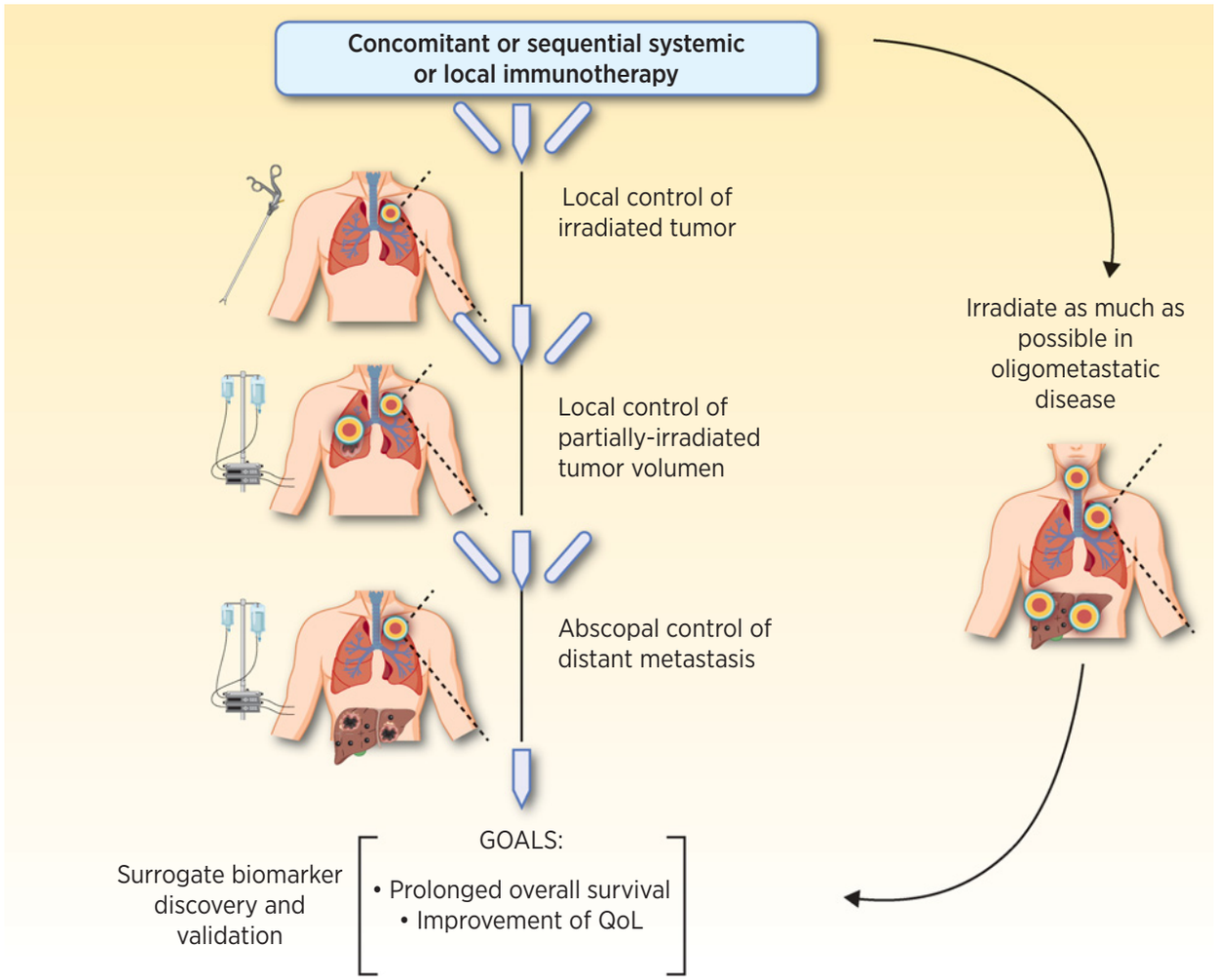

Figure 1.

Schematic representation of the goals of radioimmunotherapy. Patients with multiple tumor lesions can be approached experimentally with combinations encompassing immunotherapy agents and radiotherapy. Both modes of treatment are postulated to interact in additive or synergistic fashions. The goals of the immunotherapy agents include the consolidation of the responses in the irradiated tumors and the control of only partially irradiated lesions or non-irradiated macrometastatic or micrometastic disease.

represented in **Fig. 1**, the goals are to consolidate and prolong objective responses in irradiated tumors and control or eradicate distant disease in the form of either macro or micro metastases. In this context, comprehensive translational medicine efforts should try to elucidate mechanisms and identify predictive and pharmacodynamic biomarkers in circulation, but more importantly in sequential tumor tissue biopsies. Radioimmunotherapy may potentially become the standard treatment in various diseases. However, very complex demonstrative clinical studies would be needed. The approach to irradiate as much as feasible tumor volume, applied to oligometastatic patients makes much sense. The way we randomize and stratify comparable groups of patients and how to evaluate responses remains challenging and requires consensus. In reaching this consensus, we should not forget that the ultimate goals of radioimmunotherapy are to extend overall survival, while offering better quality of life (**Fig. 1**).

Authors' Disclosures

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