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EDITORIAL

Clinical Radiosensitization: Why It Does and Does Not Work

IMPROVING THE OUTCOME of cancer treatment by combining a chemical/biochemical agent with radiation therapy has been of interest to oncologists for many decades. The studies conducted by Eisbruch et al¹ and Clamon et al,² reported in this issue, are among many in recent years that used drugs as radiosensitizers. One drug, carboplatin, is a cytotoxic agent. The other, bromodeoxyuridine (BUdR), is not. The treatment of cancer with radiation and drugs was reviewed recently in this Journal by Tannock,³ who noted that clinical gains had been small and “new, mechanistically based approaches to combined treatment are required.” Similarly, there has been limited success with radiation modifiers.⁴ Of the positive combined modality studies, most show small gains and many other trials are null, like that of Clamon et al,² in which the radiosensitizer group did not fare better than the controls. There are also occasional examples of negative studies in which the control arm has fared better than the combined treatment group.⁵

Given the potential benefit to improved local tumor control, quality of life, and survival by combining radiation with radiation modifiers, it is worthwhile to consider the complexities of combined modality treatment.^{4,6-9} An important “bottom line” is that a null study does not necessarily negate the underlying scientific concept. Absence of proof is not necessarily proof of absence of an effect or interaction.

The clinical trials of radiation plus drugs have been divided into the following four generic types by Steele and Peckham^{6,7} according to the nature of how the radiation and drug(s) interact: (a) spatial cooperation, in which each modality treats a different anatomic site, eg, adjuvant therapy after treatment of the primary tumor or radiation therapy to treat a chemotherapy “sanctuary site”; (b) toxicity independence, in which each agent can be given in full dose because the toxicities do not overlap or enhance one another; (c) protection of normal tissue, eg, the use of amifostine as a radioprotector⁴; and (d) enhancement of tumor response, in which the drug-radiation interaction may

be additive, subadditive, or supraadditive as determined by isobologram analysis, which involves knowing the dose-response curve for the radiation and drug for the specific effect being analyzed. In practical terms, the classes of interactions are not distinct. For example, simultaneous administration of chemotherapy with radiation therapy may have properties of both local tumor radiosensitization and treatment of microscopic metastatic disease.

When weighing the use of a radiation modifier (radiation sensitizer, normal tissue protector, or standard chemotherapy) and evaluating the results of a clinical trial, there are a number of important concepts to consider¹⁰:

1. What is the target of the modifier?
 - DNA, mRNA, transcription factor
 - Specific enzyme
 - Receptor or cell membrane
 - Signaling molecule (kinase, phosphatase); alteration of protein turnover
 - Effector molecule (eg, Bcl-2)
 - Extracellular factor, microenvironment (oxygen, growth factor, metabolite, cell-cell or cell-matrix interaction)
2. Is the target stable?
 - Cell cycle variation
 - Heterogeneity among tumor cells
 - Dynamic: Does the biochemical environment alter expression or configuration of the target molecule?
 - Resistance: Is it inducible (eg, multidrug resistance)?
 - Drug tolerance: Is more required over time to achieve the same effect?
3. Can the target be reached?
 - Pharmacology
 - Macro: Can it reach the tumor (typical pharmacokinetic analysis)?
 - Mini: intratumoral distribution
 - Micro: intracellular target
 - Radiation: Does radiation alter the local (tumor or cellular) drug pharmacokinetics?

4. What is the optimal schedule?
 - Pharmacokinetics
 - How to use agent effectively, possibly with pharmacokinetic-guided therapy to optimize modifier efficacy and minimize toxicity
 - Pharmacogenetics
 - Individual variation
 - Impact of treatment on target: Will drug and/or radiation alter the target?
 - Molecular expression
 - Cell cycle perturbation
5. Can the radiation modifier be used throughout a course of fractionated radiation therapy?
 - Drug toxicity
 - Single-dose maximum-tolerated dose: Does it predict for toxicity in a combined modality regimen?
 - Cumulative administration maximum-tolerated dose for a course of fractionated radiation may be different than single-dose maximum-tolerated dose
 - Must drug be given with each radiation treatment?
 - If not, when in the course of radiation therapy is it best to administer the modifier?
 - Patient compliance over the course of treatment
 - Immunogenic response for biologics, gene therapy, etc.
6. Selectivity: tumor versus normal tissue?
 - Therapeutic ratio
 - Is modifier plus radiation therapy better than more radiation therapy?
 - Is there a differential effect on tumor and normal tissue?
 - Should normal tissue be targeted (eg, anti-angiogenesis)?
7. What is the design of the clinical trial?
 - Phase I: Will the toxicity of drug alone be of help in determining the drug plus radiation toxicity?
 - Phase II/III/IV (proper end points: local control, quality of life, and survival)
 - Will a local control end point be lost if systemic failure is predominant?
 - Can local failure be accurately determined?
 - How does the trial consider acute and chronic toxicity?
 - Acute toxicity may be severe yet transient, while the ultimate utility of the combination may be determined by the late effects. Designing a trial based on acute toxicity may miss an important effect.
 - Is the study sufficiently large to demonstrate a relatively small difference?

In the randomized trial reported by Clamon et al,² all patients received initial chemotherapy and were randomized to receive radiation with or without weekly carboplatin 100 mg/m² during the 6 weeks of radiation therapy. The primary study end point was an improvement in overall survival. The trial indicated no difference, although there was a suggestion that local control may have been improved to some minor extent without an increase in local toxicity. The authors noted the difficulty in determining local tumor control because of radiation changes on the imaging studies. Appropriately, this radiation sensitizer regimen was deemed of limited value in this patient population because control of systemic disease remained the most important factor. The authors also noted that neither the precise mechanism for radiation sensitization nor the optimum schedule for carboplatin are known, so other approaches that use this agent as a radiation sensitizer remain worthy of consideration.

Clearly, one of the most challenging aspects of effectively combining drugs with radiation is knowledge of the optimal timing and dose of each agent/modality. Although they have limitations, preclinical studies are mandatory to define the basic mechanism of radiosensitization of a particular drug and how the drug interacts with radiation in vitro and in vivo. With this information, initial clinical strategies may be identified. Ideally, biopsies and appropriate analysis of tumor (and normal tissues when possible) during the course of treatment would determine whether the basic mechanisms presumed to be operational are indeed working in the patient's tumor and whether the drug reaches the tumor in sufficient concentrations. If this is done, even if the trial produces a null result in terms of response, a scientific explanation may be forthcoming and/or alterations in timing can be rationally considered. It is not surprising that the majority of radiation modifier clinical studies do not incorporate evaluation of tumor tissue. Multiple tumor biopsies are inconvenient, add cost and time to the study, may pose certain risks to the patient, and may discourage patient participation in a trial. The location of the tumor for biopsy is often problematic, and there is the concern of doing multiple biopsies in an irradiated field. The interpretation of drug (or drug metabolite) concentration in tumor biopsies can be complicated by the infiltration of host cells into the tumor mass. Future possibilities include the use of single-cell analytical techniques for assessing the molecular phenotype¹¹ and DNA microarrays to identify and validate drug targets.¹² Unfortunately, despite the best intentions, there may not be resources or personnel available to evaluate the samples.

In light of these complexities, Eisbruch et al¹ are to be commended for incorporating multiple biopsies of tumor and normal tissue into their regimen of BUdR and radiation treatment. Incorporation of halogenated pyrimidines into cellular DNA has long been known to radiosensitize cells.

This study marks a departure from the conventional way that halogenated pyrimidines have been administered with radiation, that is, the drug is usually administered before and/or concurrent with radiation. Preclinical studies provided the rationale¹³ for the investigators to explore a unique schedule of BUdR delivery to cervical cancer patients whose radiation treatment volume contains rapidly dividing rectal mucosa and bone marrow cells. The concept is that rapidly dividing tissues, such as rectal mucosa and bone marrow, will incorporate more BUdR during a given exposure time than the tumor will. However, when BUdR exposure is stopped, a more rapid dilution of BUdR levels will occur in rapidly dividing normal tissues compared with the tumor. Thus, if radiation treatment is started several days *after* BUdR exposure is stopped, there should be a higher BUdR incorporation level in the tumor compared with normal tissues, leading to differential tumor radiosensitization.

The major objective of this phase I study, establishment of the maximum-tolerated dose of BUdR and radiation, was achieved, plus much more. The investigators obtained substantial biologic data that support the rationale of their study. The tumor-normal tissue ratios indicated increased DNA incorporation and labeling index in the tumor compared with the normal tissue, and the distribution of the BUdR indicated that there was some migration of BUdR from the intestinal crypts toward the surface. A sufficient percentage of BUdR was incorporated into DNA to produce an enhancement ratio of 1.2 to 1.3. The labeling index was approximately 50%, and it remains to be seen whether a sufficient proportion of tumor cells incorporate enough BUdR for there to be effective tumor radiosensitization¹⁴ (J.F. Fowler, personal communication, November 1998).

Although the complexity of a radiation modifier study seems daunting, the two articles in this issue of the *Journal of Clinical Oncology* are examples of well-conceived and well-designed studies. Although there is much empiricism in clinical trials, the inclusion of pharmacologic and biologic data collection will greatly enhance the ability to make appropriate changes in the treatment regimen, understand the results, and develop new scientific hypotheses. Even if the exact mechanism(s) of the drug-radiation interaction is not known before to the clinical trial, functional biologic assays can be conducted, including cell cycle (eg, flow cytometry), DNA damage (eg, comet assay), oxygenation and pH status, functional imaging, and a variety of biochemical assays. Radiation oncologists and biologists have been leaders in the development of numerous quantitative biologic assays over the years. Teamwork between basic scientists and clinicians can add a new dimension of scientific information that will undoubtedly advance the knowledge base and, most importantly, enhance the rapidity with which a new therapeutic concept will be assessed and ultimately delivered to the patient.

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