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CORR Insights®: Administration of TGF-ß Inhibitor Mitigates Radiation-induced Fibrosis in a Mouse Model

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Where Are We Now?

The WHO's International Agency for Research on Cancer predicts that the global cancer burden will grow to 27 million new cancer cases per year by 2040 [8]. If current adjuvant treatment algorithms are generally maintained, at least 13 million patients will undergo external beam radiation annually by that time [1]. External beam radiation offers enormous benefit to patients undergoing treatment for cancer and can be either an adjuvant therapy or primary therapy. However, the side effects of this treatment, particularly late fibrosis, can diminish a patient's quality of life. When radiation-induced fibrosis occurs, we have little to offer other than reductions in the radiation dose and symptomatic treatment [5]. Despite our best efforts, late fibrosis can result in cosmetic deformity, nerve symptoms, muscle shortening, stiffness, and lymphedema [6].

Current treatments have a generally modest effect on these late complications. Pentoxifylline and tocotrienol (testosterone replacement therapy) have been used with some success in the treatment of superficial radiation-induced fibrosis [5]. The complications of fibrosis, including muscular pain, spasm, and contractures, have been treated with nonsteroidal anti-inflammatory medications, muscle relaxants, and physical therapy. Severe contractures and painful spasms have also been treated with injections of botulism toxin. Novel nerve-stabilizing agents such as pregabalin also have a role in the management of neuropathic pain [6]. Because of these limited benefits, preventing radiation-induced fibrosis is desirable [5]. Intensity-modulated radiation therapy has been shown to reduce but not eliminate the severity of fibrosis as a result of improved distribution of the radiation dose to target tissue, in contrast to surrounding normal tissue [4, 7].

Truly effective prevention requires addressing the pathophysiology of the disease. After a radiation-induced injury, tumor growth factor beta (TGF-ß) is secreted by several cell types including macrophages and promotes differentiation of recruited stromal fibroblasts to myofibroblasts [10]. Subsequent fibrosis occurs 4 to 12 months later and can progressively worsen for up to 2 years. Gans et al. [3], in this experiment, demonstrated that inhibiting TGF-ß in a nontumor mouse model can reduce radiation-induced fibrosis by nine-fold. Although others have examined the shorter-term effects of radiation on tissue [9, 11], the researchers analyzed the development of myofibrosis in mice 9 months after a single 50 Gy fraction of radiation to the hindlimb, a simulation close to the late-term effects seen in humans. This is important because it establishes the sustainability of TGF-ß inhibition in preventing this soft-tissue complication, which is known to worsen over time. The study, therefore, takes a giant step toward the development of an effective treatment option for this debilitating condition.

Where Do We Need To Go?

Gans et al. [3] have provided early evidence in a nontumor animal model that inhibiting TGF-ß at the time of

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irradiation can dramatically reduce radiation-induced fibrosis at later follow-up. However, similar to all good research, it raised as many questions as it answered, and I hope that future studies might expand on the discoveries made in this paper, perhaps first by replicating the work with an experiment that includes a tumor in the irradiated field. It would be important to determine whether treatment with a TGF-ß inhibitor in the presence of a malignancy would result in a different result. A follow-up experiment to that of Gans et al. [3] might also include a surgical procedure to see how surgical manipulation of tissue influences the inhibition of TGF-ß activity, or whether the timing of surgical manipulation plays a role in the development of post-irradiation fibrosis in the presence of a TGF-ß inhibitor. Such experiments could help us to determine the best timing, dose, and delivery of TGF-ß inhibition with or without surgery in relation to radiation therapy. We could also determine whether TGF-ß inhibits wound healing, and if so, how this is influenced by the timing, dose, and delivery. Each of these questions is critically important as TGF-ß inhibitor therapy is considered for human use. The answers may impact established algorithms currently in use in cancer care.

How Do We Get There?

Murine cancer models are an established preclinical method for evaluating various cancer therapies, but the translation of findings from experimental studies to clinical use is an emerging science. Commonly, studies on the efficacy of chemotherapeutics and targeted small-molecule tumor inhibitors can be done by transplanting tumors derived from human patients or from in vitro cell cultures into immunocompromised mice (patient-derived xenograft models or cell line-derived xenograft models) [2]. However, these models, requiring immunosuppression, are of less utility for studies examining TGF-ß inhibition.

The emergence of immunotherapeutic treatment programs has ushered the development of genetically engineered immunocompetent models. Mice can be engineered to produce tumors of human relevance and, in turn, these tumors can be transplanted into specific sites in syngeneic hosts, resulting in fully immunocompetent murine allograft tumor models [2]. This approach can be useful in investigations to answer the questions outlined above. The relationships between surgical manipulation of the tumor and local tissue, external beam radiation, and inhibition of TGF-ß with consideration of the sequence, timing, and dose can be examined with a thoughtful strategy in properly designed experiments.

First, the remarkable effect of TGF-ß inhibition on late-term radiation-induced fibrosis must be demonstrated again in the presence of an active tumor. Second, the impact of surgical manipulation on the inhibitory effect needs to be explored. Third, it should be confirmed that TGF-ß inhibition does not result in unacceptable disruption of wound healing. Finally, inhibition should be thoroughly examined as much as practicable in the preclinical setting.

The incidence of radiation-induced fibrosis is expected to increase in proportion to the known increasing incidence of cancer worldwide. Although the demonstrated mitigation of this major complication of radiation therapy with TGF-ß inhibition is promising, further work should be done to bring this therapy to clinical use.

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