Innovation abounds in cancer therapy

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For decades, the treatment modalities for patients with cancer have included surgery, chemotherapy, and radiation. Each of these, individually, have demonstrated merit in their own right, and in some situations their combinations or sequences has led to improvements over existing standards. There are many examples of this in our specialty, such as platinum-based chemoradiation, the administration of chemotherapy after debulking surgery for advanced-stage ovarian cancer, and adjuvant radiation following surgery for high-risk early-stage endometrial cancer.^{1–3} However, as good as these are in controlling disease for some individuals, overlapping toxicities, failure to augment benefit, and ultimate treatment failure have placed a cap on their leverage. Fortunately, the expanding body of science - focused mechanistically on oncogenesis, combined with a nearly equally intensive pace of drug development, has enabled each of these modalities to be revisited for the opportunity to stand among those therapies called 'standard'.⁴ Indeed, several biologically based treatments, such as those targeting tumor angiogenesis, mutations in *BRCA1/2*, and microsatellite instability have already received Food and Drug Administration (FDA) approval and are part of our current therapeutic armamentarium.^{5–7} The fruit of this investigative landscape is a decline in mortality across many individual diseases and an expanding prevalence population of cancer survivors.⁸ Nevertheless, innate and emergent tumor resistance continues to be encountered, driving the need to explore novel strategies for treatment.

In the current issue of this Journal, Dr Lin and her colleagues provide an overview of how one of our treatment standards, namely radiation therapy, fits into the paradigm of leveraging biologically focused combination therapy in an attempt to define new avenues of treatment. Several of the mentioned ongoing clinical trials are supported by rationale that exploits 'in-field' tumor-tissue interactions of radiotherapy and various biological agents. Since radiotherapy can cause direct injury to tumor DNA, many of the most promising strategies are directed at perturbation of high-fidelity DNA damage response (DDR) repair.⁹ Although mechanistically, inhibition of DNA damage response elements and cell-cycle checkpoints appear to have differing levels of individual lethality, their combination with radiotherapy increases the probability of success through sensitization or modality-drug synergy. This

latter effect can occur through active, dual-modality potentiation, such as combinations with adavosertib (anti-WEE-1) or poly(ADP-ribose) polymerase (PARP) inhibitors, where DNA damage response is incited due to resident tumor injury. Lack of single-agent treatment efficacy is not necessarily a deterrent in these situations since these agents are 'context-defined', that is, they are somewhat dependent on vulnerabilities of the tumor microenvironment, which are inducible by radiation. The reverse is also true; drug-induced contextual alterations in the tumor microenvironment can augment radiotoxicity or sensitize resistant tissue to radiation. Chemotherapy, as mentioned above, has already demonstrated its merit in this regard. However, targeting other elements of oncogenic cell signaling, such as those involved in growth receptor pathways, can remove restrictions to effective cell-kill caused by radiotherapy. The trick with these strategies is clearly understanding the 'chicken or the egg' principle; clinical trials need to clearly examine how sequencing is related to successful tumor control.

One of the more intriguing interactions under intense clinical investigation is that involving immunotherapy. This is not a new concept. Radiation therapy is known to induce a number of both immunostimulatory and immunosuppressive effects in the tumor microenvironment and in the host and, as such, holds great promise for cancer patients.¹⁰ Some of the direct effects involve the release of tumor-specific antigens which, in a competent host, should educate the immune system, promoting cytotoxic immune cell trafficking to the tumor microenvironment. This principle has also been leveraged in vaccines and cellular-based immune therapy.¹¹ However, radiation therapy can also induce the release of a number of protective circulatory cytokines, as well as expansion of immunosuppressive regulatory T-cells contravening clinical efficacy. It is in this latter case that the availability of specific immune checkpoint inhibitors, such as those targeting PD-1/PD-L1, have changed the landscape of systemic therapy for a number of solid tumors, including gynecologic cancer. Lin and colleagues outline these effects and strategies nicely in their review.⁹ Perhaps one of the most intriguing effects is that related to remote tumor control following localized radiation - termed the 'abscopal' (or ab scopal, 'away from target') effect. The first report of an abscopal effect was published in

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1953, and although the exact mechanism remains elusive, immune editing is believed to play a dominant role.¹² However, the event is rare in medicine and likely reflects global immune tolerance at the time treatment is initiated. The revolution of immunotherapy, principally driven by immune checkpoint inhibitors, has rekindled interest in designing novel treatment algorithms that may optimize or accentuate a potential abscopal effect. In addition to immune checkpoint inhibitors (anti-PD1/PD-L1, anti-CTLA4, and so on), alternate radiation dosing, alternate dosing fractionation, concomitant combined immunotherapeutics, intra-tumor administration of immunostimulants and immunotherapy, charged nanoparticles, and nanodelivery systems have been suggested.¹³ Indeed, several protocols are adding localized stereotactic radiation to systemic therapy in an effort to optimize systemic control. The expanding array of immune-manipulating agents are providing new avenues of exploration for cancer control.

While radiation therapy is frequently considered an effective strategy in controlling disease that can be seen, the explosion agents targeting biology effects in the tumor microenvironment are greatly expanding the reach of this modality to tumors that can not be seen. Augmentation of effect, overcoming innate and acquired resistance, and systemic control from localized delivery are all under investigation in women with gynecologic cancer and are revitalizing what was once considered a 'one trick pony' modality. Optimization of approach will need to effectively evaluate the short term and, perhaps more importantly, the long-term toxicities of these novel approaches. However, the renewed optimism is spurring novel clinical trial development and is expanding true multimodality individualized treatment opportunities.

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