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Radiation and immunotherapy
Renewed allies in the war on cancer

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Anticancer immunotherapy holds great promises, as long-term responses to interleukin-2 have been observed in metastatic melanoma and renal cell carcinoma patients. However, improving the relative low rates of such responses has constituted a great challenge. In our experience, high-dose radiation combined with interleukin-2 provided encouraging results that are worth exploring further.

"The art of war is of vital importance to the State. It is a matter of life and death, a road either to safety or to ruin. Hence it is a subject of inquiry which can on no account be neglected."

-Sun Tsu

On December 23rd, 1971, President Richard Nixon signed the National Cancer Act of 1971 into law. Many referred to the Act as a "declaration of war on cancer." The hope was to cure cancer within a few years. That war is still being waged.

The first clear evidence of tumor-specific immune responses was provided by Prehn and Main in 1957.[1] Since then, decades of studies have elaborated our understanding of oncogenesis and tumor escape from immunosurveillance. Alongside, different strategies have been designed to fight cancer by manipulating the immune system, and countless mice have been cured with these approaches. Translating this success from animal models to humans, however, has been more challenging.

The first report on the efficacy of interleukin (IL)-2 in patients affected by metastatic melanoma appeared in 1985. A subsequent publication reported a complete response (CR) and partial response (PR) rates of 6% and 10%, respectively. Many of these responses continue to this day.[2] Since then, multiple IL-2-based therapies have been investigated to increase the response rates, without much success. In pre-clinical models, the combination of radiotherapy and IL-2 provided encouraging results, but similar benefits were not reproduced in clinical settings.[3]

Since the 1890s, radiation has been one of the most effective measures against cancer. For years, the dogma has been that irradiation would directly kill tumor cells by inducing irreparable double-strand DNA breaks. Now we know that radiation-induced tumor cell death provides a source of tumor-associated antigens (TAAs). In addition, radiation can destroy multiple components of the tumor-supporting stroma.[4] Monocytes, macrophages and dendritic cells (DCs) phagocytose to process dead tumor cells and carry TAAs into draining lymph nodes. Moreover, tumor cells succumbing to irradiation can passively release high mobility group box 1 (HMGB1). By binding to Toll-like receptors (TLRs) such as TLR4 and TLR2 on the surface of DCs, HMGB1 triggers the release of IL-1β and stimulate the presentation of TAAs to T and B cells.[5] These observations delineate a model of what may be happening when a tumor is irradiated in vivo (**Fig. 1**).

Most preclinical experiments that demonstrated the activation of an antitumor immune response by radiation used doses higher than 5–20 Gy. Doses in the range of 1.5–3 Gy per fraction have been the standard for almost a century, since early experience indicated that higher doses would result in significant toxicity. At these low doses, we believe that the "danger signals" that are necessary to produce an inflammatory microenvironment are much less likely to be generated. With the advent of stereotactic body radiotherapy (SBRT), which incorporates sophisticated imaging, planning, and body immobilization protocols, doses in the range of 10–20 Gy can now be delivered to carefully selected areas while sparing normal tissues. This is what distinguishes our study from the previous work by Lange et al.[3] The dose given per fraction may hold the key to unlocking the synergy between radiation and immunotherapy. With SBRT plus IL-2 to treat 12 patients, we observed a response rate of 67% compared with the historical 15% observed with IL-2 alone.[6]

Although we are encouraged by the results of our Phase I clinical trial, many questions remain open. We observed a greater frequency of proliferating $CD4^+$ effector memory T cells in responding patients at baseline, suggesting that in these patients an antitumor response was present and only amplified by SBRT plus IL-2. We also observed changes in the proliferation of $CD8^+$ effector memory T cells in responders, although we don't know the exact antigen targeted by these cells. How other components of the innate and adaptive immune system contribute to the therapeutic efficacy of SBRT plus IL-2 also

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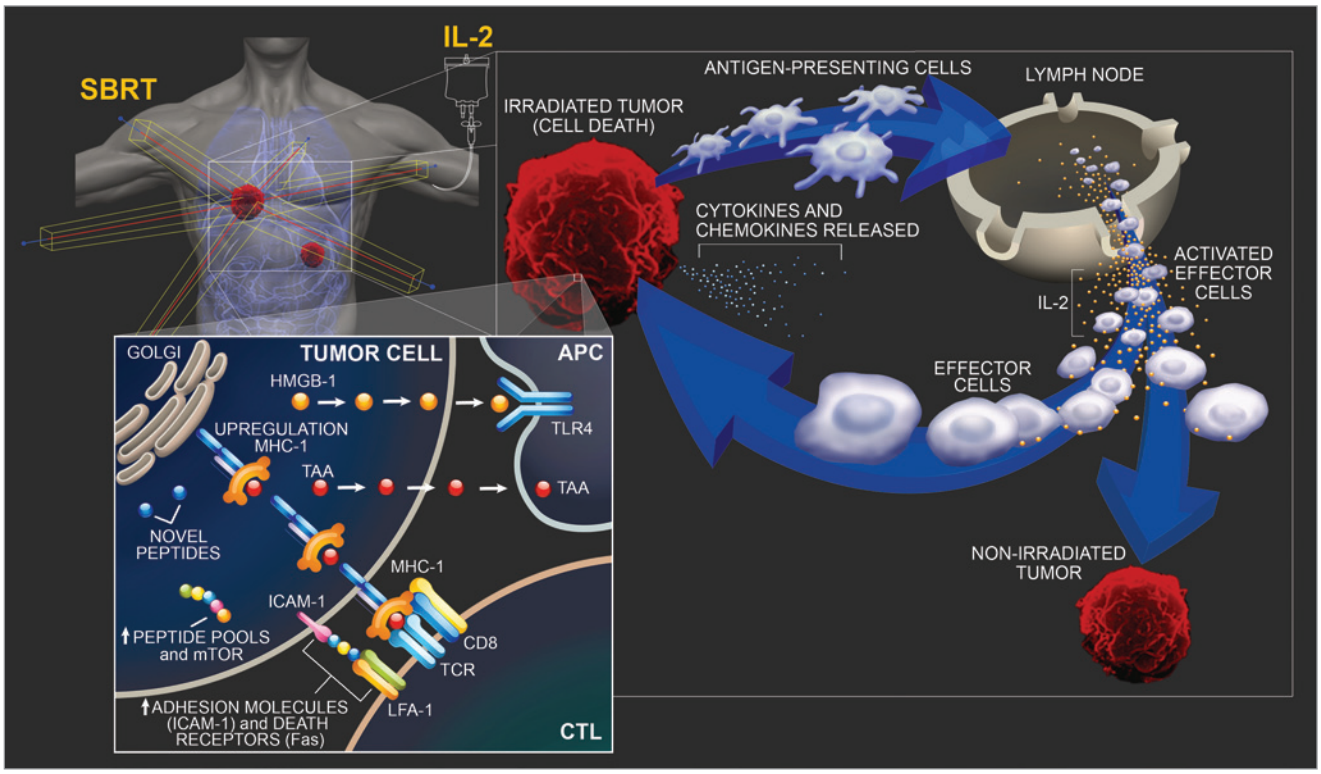

Figure 1. Immunogenic effects of irradiation. Radiation-induced tumor cell death provides a source of tumor-associated antigens (TAAs), and increases the expression of MHC Class I molecules, adhesion molecules, and a plethora of other factors involved in the immune response, including death receptors. In response to irradiation, cytokines and chemokines are released, in turn attracting antigen-presenting cells (APCs) and T cells. Radiation-treated tumor cells can passively release high mobility group box 1 (HMGB1) that, by binding to Toll-like receptors (TLRs) on the surface of APCs, stimulates TAA presentation to effector cells. APCs process dead tumor cells and carry TAAs into draining lymph nodes, where antigen presentation and T-cell stimulation occur. Activated effector cells, expanded by interleukin-2 (IL-2), eventually target both irradiated and non-irradiated tumor cells.

remains unknown. Radiation induces the upregulation of MHC Class I molecules, on both tumor cells and antigen-presenting cells (APCs), improves antigen presentation and may enhance tumor cell recognition by activated $CD8^+$ T cells, which hence may infiltrate the tumor at an increased rate.[7,8] Yet how effector cells overcome the immunosuppressing tumor stroma at non-irradiated tumor sites is unclear. Furthermore, we don't know if the responses to SBRT plus IL-2 will be as durable as those induced by IL-2 alone, or if the high response rates that we observed will be reproducible in future clinical studies.

"Strategy without tactics is the slowest route to victory. Tactics without strategy is the noise before defeat."

-Sun Tsu

Recently, there have been several innovations for the treatment of melanoma patients, including the FDA approval of the anti-CTLA4 monoclonal antibody ipilimumab, based on the results of a Phase III clinical study showing a four-month increase in median survival.[9] Along similar lines, BRAF-targeted therapy promotes tumor regression in greater than 50% of selected patients.[10] However, complete or durable regressions with these new agents are infrequent and do not appear superior to those induced by IL-2 at this time. Our strategy is to leverage the immune boosting properties of high-dose radiation with other immunotherapies. To this aim, we need to figure out the most effective tactics by completely understanding the mechanisms that underlie anticancer immune responses. More work is therefore needed to determine the best T-cell stimulatory measures and the types of cancers for which radiation and immunotherapy can be successfully combined. CTLA4, PD-1, OX40 and 4–1BB are the T-cell receptors that nowadays show the most promising clinical potential. Or perhaps, SBRT plus IL-2 may turn out to be, in the long run, the best tactic to help our patients win their battle against melanoma or renal cell carcinoma. We have a strategy. We need to figure out the most effective tactics.

References

1. Prehn RT, Main JM. Immunity to methylcholanthrene-induced sarcomas. J Natl Cancer Inst 1957; 18:769-78; PMID:13502695.
2. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999; 17:2105-16; PMID:10561265.
3. Lange JR, Raubitschek AA, Pockaj BA, Spencer WF, Lotze MT, Topalian SL, et al. A pilot study of the combination of interleukin-2-based immunotherapy and radiation therapy. J Immunother (1991) 1992; 12:265-71; PMID:1477077; http://dx.doi.org/10.1097/00002371-199211000-00007.
4. Yu P, Rowley DA, Fu YX, Schreiber H. The role of stroma in immune recognition and destruction of well-established solid tumors. Curr Opin Immunol 2006; 18:226-31; PMID:16459066; http://dx.doi.org/10.1016/j.coi.2006.01.004.
5. Ma Y, Aymeric L, Locher C, Kroemer G, Zitvogel L. The dendritic cell-tumor cross-talk in cancer. Curr Opin Immunol 2011; 23:146-52; PMID:20970973; http://dx.doi.org/10.1016/j.coi.2010.09.008.

6. Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2--tumor and immunological responses. Sci Transl Med 2012; 4:137ra74; PMID:22674552; http://dx.doi.org/10.1126/scitranslmed.3003649.
7. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med 2006; 203:1259-71; PMID:16636135; http://dx.doi.org/10.1084/jem.20052494.
8. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol 2005; 174:7516-23; PMID:15944250.
9. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711-23; PMID:20525992; http://dx.doi.org/10.1056/NEJMoa1003466.
10. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012; 366:707-14; PMID:22356324; http://dx.doi.org/10.1056/NEJMoa1112302.