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Everything Old Is New Again: Using Nelfinavir to Radiosensitize Rectal Cancer

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Summary

Repurposing agents approved for other indications to radiosensitize tumors may be advantageous. The study by Hill and colleagues utilizes Nelfinavir, an HIV protease inhibitor, in combination with radiotherapy in rectal cancer in a prospective study. This combination may improve tumor perfusion and regression compared to radiotherapy alone.

In this issue of *Clinical Cancer Research* (CCR), Hill and colleagues combine Nelfinavir (an HIV-protease inhibitor) with short course, hypofractionated radiotherapy (SCHRT) in rectal cancer and examine tumor perfusion and tumor cell density (TCD) (1). This study was performed to determine both the toxicity of the combined regimen as well as examine the utilization of imaging modalities (perfusion CT and DCE-MRI) to investigate tumor perfusion over the course of treatment. Ultimately the authors conclude that the treatment regimen has minimal added toxicity and enhances tumor perfusion.

Despite multiple decades of laboratory effort, the development of targeted radiosensitizers has yielded little in the way of clinical success. With the exception of cetuximab in head and neck cancer, few targeted agents are used clinically in conjunction with radiotherapy. Even more despairingly, the addition of cetuximab to combined cytotoxic chemotherapy and radiation does not improve outcomes compared to chemoradiation alone (2). The underlying reasons for the lack of success in developing more efficacious radiosensitizers are almost certainly multifactorial. Principal among these are the dearth of strong preclinical studies in appropriate animal models, the scarcity of preclinical data on the addition of drug to standard of care chemoradiation therapy, the lack of biomarker-based enrichment strategies in study design, insufficient understanding of molecular mechanisms of drug-radiation interaction, the absence of sufficient rationale for sequencing of drug and radiation, the potential for additive or synergistic toxicity, and the shortage of clinical success stories which further reduces enthusiasm of pharmaceutical companies to support combination

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drug-radiation studies. Consequently, one is presented with the current situation in which the most common radiosensitizer is cytotoxic chemotherapy. This status quo has persisted for nearly two decades.

However, all is not lost. With the scientific research community rediscovering the possibilities of combining radiotherapy with other therapies, albeit primarily in the field of tumor immunology, a new cohort of researchers are looking at ionizing radiation with fresh eyes. Additionally, several investigators are re-examining and re-purposing agents utilized in other diseases to radiosensitize solid tumors. This has a significant benefit in both decreasing the administrative burden and possibly the cost of conducting clinical trials of radiosensitizers as well as, hopefully, minimizing toxicity, by using agents that, on their own, are almost invariably less toxic than most cytotoxic agents. Commonly prescribed medications ranging from beta-blockers to metformin to, in the current study and others, protease inhibitors have been and are being examined to determine their potential for radiosensitization. Pre-clinical efforts in this vein have led to several clinical trials including the one presented in this issue of *CCR*.

A unique feature of this study is the patient population the evaluation of drug-radiation combination was conducted in. Patients with metastatic rectal cancer are often treated with hypofractionated radiation alone (without chemotherapy) to their primary site so as to achieve local control without significant delays to systemic therapy for their metastatic disease. Combining a putative radiosensitizer with this hypofractionated radiotherapy affords an opportunity to dissect out the true benefit of drug-radiation combination therapy. Utilizing this unique window of opportunity in clinical practice to evaluate the combination of a new agent and radiation alone, the authors circumvent the need to establish the superiority of the addition of drug to capecitabine-radiation over capecitabine-radiation alone in locally advanced rectal cancer. While those studies will need to be conducted in the future if nelfinavir is to be combined with neoadjuvant chemoradiation therapy for rectal cancer, this study provides valuable information on the combination of drug and radiation alone.

Nelfinavir is an HIV-1 and HIV-2 protease inhibitor (PI) that has been utilized as part of highly active retroviral therapy (HAART) for patients with HIV/AIDS. It has been extensively studied for its *in vitro* and *in vivo* anti-cancer activity alone or in combination with cytotoxic chemotherapy and radiation (3-9). The authors focus primarily on the ability of nelfinavir, and PIs more generally, to inhibit Akt. However, this agent can modulate a variety of signaling molecules and pathways leading to cellular cytotoxicity (Figure 1). This highlights a difficulty of re-purposing existing agents as radiosensitizers in that the vast majority are, in effect, “dirty drugs” with no single specific targets. Indeed, an effect on any one of the pathways in Figure 1 could reasonably lead to radiosensitization. Thus, the effects of this agent and other PIs on radiosensitization could be, and likely are, multifactorial.

But this is not a reason for discouragement. This multifactorial mechanism may be advantageous from a clinical perspective, as simultaneously targeting multiple pathways could minimize acquired resistance. It may simultaneously abrogate multiple pathways of radiation resistance thereby overcoming redundancies in pro-survival signaling that

circumvent radiation-induced cell death. The drawback is that from a scientific perspective, this adds a significant degree of difficulty. Additionally, a promiscuous agent also presents a challenge in developing rationally designed clinical trials, as selecting the patient population most likely to benefit would be difficult *a priori*.

Building on previous pre-clinical work showing increased tumor perfusion following treatment with nelfinavir (9,10), the authors utilized DCE-MRI and perfusion CT to examine effects of nelfinavir as monotherapy as well as in combination with SCHRT. The agent alone did not affect tumor perfusion by these measures, however increased tumor perfusion was observed following the combination therapy. Additionally, the authors examined pre- and post-treatment biopsies for the proportion of tumor cells to stroma, which they have previously investigated as a prognostic marker in colorectal cancer (11). Decreases in tumor cell density (TCD) were seen in the majority of samples post treatment. Since patients did not routinely undergo surgery after SCHRT, an MRI-based assessment of response was used as a surrogate for pathologic tumor regression grade (TRG). Five of 9 evaluable patients exhibited “good” tumor regression on post-treatment MRI. Toxicity was reasonable compared to what would be expected with SCHRT alone.

Unfortunately due to the small sample size (10 patients) as well as the lack of a comparison arm we have to be careful with possible conclusions. The authors rightly point out that SCHRT alone can indeed induce alterations in tumor perfusion as measured by available imaging techniques. Thus, the additional effect of nelfinavir is difficult to discern in this study. Further, TCD has not been used in this context previously so it would be difficult to cross-compare with other similar studies. Nevertheless, the authors have demonstrated that the combination of Nelfinavir and SCHRT is reasonably safe to investigate further and variables such as TCD and tumor perfusion can be measured and investigated in this context.

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Figure 1. Possible mechanisms by which HIV protease inhibitors modulate tumor radiosensitivity. ER, endoplasmic reticulum; ROS, reactive oxygen species; SOD, superoxide dismutase.