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Radiation—Therapeutic Agent Clinical Trials: Leveraging Advantages of a National Cancer Institute Programmatic Collaboration

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A number of oncology phase II radiochemotherapy trials with promising results have been conducted late in the overall experimental therapeutic agent development process. Accelerated development and approval of experimental therapeutic agents have stimulated further interest in much earlier radiation-agent studies to increase the likelihood of success in phase III trials. To sustain this interest, more forward-thinking preclinical radiobiology experimental designs are needed to improve discovery of promising radiochemotherapy plus agent combinations for clinical trial testing. These experimental designs should better inform next-step radiation-agent clinical trial dose, schedule, exposure, and therapeutic effect. Recognizing the need for a better strategy to develop preclinical data supporting radiation-agent phase I or II trials, the National Cancer Institute (NCI)-Cancer Therapy Evaluation Program (CTEP) and the NCI-Molecular Radiation Therapeutics Branch of the Radiation Research Program have partnered to promote earlier radiobiology studies of CTEP portfolio agents. In this *Seminars in Radiation Oncology* article, four key components of this effort are discussed. First, we outline steps for accessing CTEP agents for preclinical testing. Second, we propose radiobiology studies that facilitate transition from preclinical testing to early phase trial activation. Third, we navigate steps that walk through CTEP agent strategic development paths available for radiation-agent testing. Fourth, we highlight a new NCI-sponsored cooperative agreement grant supporting in vitro and in vivo radiation-CTEP agent testing that informs early phase trial designs. Throughout the article, we include contemporary examples of successful radiation-agent development initiatives.

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Introduction

Modern studies in radiation biology have elucidated exploitable DNA damage responses that either lead to cell cycle arrest or that induce repair or bypass mechanisms of DNA damage, some of which are relatively target-specific to cancer cells because of disruption of these pathways.[1] To better translate new experimental therapeutic agents to clinical trials, the National Cancer Institute (NCI)-Cancer Therapy Evaluation Program (CTEP) portfolio of anticancer agents now available for radiobiological investigation could best be utilized through an efficient program to evaluate expeditiously radiation-agent combinations that may hold promise for phase I or II testing.

A previous NCI-sponsored summary workshop recommended that agents of interest should augment radiation effects through either synergistic or additive mechanisms, and if short of those effects, should at least exhibit single-agent or combinational activity with coadministered chemotherapy without diminishing the radiation effects.[2] An alternative recommendation encouraged trials of neoadjuvant treatment (here, radiation-agent combinations) followed by

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Table 1 Examples of Radiation-Agent Combinations That Led to Positive Phase II or III Studies.

Radiation	Agent	Target	Comparator*	Disease	Phase	Comment	References
Fractionated	Cetuximab	EGFR	RT alone	Head/neck	III	NCT00004227	51
Fractionated	Cisplatin	DNA	RT alone	Vulva	II	NCT00006096	52
Fractionated	Temozolomide	DNA	RT alone	Glioblastoma	III	NCT00006353	53
Fractionated	Triapine	RNR	-	Uterine cervix	II	NCT00941070	19
Fractionated	Any completed trial CTEP agent† (1977-2016)	Various	Standard-of-care	Variable	II/III	12/994 (1%) + clinical benefit among radiation-agent studies	-

Abbreviations: EGFR, epidermal growth factor receptor; RT, radiation therapy.

*Where comparator is indicated, the agent is combined with the then standard-of-care radiation alone or radiation-drug regimen.

†Here, we searched CTEP databases with the terms "radiation," phase "II," "II/III," or "III," and "complete," "closed to accrual," or "closed to accrual & treatment" status to identify radiochemotherapy trials supporting modern radiation oncology practice. An assignment of clinical benefit to an identified radiation-agent study was subjective.

surgery. This view is predicated upon pathologic complete response serving as a best surrogate for therapeutic efficacy, and thus, predictor for phase III testing success.[3]

We align with the first notion in that scientifically provocative radiobiology effects from experiments carefully crafted for clinical relevance might predict success in early phase trials, thus conserving total research effort and scarce funding (acknowledging that the 2 propositions are not mutually exclusive). Approximately 1% of radiation-agent combinations tested in phase II or III trials advance successfully to actual radiotherapeutic practice in oncology (Table 1). This contrasts sharply to the 5% success rate of agent monotherapy progressing to the oncology drug market, and to the 11% mean success rate observed among other clinical medicine drug markets.[4]

An obstacle to more efficient and more successful radiation-agent development arises from preclinical-to-clinical complexity surrounding optimal radiation-agent dose, schedule, exposure, and effect, which could be overcome by developing mechanisms to generate the necessary preclinical data. Moreover, the agent mechanism of action when combined with radiation may be different than that for the agent alone, which is both an additional complexity and a possible "repurposing" of the agent. In this article for *Seminars in Radiation Oncology*, 4 key parts, focusing on agent access, radiobiology, strategic development, and collaborations, are discussed from the perspective of NCI-CTEP and the NCI-Molecular Radiation Therapeutics Branch (MRTB) of the Radiation Research Program (RRP).

Agent Access for Preclinical Radiobiology

Since 2009, the NCI Experimental Therapeutics (NExT) Program has brought 58 new agents into the CTEP experimental therapeutic agent portfolio that are potentially active against cancers and are available for clinical development. This is usually carried out under an NCI-brokered cooperative research and development agreement. Most of the NExT-approved anticancer agents in the CTEP portfolio have molecularly distinctive targets against well-characterized cancer cell signaling pathways or "fingerprints." The selection of agents to combine with radiation is an important consideration based on an agent's presumed molecular selectivity, monotherapy activity, and its putative radiation-enhancing effects (Fig. 1).

Given the need for information regarding the cellular radiation-agent interactions to target, there are essential radiobiology experiments that should be done before initiating early phase targeted agent radiochemotherapy trials.[5] A first step in this experimental path involves agent acquisition by an interested investigator through the CTEP agent material transfer agreement (MTA) mechanism. A templated MTA contract addresses the exchange of agent research materials between extramural investigators and CTEP. Under an approved 3-year MTA, there are provisions for CTEP-to-investigator transfer of a prespecified agent allotment, exclusive use of an agent in investigator-defined research, concession that agent exchange is for immutable non-human use, and overarching agent intellectual property rights. The MTA permits unrestricted investigator presentation and peer-review publication after a 45-day NCI and industry collaborator review period. A particular advantage of the MTA is the pre-existing provision for radiation-agent "A" –agent "B" combinations or radiation-agent "A" vs radiation-agent "B" comparisons when distinct industry collaborators supply agents of interest. From the NCI vantage, MTA investigator-defined research should be sufficiently broad such that the in vitro and in vivo radiobiology experiments enable a thorough exploration of radiation-agent and radiochemotherapy-agent activity and biomarker development and performance.

Informative Studies in Preclinical Radiobiology

Properly designed and executed preclinical radiobiology studies and their underlying mechanisms can effect fundamental aspects of a radiation-agent clinical development plan (Table 2). A clinically informative radiobiology study includes: (A) fractionated radiation delivery, (B) radiation dose demonstrating synergistic or additive radiation-enhancing effect with the novel agent, (C) clinically relevant novel agent concentrations, and (D) radiation-agent schedules that both optimize