EDITORIAL

When Old Becomes New—Repurposing Cytotoxic Chemotherapy With Radiation to Improve Outcomes in Women With Aggressive Forms of Breast Cancer

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Breast cancer locoregional recurrence rates have decreased in recent years due to advances in the multidisciplinary management of the disease, most notably improvements in systemic therapy. Thus, investigating treatment de-escalation strategies in favorable subsets has been a prominent focus of recent trials. In contrast, outcomes remain unsatisfactory in some subtypes despite aggressive chemotherapy, surgery, and radiation therapy. Triple negative breast cancer (TNBC) lacks expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 gene and is characterized by higher rates of relapse and death compared with other subsets of the disease. In this issue of the International Journal of Radiation Oncology • Biology • Physics, Bellon et al report the results of a phase 1b dose-escalation trial establishing recommended phase 2 doses of cisplatin in combination with radiation therapy after lumpectomy or mastectomy in patients with TNBC. They demonstrate encouraging safety and tolerability in this patient population.

There is sound rationale for investigating this combination in TNBC. Not only is there proven efficacy of platinum-based radiosensitization across multiple disease sites, but cisplatin has established single-agent activity in TNBC. TNBC is also enriched for deficiencies in homologous recombination DNA double-strand break repair, which predicts heightened sensitivity to this agent. Cisplatin and many other chemotherapeutic agents introduce or potentiate DNA damage in tumor cells, which can enhance the cytotoxicity of radiation therapy, and the concept of combining chemotherapy with radiation in women with breast cancer is not new. Previous single-arm trials have investigated concurrent agents, such as gemcitabine, docetaxel, capecitabine (NCT03958721), and paclitaxel (NCT00006256, NCT00003050), in breast cancer and demonstrated apparent feasibility.

Multichemotherapy combinations have also been investigated with reportedly acceptable toxicity. However, concurrent chemoradiation has yet to display proven efficacy. For example, in the phase 3 ARCOSEIN trial, 716 patients with stage 1 to 2 breast cancer were randomized to sequential chemotherapy followed by radiation therapy versus concurrent multiagent (mitoxantrone, fluorouracil, cyclophosphamide) chemoradiation therapy after breast-conserving surgery.1 Although 5-year locoregional recurrence-free survival was improved in the concurrent arm, there was no difference in disease-free survival, which was the primary endpoint of the study. This may have been due to the favorable population enrolled, including a significant fraction of patients with small, hormone receptor—positive tumors with no or low nodal burden. Most of these patients achieve

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excellent locoregional control with sequential chemotherapy sequencing or no chemotherapy at all.\(^2\) Indeed, optimizing patient selection for the integration of radiosensitizing strategies in breast cancer will be critical to demonstrate improved outcomes with this approach. In the study by Bellon et al., the majority of patients received chemotherapy preoperatively and had residual TNBC at the time of surgical resection. Achieving pathologic complete response to preoperative chemotherapy is predictive of excellent long-term disease control, whereas residual TNBC in the breast, and particularly in the lymph nodes, is associated with high rates of locoregional relapse after conventional adjuvant therapy.\(^3\) The elevated locoregional recurrence risk in these patients suggests that chemotherapy-resistant TNBC is also a more radiosensitive disease biology.\(^4\) Most patients who relapse will ultimately die of their disease. Thus, using residual disease as a biomarker to select patients most likely to benefit from radiosensitizer treatment intensification protocols is an attractive strategy in TNBC and potentially other subtypes, such as luminal B and human epidermal growth factor receptor 2 amplified disease, where high residual disease burden after preoperative chemotherapy also predicts elevated relapse rates.\(^5\) In addition, genomically stratified tests, such as the adjuvant radiation therapy intensification classifier or genomically adjusted radiation dose, may be useful in identifying patients with intrinsically radiosensitive tumors who may be most likely to benefit from novel combined-modality approaches.\(^6\)

Importantly, although the selection of patients at the highest risk of locoregional relapse is generally desired for radiosensitizer studies, most genomic, clinical, and pathologic factors associated with locoregional relapse are also predictive of distant recurrence, which is the main cause of death from breast cancer. Locoregional treatment intensification with a radiosensitizer is unlikely to benefit patients with subclinical metastatic disease at the time of radiation therapy who are destined to fail distantly. Radiosensitizing treatment intensification may also increase the risk of both early and late adverse events, which could detrimentally affect their quality of life.\(^6\) These patients would be better served with enrollment on trials investigating novel systemically directed approaches. Thus, an optimal patient population for breast cancer radiosensitization would include those who are at high risk of locoregional recurrence but whose risk of distant disease progression is low enough to make improvements in locoregional control clinically relevant to the natural history of their disease.

Circulating tumor cells and circulating tumor DNA are 2 examples of promising blood-based biomarkers being investigated to help identify patients with molecular residual disease. These and other liquid biopsies could aid in identifying which patients with breast cancer may benefit from the addition of a radiosensitizer. However, at present, there is no established way to differentiate whether detectable circulating tumor cells and circulating tumor DNA are indicative of residual locoregional versus subclinical metastatic disease. Prospective evaluation of these minimal residual disease markers, ideally at multiple time points before, during, and after the course of radiation therapy such that their dynamics can be monitored and correlated with disease control outcomes, is an important area of ongoing research. In the future, response to neo-adjuvant chemotherapy, genomic predictors of radioresistance, and liquid minimal residual disease biomarkers may all be used to guide and adapt radiation therapy in high-risk patients.

Beyond optimizing treatment selection, a precision medicine approach would involve customizing the radiosensitizer to the distinct genomic and molecular features of each patient’s individual tumor. Despite the promise of platinum-based or other cytotoxic chemoradiation therapy, the addition of targeted agents in combination with radiation may be better suited to such an approach and is of increasing interest in breast cancer. The DNA damage response (DDR) regulates cell cycle arrest, DNA repair, and cell survival after ionizing radiation. Recently, there has been a rapid expansion of our understanding of the intricacies of this complex signaling pathway and how DDR factors may become dysregulated in cancer through both genetic and epigenetic mechanisms.

In parallel, there has been an influx of new selective small molecule inhibitors of the DDR. Targeting DDR vulnerabilities in cancer, such as homologous recombination defects in TNBC, is a promising strategy to improve the therapeutic ratio, because normal tissues typically have their full complement of DDR elements intact. Novel DDR drug–radiation combinations being explored in breast cancer clinical trials that are currently open include trials targeting DDR elements, such as Poly [ADP-ribose] polymerase 1 (PARP1, NCT03598257) and ATR (NCT03188965). Other promising targets include CDK4/6 signaling, the PI3K and Akt pathway, or the androgen receptor, which is expressed in a significant fraction of TNBC.

In addition, emerging data suggest that some inherent or pharmacologically induced deficiencies in the DDR may render tumors distinctly hypersensitive to irradiation with higher linear energy transfer. This avenue of research could lead to tumor-specific patient selection for linear energy transfer–optimized proton or carbon ion therapy and novel particle therapy–radiosensitizer combinations.\(^7\)

There is compelling evidence that unrepaired DNA damage induced by radiation therapy may also upregulate innate immunity, leading to a more robust antitumor immune response. Anti PD-1/PD-L1 immune checkpoint inhibitors have improved pathologic complete response rates in early stage PD-L1−negative and PD-L1+positive TNBC and are already approved in metastatic PD-L1+positive TNBC. The proposed strategy of using radiation therapy to create an in situ vaccine that augments the efficacy of anti-PD-1/PD-L1 or other immune checkpoint inhibitor therapy is being investigated in both early stage and metastatic breast cancer.\(^8\) The interconnectedness of the DDR with tumor immune surveillance may be even more effectively exploited when radiation therapy is combined with certain inhibitors of the DDR.\(^9\) Therefore, optimizing the selection of the most appropriate DDR inhibitor to
combine with radiation therapy and immunotherapy, as well as therapeutic sequencing, will be of particular interest to the field in the years ahead.

Finally, novel clinical trial designs should be explored to facilitate the systematic examination of these approaches. Such trials could use a master protocol that provides a regulatory framework to study multiple radiosensitizers in the same study, akin to the I-SPY 2 neoadjuvant chemotherapy platform design. This would allow new agents to enter and leave the study without having to halt enrollment or resubmit the entire clinical trial protocol for regulatory review, potentially increasing cost effectiveness and efficiency.

Depending on which DDR element is targeted, DDR inhibitors can be highly potent radiosensitizers; thus, long-term follow up for subacute and late adverse events will be important. In addition, investigation of new early predictors of late toxicity are desperately needed. For example, although in a recent phase 1 trial of concurrent veliparib (a PARP inhibitor) concurrent with radiation demonstrated an acceptable safety profile, dose-limiting acute adverse events were not associated with late grade ≥3 adverse events, which affected 47% of patients at year 3. Thorough hypothesis-based preclinical testing of combination approaches in clinically relevant models with both efficacy and normal tissue endpoints will be needed before proceeding to clinical trials to have the greatest chance of benefitting patients. The study by Bellon et al is an example of the rigorous clinical investigations that will be needed on the road to future phase 3 radiosensitizer studies in high-risk early stage and locally advanced breast cancer.

References