Decreasing the Adverse Effects of Cancer Therapy:

National Cancer Institute Guidance for the Clinical Development of

Radiation Injury Mitigators

Benjamin Movsas¹; Bhadrasain Vikram²; Martin Hauer-Jensen³; John E Moulder⁴; Ethan Basch⁵; Stephen L Brown¹; Lisa A Kachnic⁶; Adam P Dicker⁷; C Norman Coleman²; and Paul Okunieff⁸

¹Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI; ²National Cancer Institute, Rockville, MD; ³Division of Radiation Health, University of Arkansas for Medical Sciences, Little Rock, AR; ⁴Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; ⁵Memorial Sloan-Kettering Cancer Center, New York, NY; ⁶Department of Radiation Oncology, Boston Medical Center, Boston, MA; ⁷Department of Radiation Oncology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; and ⁸Department of Radiation Oncology, University of Florida Shands Cancer Center, Gainesville, FL

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Corresponding Author:

Benjamin Movsas, MD
Chairman, Radiation Oncology
Henry Ford Hospital
2799 West Grand Blvd.
Detroit, MI 48202
Phone: 313-916-5188; Fax: 313-916-3235
bmovsas1@hfhs.org

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Statement of Translational Relevance

This article presents guidelines to facilitate the development and clinical testing of potential radiation injury mitigators. It reviews the mechanisms of radiation injury, the clinical challenges, and the design and conduct of clinical trials. The goal is to be able to translate such promising agents into the clinic to improve the quality of life for patients receiving radiotherapy or chemoradiotherapy for cancer.
Abstract

Recently, many agents have been identified that target molecular pathways that can mitigate radiation toxicity. To date, no drugs have been approved as radiation injury mitigators (RIM), defined as agents administered after irradiation but before toxicity is manifest. In order to accelerate the application of potential mitigators for cancer patients, a meeting sponsored by the National Cancer Institute (NCI) and National Institute of Allergy and Infectious Diseases (NIAID), was held in January, 2010. This article presents an algorithm to guide clinical trials for such agents in patients receiving radiotherapy or radiochemotherapy. It reviews the mechanisms of radiation injury, the clinical problem, the preclinical and clinical development of candidate agents, and the design and conduct of clinical trials. The central role of patient reported outcomes is outlined, as well as key lessons learned from prior clinical trials. Ultimately, the goal is to be able to apply such promising agents to improve the quality of life for patients receiving radiotherapy or chemoradiotherapy for cancer.
Introduction

The deleterious effects of radiation exposure, whether administered for treating cancer or malevolent in nature, are well known. However, there are currently no drugs approved to mitigate radiation toxicity when given after exposure and only one, amifostine, has been approved as a radioprotector for administration before or during radiation therapy (1). When vulnerability to terrorist attack became clear after the events of September 11, 2001 the United States government funded the Centers for Medical Countermeasures against Radiation (CMCR) under the Project BioShield Act of 2004 to develop agents to be used in case of a malevolent radiation event. The potential applications of such agents for patients receiving radiation therapy for cancer, however, could have substantial peacetime benefits well beyond their original purpose.

Important in this regard is the recent discovery that many agents (some identified within the CMCR program) target newly identified molecular and physiological pathways and thereby can mitigate radiation toxicity (2-10). The overwhelming majority of putative agents have only been investigated to date for their potential to reduce the toxicity of radiotherapy and not combined modality radiochemotherapy. The term ‘mitigators’ is reserved for agents that are administered after irradiation but before toxicity is manifest (11). It is reasonable to expect that these agents will be less likely to also protect cancer cells than a radiation ‘protector’ which, by definition, is administered before or during radiation. As discussed later, some agents studied have shown no adverse effect on the tumor response and some even appear to enhance tumor response to radiation. There remain, however, several logistical, regulatory, and scientific barriers that impact the clinical application of these agents in patients with cancer.
In order to better understand those barriers and to accelerate the application of appropriate mitigators in the cancer clinic, a meeting co-sponsored by the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID) was held in Rockville, Maryland, on January 25, 2010. More than 50 experts from around the world participated. CMCR and oncology clinical trial group leaders were joined by experts in epidemiology and quality of life issues, representatives from the pharmaceutical industry, patient advocates and FDA officials. The meeting agenda, participants, abstracts, slides and video are accessible at http://www3.cancer.gov/rrp/index.shtml. The key objectives were to:

1. Recommend best preclinical practices for evaluating agents in the CMCR pipeline for applications in cancer patients
2. Recommend clinical trial designs that could efficiently move the most promising agents into appropriate clinical trials
3. Establish the scientific rationale that might be applied by regulatory agencies to evaluate agents for investigational new drugs (IND) applications and final approval.

We present an algorithm (Fig. 1) to guide clinical trials for such agents in patients receiving radiotherapy or radiochemotherapy.

**Mechanisms of Radiation Injury**

For reducing toxicities it is important to understand the cellular and tissue mechanisms underlying radiation injury of normal tissues, which can be significantly different than those related to cellular death of tumors from ionizing radiation. Biomarkers may then be
developed to identify the patients most likely to suffer adverse events, or identify the cancers in which treatment de-escalation may perhaps be the best strategy for decreasing adverse events (e.g., HPV positive cancers of the pharynx) (12).

The response to radiation consists of several molecular events up to and even beyond the development of overt injury (13). According to one model, radiation-induced injury is the result of a dysregulated wound healing response involving multiple cellular compartments and molecular pathways (14). There are multiple potential targets for therapeutic interventions to decrease injury, as well as for developing biomarkers to predict injury (15,16).

TGF-β appears to be a key mediator of fibrosis (17); TGF-β signal activity may decrease radiation-induced fibrosis. Furthermore, it may also improve the response of the tumor to radiation by attenuating the proliferative impact of inflammation on the tumor cells, thereby preventing the selection of resistant clones. Other cytokine-modifying agents may also show such dual benefits (18), as early response genes activated by ionizing radiation can have lasting downstream effects on other signal transduction pathways (19,20).

Promising agents may be grouped by mechanism of action and timing of administration. Those with the greatest effect when administered within hours after irradiation (e.g., histone deacetylase [HDAC] inhibitors) probably enhance DNA repair in normal tissues and/or impair DNA repair in tumors (21). Other early mechanisms may include effects on apoptosis and other mediators of cell death (13). Those agents exhibiting their effects when administered days or weeks after irradiation (e.g., angiotensin-converting enzyme [ACE] inhibitors, tetracycline analogs, Cox-2 inhibitors
and statins) may do so by reducing inflammation that would have led to subsequent injury to normal tissues (10,22-25). As discussed above, decreasing inflammation may enhance anticancer efficacy as well (1,2,18). Some of the best-studied agents are those that suppress the renin-angiotensin system via ACE inhibition or angiotensin II receptor blocking. They mitigate radiation nephropathy (2,6), lung injury (26,27) and CNS injury (28) in experimental animals, as well as clinical radiation nephropathy (29). The efficacy of these agents at clinically relevant drug doses, combined with their widespread clinical use for other indications, makes them attractive for the mitigation of radiation injuries.

The third group of agents, perhaps best applied weeks or months after irradiation, includes regenerative agents, such as stem cells (30).

It is important to remember that an agent may produce different effects in different organ systems. For example, inhibition of p53 leads to protection of the bone marrow from radiation but may radiosensitize the gastrointestinal tract (31,32).

**The Clinical Problem**

The first step in designing a clinical trial is to define the clinical problem and develop the trial hypothesis (Fig. 1). Grade 3 or worse adverse events are not uncommon during and after radiation therapy (33). They are often accompanied by many other, less serious symptoms that nonetheless adversely affect patients’ quality of life. Issues related to the quality, as well as quantity of life, need addressing and the informed consent process should ensure that patients and their families better understand the effect of treatment on quality of life. Advances in the fields of radiation oncology and medical physics have created sophisticated treatment-planning tools and delivery systems that have helped
reduce some of the known toxicities experienced by cancer patients receiving radiotherapy or chemoradiotherapy (34). For example, studies suggest that intensity-modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT) may reduce the risk of xerostomia in patients with head and neck cancer (35), as well as the risk of radiation pneumonitis in patients with lung cancer (36). Moreover, the definition of normal tissue tolerance has evolved and led to a deeper understanding of the multiparametric inputs that influence toxicity (37). Yet, the impact of such newer radiation technologies and normal tissue constraints have been offset in some cancers by escalation of the radiation dose and concurrent chemotherapy aimed at improving the tumor response.

There is abundant evidence that clinicians underestimate the frequency and severity of patients’ symptoms and, therefore, the published data underestimate the true toxicity burden (38). In NCI-sponsored trials, for instance, the standard lexicon for reporting adverse events is the Common Terminology Criteria for Adverse Events (CTCAE) (39), an entirely clinician-reported tool, including the 10% of its items that represent symptoms rather than clinical signs/observations. To redress this, in 2008, the NCI initiated the Patient-Reported Outcomes project (PRO-CTCAE) to create patient versions of those symptoms (40). To date, 77 symptoms of the CTCAE have been converted to PRO-CTCAE items and are currently undergoing validation. In a related development, the FDA Guidance document on PROs was recently released in its final form (41), wherein a PRO is defined as any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by anyone else. Examples include symptoms, quality of life, treatment
preferences, satisfaction with care, and medication compliance. PROs have become the gold standard for reporting on these areas and methodological standards, for developing and administering PRO instruments and reporting data collected by such instruments, have matured over the past several years. The FDA Guidance encodes these standards and specifies that PRO measures should demonstrate reliability, validity, sensitivity to score changes, and have appropriate recall periods. These properties should, therefore, be demonstrated for the population of interest in any given trial.

**Preclinical and Clinical Development of Candidate Agents**

Guidelines for generating the necessary preclinical data before moving candidate agents into appropriate clinical trials will be published as a separate report. Briefly, agents should be selected based upon:

1. Protection from or mitigation of radiation injury in at least one normal tissue system
2. Lack of tumor protection, or tumor protection that is substantially less than the reduction of damage to the normal tissue(s) of interest; in other words, there is substantial potential for improving the therapeutic ratio.

Many drugs in clinical development fail. The reasons include inadequate biological plausibility, inadequately predictive animal models, lack of understanding of the optimal scheduling of the agent, and suboptimal design of the clinical trials. One instructive example is Radiation Therapy Oncology Group (RTOG) study 0315, a 233-patient prospective, placebo-controlled randomized trial of octreotide, a somatostatin analog, for reducing CTCAE grade 2-4 acute diarrhea among patients receiving radiation therapy to
the pelvis for cancers of the rectum or anus (42). RTOG 0315 found no difference in the incidence of diarrhea between the placebo and octreotide arms. One reason for this result may be that diarrhea in the placebo arm was lower than predicted due to improvements in the technique of irradiation over time. Another factor relates to the use of concurrent chemotherapy in this study. Since octreotide decreases diarrhea related to chemotherapy, this study was not a pure test of the effect of octreotide on radiation bowel injury. Another reason may relate to the underlying mechanism of action of somatostatin in radiation-induced gastrointestinal injury. The contents of the small bowel, most notably the exocrine pancreatic digestive secretions, augment the damage to already compromised small bowel mucosa. Animal studies demonstrated that surgical removal of the pancreas, pancreatic duct-occlusion or inhibition of pancreatic enzymes in the bowel lumen reduced deaths after abdominal irradiation (10). Somatostatin analogs inhibit exocrine pancreatic secretions; therefore, this strategy would be most appropriate for protecting the small bowel. Yet, the volume of small bowel irradiated may have been limited in this study that focused on the treatment of anal or rectal cancers. This experience highlights the importance of considering the biological mechanism and the limitations inherent in extrapolating from animals to human studies for cancer patients (6,9) and suggests how clinical trials in cancer patients can inform the attempts to develop radiation countermeasures for protecting healthy soldiers and civilians.

‘Phase Zero’ Trials

The failure rate in clinical trials may also be reduced by applying the principles of phase zero trials during the earliest phases of clinical development. Phase zero trials are ‘first-
in-human’ trials designed to evaluate the pharmacodynamic and pharmacokinetic properties of investigational agents in small numbers of patients before initiating larger, traditional trials (43). One type of phase zero trial is designed to evaluate the effect of a drug on its molecular target/pathway in humans, utilizing procedures validated in preclinical models. A phase zero trial involves relatively low doses of the drug administered over a short period; therefore it may be initiated in accordance with the FDA Exploratory IND Guidance [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf] with less preclinical toxicity data than required for traditional first-in-human studies.

The properties of good drug candidates for phase zero trials include:

1. A wide therapeutic window is anticipated (toxicity is not the primary endpoint).

2. Measurable target/biomarker modulation is anticipated following treatment with low, nontoxic doses given for 7 days or less (biomarker modification is the primary endpoint).

3. A robust effect is anticipated that can be adequately assessed in a small number of patients using analytical methods validated in preclinical models.

In addition to or instead of formal phase zero trials, these same principles can be employed in more traditional, early-phase trials involving patients with cancer, in order to inform the design of subsequent, larger trials. Such studies in patients with cancer may also add substantial value to radiation countermeasure development, by providing much richer data regarding the dose ranges of a novel agent, its pharmacokinetics and pharmacodynamics and, of course, clinical efficacy, than might be ethically justifiable in
studies restricted to healthy volunteers. Phase zero studies in the traditional cancer drug development pathway typically use normal tissues surrogates (e.g., peripheral blood mononuclear cells) along with tumor for pharmacokinetic and pharmacodynamic evaluation. The use of “normal” tissue is precisely what a mitigator trial will require to ensure that the agent in question is having its desired effect. For example, a hypothetical agent, based on preclinical data, could reduce radiation-induced cytokines by 50%, which might correlate with a 20% reduction in acute toxicity.

**Design and Conduct of Clinical Trials**

Some important lessons with regard to designing and conducting clinical trials of radiation protectors/mitigators were learned from RTOG 9801, a 243-patient prospective, randomized trial of the radioprotector amifostine, aiming to reduce esophagitis in the setting of lung cancer treated with radiochemotherapy (44). Accrual was slow initially partly due to concern among some clinicians regarding the potential for tumor protection seen in some animal studies (45). Ultimately, RTOG 9801 did meet its accrual goal and showed no difference in tumor control or overall survival between the two arms. Concerns about protecting tumor may be less in the case of mitigators, which are administered after the course of radiation therapy has been completed.

Another challenge was ‘correctly’ interpreting the results because RTOG 9801 demonstrated the disconnect that can occur between endpoints measured by clinicians versus patients (46). According to its primary endpoint (NCI-CTCAE grade of esophagitis, determined by clinicians), the result of RTOG 9801 was null (p=0.9), yet patients in the amifostine arm in their daily diaries reported significantly fewer
swallowing problems (p=0.025) as well as significantly less pain (p=0.003) using a validated quality of life instrument. While a placebo effect cannot be excluded, other studies have demonstrated a similar disconnect between physician and patient reported outcomes (47,48). The ongoing PRO-CTCAE project described earlier may in the future facilitate better trial design and reduce such discrepancies.

Meeting with the FDA at the pre-IND stage is strongly recommended for addressing concerns regarding tumor protection, as well as selection of the most appropriate endpoint(s). A statistical analysis of the degree of tumor protection that may occur can also be performed before the IND stage. One strategy is to perform a competing risks analysis, considering the severity and frequency of toxicity and balancing that against the impact on survival in the event of unexpected tumor radioprotection. Thus, a quality-adjusted survival analysis can be considered a key goal in designing the study. Early stopping rules based on tumor control endpoints should also be incorporated. In addition, prospective trials in this area will require quality assurance criteria with appropriate imaging studies to objectively evaluate the radiation treatment planning/delivery and quantify the volume of normal tissue receiving ionizing radiation.

The RTOG Health Services Research and Outcomes (HSRO) Committee has developed a framework to guide the assessment and testing of an increasingly comprehensive and complex set of outcomes in Phase II and III treatment trials (49). This framework has evolved from a triad of clinical, humanistic, and economic endpoints to a model that also includes biological and physical outcomes. The goal is to collect data that will help elucidate the mechanisms of the effects of irradiation on normal tissues and the impact on patients’ experiences. It also acknowledges that there can be significant inter- and
intratient variability in early and late side effects reflecting inherent genetic variation (50). Recently, for symptom management trials conducted through the Community Clinical Oncology Program (CCOP), the RTOG incorporated the framework proposed by the NCI Translational Research Working Group (TRWG) which conceptualized translational research as a set of six developmental pathways focused on various clinical goals (51). The lifestyle alterations pathway (52) may be the most pertinent for symptom reduction and quality of life improvement studies.

In summary, among the priority areas for the oncologic development of promising agents, especially those being developed as radiation countermeasures are:

1. Support for preclinical studies to demonstrate lack of protection of tumors.
2. Support for incorporating suitable biomarkers (including imaging agents for normal tissue injury) and patient-reported outcomes into early-phase clinical trials
3. Support for developing biomarkers, assays or “signatures” that may help select the most appropriate patients for those trials.
4. Support for the development of “Go/No-Go” decision criteria and objectives to advance an agent forward.

Funding for such studies may be available, among other sources, from the National Institute of Health (NIH) as research project grants and/or Small Business Innovation Research (SBIR) grants and/or Small Business Technology Transfer Research (STTR) grants.
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Figure Legend

Figure 1: Algorithm for development of appropriate clinical trials to test radiation injury mitigators.
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THINK TANK

I
Clinical problem defined (i.e., trial hypothesis)?

YES
CONSIDER:
1. Is toxicity relevant to patients?
2. Mechanism underlying toxicity.
3. Which disease site(s)?

NO

II
Promising agent identified?

YES
CONSIDER:
1. Has agent met preclinical criteria (Ref 9)?
2. Is agent relevant to disease site(s)?
3. Mechanism of action/timing with RT and/or chemo
4. FDA-approved (for another indication)?
5. Does agent also sensitize tumor? If yes, does it nonetheless improve the therapeutic ratio?
6. Sources of funding (RPG, SBIR/STTR grants, etc).

NO

III
Is the optimal endpoint selected?

YES
CONSIDER:
1. Validated PRO endpoint.
2. Patient burden/compliance.
3. Biological/physical correlates.

NO

IV
Can an appropriate clinical trial be designed?

YES
CONSIDER:
1. Begin FDA (pre-IND) discussions.
2. Phase 0/I vs. II/III design.
3. Early stopping rule re: outcome.
4. Presenting to cooperative group mechanism.
5. Statistical design.
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