Editorial

Molecular Targets for Radiation Therapy: Bringing Preclinical Data into Clinical Trials

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Studies aimed at understanding the mechanisms responsible for regulating cellular response to ionizing radiation have resulted in the identification of a wide variety of molecules that can influence tumor cell radiosensitivity (1–4). This fundamental information has, in turn, suggested that targeting such radioresponse regulatory molecules can serve as a strategy for developing radiation sensitizers. In general, the molecules that influence intrinsic radiosensitivity are involved in DNA repair, cell cycle checkpoint control, apoptosis, and signal transduction. Other current approaches to radiation enhancement target aspects of the tumor microenvironment, such as hypoxia and angiogenesis. It must be emphasized that combined modality therapy with radiation plus other agents may be effective in the clinic by mechanisms other than radiation sensitization per se (5, 6), so that terminology such as sensitization versus additivity is important when describing the radiation-drug interaction. In addition, normal tissue toxicity must be evaluated to determine the therapeutic index of tumor versus normal tissue injury.

There are a large number of potential molecular targets available against which to develop radiosensitizers. However, because the goal of any combined modality therapy is to improve the therapeutic index, the established differences in signal transduction processes between normal and neoplastic cells suggest that targeting specific signaling proteins would be well suited for selectively enhancing the tumor radiosensitivity.

Along these lines, EGFR1 has received considerable attention as a target for radiosensitization (7–12). In general, EGFR and its family members stimulate proliferation and are considered to be cytotoxic. Importantly, tumor cells often overexpress EGFR and the other members of the ErbB family or express mutated versions of the proteins resulting in constitutive activation (11). Consistent with results generated with DNA-damaging chemotherapeutic agents, the inhibition of EGFR activity via antibody-mediated receptor blockade, genetic manipulation, or small molecules has also been shown to enhance tumor radiosensitivity in a number of experimental systems (8–12). The report by She et al. (7) in this issue has extended these studies to four additional human xenograft models treated with the EGFR tyrosine kinase inhibitor ZD1839 (‘Iressa’) showing a significant increase in radiation-induced tumor growth delay. Although this study clearly demonstrates that ZD1839 enhances the tumor growth delay induced by a fractionated radiation protocol, it also raises a number of issues pertaining to the clinical potential of the combination EGFR inhibitors and radiotherapy.

The first issue is one of normal tissue toxicity. Although there have been many reports demonstrating enhanced tumor response, the possible effect of an EGFR inhibitor combined with radiation on a critical normal tissue has received limited attention. She et al. (7) addressed the potential for lung toxicity by irradiating tumors implanted over the breast and rib cage. No lung toxicity was detected using combination protocols that had significant antitumor activity. However, whereas these results are useful for developing a clinical strategy, the toxicity studies extended to only 41 days posttreatment. Longer observation periods are required to detect pneumonitis and fibrosis, which are the primary radiation-induced pulmonary injuries (13, 14). Although the studies of She et al. provide important information, given that EGFR does have a role in normal tissue biology, the potential for toxicity of the combination of EGFR inhibition and radiation warrants further investigation in murine systems and careful evaluation in any clinical trial.

The second issue is that of patient selection. The xenograft data of She et al. (7) indicate that the degree of radiosensitization induced by ZD1839 is independent of EGFR or ErbB2 expression. Furthermore, there is no indication that EGFR activity is actually being inhibited by the ZD1839 dose delivered (target validation). These results point to a significant impediment to the clinical application of EGFR inhibitors/radiation combination, which is the lack of a complete understanding of the mechanism through which EGFR contributes to radiosensitivity. Whereas MAPK activation has been implicated in some cell models, it is unclear whether this effect is applicable to other cell systems. More importantly, the specific events downstream from MAPK, or other proximal signaling molecules, that directly determine radioreponse have not been identified. As recently described by Dent et al. (4), EGFR regulates a number of interacting signaling pathways that can ultimately affect radioreponse. Moreover, the contribution of a given signaling pathway or molecule downstream of EGFR will depend on the activity of other parallel survival pathways. Thus, delineating the relationship between EGFR and radiosensitivity will require considerably more research. Defining the specific molecules and

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3 The abbreviations used are: EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; NSCLC, non-small cell lung cancer.

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events mediating EGFR-dependent radioresistance would also have an immediate impact on the clinical application of the combination of its inhibitors and radiotherapy.

Small-molecule EGFR inhibitors such as ZD1839 have been most widely tested clinically in patients with NSCLC. Two large randomized Phase II trials comparing two doses of ZD1839 (250 mg versus 500 mg daily) in patients with previously treated recurrent/refractory NSCLC demonstrated response rates between 10 and 18%. There was no apparent difference in response seen between the two doses. Simultaneously, two large randomized Phase III trials were reported comparing chemotherapy with or without ZD1839 in first-line NSCLC patients. Despite the notable response rates seen in the Phase II studies, these well-conducted and highly powered Phase III trials failed to demonstrate any survival advantage with the addition of the EGFR inhibitor. Several explanations for this seeming inconsistency have been proposed, including the possibility of a negative interaction between the chemotherapy and EGFR inhibitor. There is little preclinical or clinical evidence, however, to suggest that this is true. Indeed, the preclinical models examining the coadministration of cytotoxic chemotherapy and ZD1839 demonstrated a marked potentiation of growth inhibition with the combination compared with either ZD1839 or chemotherapy alone, similar to the potentiation seen with EGFR inhibition and radiation therapy, as noted above.

A more plausible explanation is that when viewed together, these studies demonstrate that only a small number of patients have tumors with the relevant “target” and, thus, only a small number of patients are potentially able to derive benefit from the agent. Even when large-scale trials are conducted in an unselected population of patients, any survival advantage, for the subset of patients in whom the target is actually expressed, is diluted in the overall population and may not be detected. In retrospect, given the genetic complexity of malignancies, it should not be surprising that an agent targeting a specific pathway is found to be ineffective when patients are chosen without regard to whether their tumors have a molecular phenotype likely to be sensitive to the targeted agent. The necessity for preselection of patients whose tumors have the appropriate target for the drug has certainly been true in other diseases for which targeted therapy has been effective, including STI571 (Gleevec) in chronic myelogenous leukemia and gastrointestinal stromal tumors, tamoxifen and trastuzumab (Herceptin) in breast cancer, and rituximab (Rituxan) in non-Hodgkin’s lymphomas.

The most commonly used assays for assessing EGFR have been immunohistochemistry with anti-EGFR monoclonal antibodies and reverse transcription-PCR measurements of EGFR gene expression. However, to date, the level of EGFR expression has not been found to correlate with the response to the small-molecule EGFR inhibitors in either the preclinical models (15) or the NSCLC clinical trials.4 As noted, the study by She et al. (7) similarly found that enhancement of radiotherapy by ZD1839 was not dependent on the levels of expression of EGFR in the cell lines being tested. This may relate to the characteristics of the assays themselves (16) as well as to the as-yet-unknown molecular mechanism of radiation sensitization. Clearly, an understanding of the molecular mechanism involved may provide a reliable marker for selecting the appropriate patients.

The third issue is how to proceed with clinical evaluation with radiation modifiers designed for a specific target, such as EGFR. For the reasons discussed above, the clinical use of EGFR inhibitors with radiation should ideally be studied only with an appropriately selected patient population. In the setting in which such selection criteria are as yet uncertain, then limited-sized, well-designed, focused empiric trials, in which biological correlates are rigorously assessed and correlated to a clinical outcome, can be of value in delineating the mechanism(s) of interaction. Careful trial design and analysis are essential because the human, time, and financial expense of large empiric trials can be substantial and not cost-effective, particularly in our current era of rapidly emerging molecular-targeted therapies. In that many agents may ultimately have clinical applicability in conjunction with ionizing radiation, it may be wise to evaluate novel targeted therapies with radiation earlier rather than later in the drug development strategy.

References


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