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Focus On

Strategies to enhance radiosensitivity in breast cancer

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Abstract Radiotherapy is an important component in the treatment of breast cancer. However, the individual tumor response to radiation is variable, reflecting both the intrinsic properties of the tumor and its microenvironment as well as the different, inherited sensitivity of the patient's normal tissue when exposed to the effect of ionizing radiation. These differences have inspired research to discover the underlying signal transduction pathways and to understand when they pertain to the tumor, the host or both. In fact, understanding the mechanisms underlying radiosensitivity of breast cancer not only does it permit to design more effective radiation treatments, but it sheds light on the complexities of tumor-host interactions in this disease.

Keywords: Radiosensitivity; Radiotherapy

The modern clinical management of breast cancer frequently requires the use of ionizing radiation either to permit breast preservation, to enhance local control of the axillary and supraclavicular lymph nodal area or to improve pathological response to concurrent chemotherapy in locally advanced breast cancer (LABC). In each of these settings, failures after radiotherapy have warranted research to understand their underlying causes and how to overcome them. Moreover, normal tissue response to ionizing radiation reflects the inherited genetic predisposition to heal and repair to different degrees: recognizing these differences has already shown to be important in the clinic [1].

While no preclinical models can adequately recapitulate the clinical complexity and heterogeneity of human breast cancer, they have revealed to be a useful tool to understanding this disease. A good example is the work done to explain how a tumor's over-expression of HER-2*neu* influences its radiosensitivity [2]. Pietras *et al*. first demonstrated that the MCF7 cell line engineered to over-expressed HER-2 was more radioresistant than the parental line, since HER-2 overexpression resulted in increased repair of the radiation damage. Treatment of the HER-2 over-expressing cells with a monoclonal antibody against HER-2 resulted in increased radiosensitivity when compared with that of the parental cell line. Subsequent studies linked the PI3-K pathway to this process, and demonstrated that trastuzumab reduces phosphorylation levels of Akt and MAPK in MCF7-HER2+ cells [3–5].

During the same years, we conducted a multiinstitutional Phase II trial in LABC that combined the radiosensitization properties of paclitaxel with radiation in the neoadjuvant setting [6,7]. Patients with previously untreated LABC were eligible to receive a regimen of preoperative concurrent paclitaxel, 30 mg/m^2 twice a week for a total of 8 weeks, and radiation delivered at weeks 2–6, 45 Gy at 1.8 Gy per fraction to the breast, ipsilateral axilla and supraclavicular nodes. The choice for a bi-weekly schedule of the taxane was derived from work our group conducted, demonstrating the kinetic of breast cancer apoptosis and mitotic arrest after infusion of the drug, by performing sequential fine needle biopsies in volunteer breast cancer patients who enable the acquisition of this important, in vivo information [8].

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At mastectomy, pathologic findings were classified as pathological complete response (pCR) if no residual invasive cells in the breast and axillary contents were detected, pathological partial response (pPR) if presence of <10 microscopic foci of invasive cells was detected, and no pathological response (pNR) if persistence of tumor was detected. Pathological assessment of response was correlated with gene-expression profiles from an initial pre-treatment core biopsy of the cancer. Interestingly, patients with breast cancers over-expressing the estrogen receptor (ER) and HER-2*neu* genes at reverse transcription-polymerase chain reaction (RT-PCR) were significantly less likely to achieve a pathological response after chemoradiation [9,10].

In view of these findings, our current neoadjuvant chemoradiation study includes treatment with concurrent trastuzumab for HER-2*neu* over-expressing tumors: this study is actively accruing patients and it will enable us to explore whether adding a monoclonal antibody against HER-2*neu* results in increased pathological responses to the same regimen of chemoradiation.

A specific concern in combining a radiosensitizing agent with radiation is the potential to enhance its normal tissue toxicity within the field of radiation. Signal transduction pathways targeted by trastuzumab are shared by normal tissue and cancer, and enhanced cardiotoxicity of systemic chemotherapy has been reported in women treated by trastuzumab [11,12]. Fortunately, results from two multi-institutional Phase III trials (North Central Cancer Treatment Group N9831 and National Surgical Adjuvant Breast Cancer and Bowel Project B-31), addressing the efficacy of combining chemotherapy and radiotherapy with trastuzumab, will provide important information about the toxicity added by trastuzumab to the combination of chemotherapy and radiation in the adjuvant setting of breast cancer.

It is impossible to determine whether hormonal receptor expression is associated with enhanced response to radiotherapy in early breast cancer, or whether it just represents a marker of less-aggressive cancers, with a lower propensity to recur locally, independently of treatment. In the National Surgical Adjuvant Breast and Bowel Project trial B-21, an arm included women with <1 cm tumors who received radiotherapy. Carriers of ER-positive tumors had a lower local recurrence rate than patients with ER-negative cancers, 6.9% vs. 19.1%, respectively. While the addition of tamoxifen (tested in a different arm of the study) further enhanced local control, optimal sequencing of radiotherapy and anti-hormonal therapy has not been determined [13].

An inherited genetic predisposition to respond to radiation damage controls normal tissue response to radiotherapy. Understanding individual predisposition enables a rational approach to the dose and scheduling of radiation [1]. For instance, carriers of germline mutations of genes involved in DNA repair pathways have shown to be exquisitely sensitive to the DNA-damaging effects of radiation [14,15]. Specifically, inherited mutations of BRCA1 and BRCA2 have important consequences on DNA double-strand break repair by homologous recombination. Mouse models have contributed to reveal many of BRCA1 functions, through mutation analysis using gene targeting to create null mutations or disrupt BRCA1 full-length isoforms [16]. New targets were identified, highly specific for BRCA1 mutation carrier, like poly(ADP-ribose) polymerase (PARP), an enzyme involved in base excision repair, a key pathway in the repair of DNA single-strand breaks [17]. When combined with ionizing radiation, anti-PARP drugs are likely to be synergistic. Normal tissue toxicity, however, could be prohibitive, in view of the systemic effects of these drugs, with potential severe complications in the tissue included in the radiation field. Careful dose titration studies need to be conducted to establish how to best reduce the amount of radiotherapy necessary to achieve the same effects.

Recent laboratory evidence supports an intrinsic radio-resistance of stem cells [18,19], consistent with the observed clinical patterns of recurrence we observe in some patients and warranting new strategies to address this challenge, for instance by exploring optimal sequencing of targeted therapy with radiation [3].

Finally, a new area of research regards the complex ‘danger effects’ that ionizing radiation elicits and the opportunities they offer when combined with immunotherapy. In such setting, ionizing radiation to the primary tumor can be used an adjuvant to a systemic strategy that aims at recovering the patient’s immune response to cancer [20–22].

Preclinical insight about strategies to enhance radiosensitivity of breast cancer has been instrumental to designing and sequencing multi-modality therapy. While effects observed experimentally have often been confirmed clinically, preclinical models can underestimate potential acute or late effect on the normal tissue revealed only when tested clinically, in the setting of a clinical trial [23].

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