Clinical Development of Novel Drug–Radiotherapy Combinations

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Abstract

Radiotherapy is a fundamental component of treatment for the majority of patients with cancer. In recent decades, technological advances have enabled patients to receive more targeted doses of radiation to the tumor, with sparing of adjacent normal tissues. There had been hope that the era of precision medicine would enhance the combination of radiotherapy with targeted anticancer drugs; however, this ambition remains to be realized. In view of this lack of progress, the FDA–AACR–ASTRO Clinical Development of Drug–Radiotherapy Combinations Workshop was held in February 2018 to bring together stakeholders and opinion leaders from academia, clinical radiation oncology, industry, patient advocacy groups, and the FDA to discuss challenges to introducing new drug–radiotherapy combinations to the clinic. This Perspectives in Regulatory Science and Policy article summarizes the themes and action points that were discussed.

Introduction

The FDA–AACR–ASTRO Clinical Development of Drug–Radiotherapy Combinations Workshop took place on February 22–23, 2018, in Bethesda, Maryland. The meeting was conceptualized by Dr. Amanda Walker, Associate Director (Acting) of the FDA’s Oncology Center of Excellence, in response to a consensus paper published on this topic led by Professor Ricky Sharma on behalf of the CTRad group of the UK National Cancer Research Institute (NCRI; ref. 1). The workshop’s principal aim was to bring together over 400 stakeholders and key opinion leaders from academia, clinical radiation oncology, industry, patient advocacy groups, and the FDA to provide a forum to discuss real and perceived challenges to introducing new drug–radiotherapy combinations to the clinic. The primary outputs of this workshop are summarized here (Box 1). In this article, we discuss the current perspectives in Regulatory Science and Policy.

Box 1: Key Messages

- There is great potential for drug–radiotherapy treatment strategies to improve clinical outcomes for patients.
- Early and frequent communication between multiple stakeholders, including industry, academia, regulatory agencies, and patient advocates, is essential.
- Intelligent trial design is required to increase the number of studies that efficiently meet their primary outcomes.
- Endpoints including local control, organ preservation, and patient-reported outcomes may demonstrate clinical benefit and should be considered in clinical trials of drug–radiotherapy combinations.
- Novel approaches including immune-oncology or DNA-repair inhibitor agents combined with radiotherapy should be prioritized.

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landscape of drug-radiotherapy combinations, challenges associated with the development and approval of drug-radiotherapy combinations, and strategies that may be adopted by stakeholders to help overcome them.

The Unrealized Potential of Drug-Radiotherapy Combinations

Radiotherapy is a key component in the management of 40% of cancer patients cured of their disease (2). Moreover, it provides a highly effective treatment strategy for the palliation of symptoms in individuals suffering with advanced disease. Despite major advances in radiation technology over recent years, it remains one of the most cost-effective treatment modalities in oncology (3).

In the radical treatment of cancer when the treatment intent is cure, radiotherapy is often combined with conventional cytotoxic drugs such as cisplatin or 5-fluorouracil. This radiosensitization approach is supported by robust level 1 evidence (4). Within recent decades, the advent of precision medicine has shifted the focus of cancer drug discovery toward targeting specific proteins and pathways for therapeutic gain. This, along with advances in immuno-oncology (IO), has been associated with dramatic improvements in clinical outcomes (5–7). These observations have led researchers to hypothesize that similar benefits may be realized through combining novel targeted drugs with radiation.

The scientific rationale for combining radiotherapy with novel targeted agents has been appraised in previous reviews (1, 4). The aim of any treatment combination is to improve the therapeutic ratio such that the anticancer effect is enhanced over and above any corresponding increase in normal tissue toxicity. Importantly, this strategy is therefore not only limited to drugs that enhance tumor death but may also involve agents that limit toxicity in normal cells (8).

The FDA granted approval to a combination of radiotherapy with a targeted agent in March 2006. However, in the 12 years that have followed, no new drug–radiotherapy combinations have been approved (9). The combinatory drug approved at that time was cetuximab—an antiepidermal growth factor receptor (EGFR) monoclonal antibody—for use in head and neck cancers. It had been widely perceived that, as more novel targeted agents entered the clinic, the number of clinically effective drug-radiotherapy combinations would also significantly increase.

While no new drug–radiotherapy combinations have passed regulatory approval during this period, the FDA has approved more than 130 novel drug indications in oncology. A significant number of these indications involve novel agents in combination with cytotoxic chemotherapy (e.g., pertuzumab and cetuximab in breast and colorectal cancers, respectively). Moreover, a PubMed database search for entries from 2006 onward using the keyword “radiosensitization” identifies 1,713 articles published, suggesting that preclinical and clinical research in this area remains highly active. So what is driving this stark disparity?

What Guidance Is Required to Make Progress?

A number of factors were identified that implied that the pathway to approval of a novel drug-radiotherapy combination is hindered from day 0. To date, the FDA has not published a regulatory guidance document specifically detailing the approval pathway for a drug-radiotherapy combination. Pharmaceutical industry representatives cited the lack of regulatory guidance as a significant hurdle. Without regulatory guidelines to support drug development, strategic decisions on investment into drug-radiotherapy combinations cannot be derisked against specific criteria pertaining to approval. This may result in combination strategies being deprioritized. However, there is no published evidence that the publication of a specific regulatory guidance document increases industry-led drug development within that area. Some of the existing regulatory guidance on drug–drug combinations may in fact be applied to drug-radiotherapy combinations (see below; ref. 10).

There is evidence of a significant lag time in testing drugs in combination with radiotherapy during the clinical development of a novel agent (11, 12). One study demonstrated the median interval between the opening of phase I trials without radiotherapy, and those with, was 6 years. Further, phase I trials with radiotherapy were typically published after 9 years of the drug patent had lapsed (12). With drug patents limited to 20 years, a lag of this magnitude would significantly diminish the potential profitability of a drug-radiotherapy combination. In light of this, there are few incentives for pharmaceutical companies to take promising phase I data through to a costly phase III registration study with radiation. This is particularly true given the high attrition rates seen from phase I to phase III.

Pharmaceutical companies are further discouraged from investigating drug-radiotherapy combinations due to misconceptions and uncertainty around the preclinical data required for regulatory approval, particularly regarding safety. Moreover, generating optimal preclinical data in the context of radiation requires specific knowledge and assays to which pharmaceutical companies may not have access. At the workshop, FDA representatives provided detailed clarification on this matter, and a summary is provided in Box 2.

Regulators highlighted the challenge of providing a comprehensive guidance document due to the many possible development scenarios for drug-radiotherapy approaches. As with many development programs, each case is unique, and the most detailed advice to sponsors can be offered when the FDA performs clinical trial reviews for investigational new drug applications. It was suggested that industry representatives arrange formal meetings with the FDA at an early stage to help define a clear line of sight to registration for each individual drug-radiotherapy combination (13). For broader advice, much of the guidance relating to drug–drug combinations may be applicable to combinations with radiation (10).

Toxicity data for new treatment combinations in clinical trials may not be required by the FDA, depending on the extent of toxicity data available for each individual agent (14). A strong rationale for combining the drug with radiation should be presented with consideration given to potential organs at risk of toxicity. If this is based on clear and robust science, further preclinical experiments to support the hypothesis are not always necessary. Case-by-case discussions with regulators should be sought.

In the case of investigational compounds at early stages of development (i.e., human toxicity data remain uncharacterized), preclinical data with a particular focus on safety are necessary. A pharmacology study supporting the rationale for the
Box 2: Preclinical Data Set Required for a First-in-Human Drug–Radiotherapy Combination Study

- No formal guidance document exists detailing the preclinical data set required for regulatory purposes.
- Recommendations for preclinical data required for drug-only studies, detailing specific pharmacokinetic (PK) and pharmacodynamic (PD) data sets, are available in the ICH S9 document [ref. 10; Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use].
- The overarching message from FDA representatives at the workshop was that similar thinking should be applied to drug–radiotherapy combinations as in drug–drug combinations, and, given that cancer patients often have limited options, the focus should be on safety. Moreover, it is not always necessary to generate new preclinical data prior to testing a drug–radiotherapy combination in humans, for instance, if the drug has already received regulatory approval as a single agent and sufficient clinical data are available. A case-by-case discussion with regulators at an early stage of clinical development is therefore always recommended.

Demstrate proof-of-principle

- The rationale, mechanism of action, and preliminary activity from preclinical models (in vitro and in vivo) should be provided.
- No specific in vivo model systems (e.g., genetically engineered mouse model vs. patient-derived xenograft) are preferred in general, and thus choice should be tailored to individual cases.
- Scheduling of drug–radiotherapy combination should be assessed, e.g., does drug need to be administered daily, is an induction course needed prior to starting radiotherapy?

Efficacy data should include studies using standard of care as a backbone and/or comparator; i.e., in cervical cancer, radiotherapy with cisplatin chemotherapy is standard of care; therefore, drug + cisplatin + radiotherapy data should be generated to ensure there are no antagonistic effects associated with combining drugs.

Proof-of-principle data may also help inform potential target organs for toxicity and safety biomarkers.

Define safe starting dose of drug

- Toxicology studies are the most important aspect of the preclinical data set; it is advised to discuss each case with the regulators at an early stage.
- Toxicity data from the combination are not essential, and relevant data from individual agent (drug alone ± radiotherapy alone) are sufficient.

- Starting dose may be calculated using various methods, and this should be individualized on the basis of the drug.
- Starting dose may be based on monotherapy clinical experience and/or animal toxicity data.
- Starting dose selection can be based on STD10 (dose severely toxic to 10% of humans) and HNSTD (highest nonseverely toxic dose in nonrodents).
- The preclinical NOAEL (no observable adverse effect level) dose followed by conversion into a HED (human equivalence dose) may also be utilized.
- MABEL (minimum anticipated biological effect level) may be more appropriate for immunomodulatory agents.

Understand toxicologic profile

- Target tissue and organs, potential for reversibility of toxicity, and exposure–response relationships should be established.
- Toxicology data should be derived from at least one rodent and one nonrodent study (though single species acceptable in case of monoclonal antibodies).
- Toxicology studies should use a route and schedule representative of human clinical use; studies of 1 month duration are sufficient.
- Data on long-term toxicity (i.e., longer than 1 month) are not essential, though model systems informing long-term toxicity should be studied where possible.
- Methods of monitoring toxicity within human target tissue and organs should be established.

combinations should be provided. Such a study should demonstrate increased activity in the absence of a substantial increase in toxicity on the basis of limited safety endpoints in animals, such as mortality, clinical signs, and body weight.

The role of preclinical data within the regulatory approval process represents a relatively "easy win" for the industry. For drugs already approved in most circumstances, there may be no need to generate further preclinical data. In drugs at earlier stages of development, there are significant incentives in performing the preclinical experiments outlined in Box 2 as the drug may subsequently be approved in combination with radiation for a longer duration during the compound's patent. These experiments may be performed in collaboration with partners in academia. Indeed, throughout the workshop there were calls to improve communication between the industry and radiation oncologists.

An increasing number of assays and model systems have been studied that examine radiation-related toxicity (15). Murine models can be utilized to study the effects of thoracic radiation with and without a novel targeted agent. Early access to these model systems during the drug-discovery process would enable the prioritization of agents as clinical radiosensitizers (16). However, the development of model systems predicting radiation-related toxicity remains at an early stage and consequently data generated from these models should not be overinterpreted.
Finally, discussions between radiation oncologists and industry will ensure industry-led studies are designed to collect data on long-term toxicity. This area is often neglected in drug-only studies but is critical to radiotherapy as it is late toxicities that are dose-limiting.

How to Improve the Design of Future Clinical Trials?

A large number of clinical trials investigating novel drug-radiotherapy combinations have been negative studies. Historically, studies have not enriched for, or stratified patients based on, genotypic or phenotypic information to increase the likelihood of a positive outcome. For instance, there are compelling nonclinical data to suggest that hypoxia-modifying agents may improve radiotherapy outcomes (17). However, clinical trial data have been underwhelming, and a potential reason for this is that patients were not selected on the basis of their tumor’s hypoxic status (18).

Safety is of particular significance in the context of radiotherapy-based trials because patients are often treated with curative intent and thus may have to live with treatment-related toxicities for many decades. This has led to a number of early-phase studies investigating novel drug-radiotherapy combinations in patients receiving palliative radiotherapy for incurable or metastatic disease. This mirrors the strategy frequently adopted in single-agent and combination drug trials. An important disadvantage to this approach is that the biology of these advanced tumors may not accurately reflect the biology of early, localized disease, and this may imply that efficacy data do not translate across both patient groups. Patients receiving palliative radiotherapy are also likely to be less fit than patients with early disease, and this may affect patient recruitment and treatment tolerability.

Further, the outcome data from radiotherapy-based clinical studies may be confounded by variability in radiotherapy technique across participating centers (19). Data from the RTOG 0617 study investigating radiotherapy dose escalation in the treatment of non–small cell lung cancer demonstrated improved overall survival in patients treated at institutions with higher clinical trial accrual volumes (20).

Apart from radiotherapy technique, dose fractionation and drug scheduling are also likely to be of significance, particularly in the context of IO agents in combination with radiotherapy. For instance, preclinical data have shown that PD-L1 blockade can overcome resistance to fractionated low-dose radiotherapy but not high-dose radiotherapy (21). This observation is, by no means, generalizable, and our understanding of the interaction of radiation with the host immune system remains only partly understood (22).

A number of potential solutions may help to improve the design of clinical drug-radiotherapy trials. Biomarker-driven studies should allow more evidence-based patient selection, ensuring that the efficacy of a novel agent is more accurately evaluated. To bolster the development of biomarkers, window-of-opportunity studies in the neoadjuvant setting may be of more value as they allow access to tumor tissue to assess for pharmacodynamic (PD) studies. Furthermore, since phase I toxicity studies are often limited to specific anatomic sites and may not be generalizable to other cancers with a different spectrum of normal tissue toxicities, umbrella studies (one cancer—multiple mutations—multiple drugs) and basket studies (multiple cancers—one mutation—one drug) run using adaptive trial designs should be considered to allow more efficient use of resources and enable multiple hypotheses to be tested within one clinical trial (23).

The issues around safety and the appropriateness of conducting trials in the palliative setting may, in part, be addressed by performing trials in patients who are receiving stereotactic body radiotherapy (SBRT) for oligometastatic disease. This approach has been particularly suitable for studying IO–radiotherapy combinations where the aim has been to provide long-term disease control. However, the option of performing studies in patients with oligometastases should not detract investigators from the traditional curative setting, particularly if preclinical data suggest that the combination will be most effective in this patient group.

The role of radiotherapy quality assurance (RTQA) within all clinical studies cannot be overstated, and efforts to harmonize international RTQA standards are essential. Within the United States, the Imaging and Radiation Oncology Core (IROC) run out of The University of Texas MD Anderson Cancer Center has developed many important resources enabling robust RTQA. Within the United Kingdom, this role is taken by the RTIQA group (24). However, the challenges associated with RTQA must also be acknowledged and addressed. Providing real-time QA such that plans are appraised prior to the patient starting treatment is significantly resource-intensive. Investments in human and computing resources will partly address this problem; however, more imaginative solutions such as artificial intelligence–based QA strategies may also be of value.

Uncertainties around radiotherapy scheduling and fractionation in combination with IO and other novel agents should be informed by preclinical evidence. However, these efforts should not significantly delay clinical studies, which should be designed so that tissue samples can be used to back-translate into the laboratory to better understand the biology behind the responses seen in vivo. Adaptive clinical trials, which allow for prospectively planned modifications of the trial based on early clinical data, may be considered during the development of drug–radiotherapy combinations (25).

Classically recognized regulatory endpoints for clinical trials of systemic treatment such as disease-free survival and overall survival may be impractical for some clinical trials of new drug–radiotherapy combinations in the context of a local treatment used with curative intent. Overall survival endpoints may take many years to be reached in patients with good-prognosis diseases. Established endpoints such as disease-free survival or overall survival can still be evaluated as secondary endpoints during longer-term follow-up to confirm clinical benefit in a study that meets an earlier, primary endpoint.

Common early endpoints such as local control can provide evidence of antitumor activity and could be supported by clinically relevant endpoints such as organ preservation rates and assessment of symptoms and function using clinical outcome assessments (Table 1 and Box 3). Regulatory approval could potentially be granted based on earlier endpoints. There is a clear need to develop early and intermediate endpoints of the efficacy, and toxicity, of the new combination. Appropriate early endpoints are likely to be subsite-specific and therefore a consensus should be reached in partnership with the FDA potentially through organ-specific workshops. There are valid
therapy is selected and only patients alive at that time are included in the analysis, and then separated into two response categories according to whether they have responded up to that time.

### Table 1. Summary of clinical trial endpoints to be considered in testing new drug-radiotherapy combinations

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Universally accepted measure of direct benefit</td>
<td>- Trials in radical setting will generally be of a long duration</td>
</tr>
<tr>
<td>Symptom endpoints/patient-reported outcomes</td>
<td>Patient perspective of direct clinical benefit</td>
<td>- May capture abscopal effects of IO</td>
</tr>
<tr>
<td>Organ preservation</td>
<td>Important endpoint for patients</td>
<td>- Also influenced by surgery and/or chemotherapy, therefore, may not be a direct measure of RT effect</td>
</tr>
<tr>
<td>Locoregional control</td>
<td>Smaller sample size and follow-up duration compared with survival studies</td>
<td>- Definitions may vary based on trials</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>- In some scenarios, may correlate better with overall survival than local control</td>
<td>- As per locoregional control above</td>
</tr>
<tr>
<td>Complete or objective response rates</td>
<td>Suitable for neoadjuvant studies</td>
<td>- Not a direct measure of benefit in all cases</td>
</tr>
<tr>
<td>Progression-free survival (includes all deaths) or time to progression (deaths before progression censored)*</td>
<td>- May be suitable in IO-RT studies within metastatic setting</td>
<td>- Not valid surrogate for survival in all settings</td>
</tr>
</tbody>
</table>

Abbreviation: RT, radiotherapy.

*Landmark analyses associated with these endpoints may be particularly suitable for IO-RT trials. In landmark analyses, a fixed-time after the initiation of therapy is selected and only patients alive at that time are included in the analysis, and then separated into two response categories according to whether they have responded up to that time.

### Box 3: The Role of Patient-Reported Outcomes (PRO) in Regulatory Approvals

Measurement of symptoms and function are increasingly obtained in cancer trials and can inform both efficacy and treatment tolerability. Function can be measured through clinical outcome assessments, which may include PRO, functional performance measures (e.g., swallowing or cognitive function), and newer technologies such as wearable devices and sensors. PRO are increasingly being collected within clinical studies, and this is likely to increase as digital health solutions (e.g., digital app-based reporting) become more commonplace. Robust and fit-for-purpose PRO endpoints could potentially be used to support accelerated or traditional approval. For instance, a rigorously developed PRO assessment detailing symptomatic relief helped ruxolitinib gain traditional approval for the treatment of myelofibrosis (27). PRO can add important complementary information to the assessment of tolerability using new measurement systems like the National Cancer Institute’s PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Concerns that endpoints such as organ preservation may be influenced by bias; thus, trial protocols should seek to define prospective criteria for surgical intervention.

### Dialogue between Key Stakeholders

At the workshop, it was acknowledged that the lack of clinical trial activity investigating novel drug-radiotherapy combinations has contributed to the lack of successful regulatory approvals. The incentives underlying academic interest in combining radiation with novel drugs are likely to differ significantly from those within industry. Within the United States, perceived tensions between medical and radiation oncologists may also exist due to historically low levels of research collaboration. Moreover, the FDA as a regulatory body weighs the balance between safety and efficacy from a different perspective for a patient with early-stage disease compared with a patient with terminal cancer with no treatment options available. Consequently, dialogue and collaboration between the stakeholders involved in the clinical development of drug-radiotherapy combinations is critical to enable a better understanding and alignment of interests.

Initiatives should be prioritized to improve collaboration, and this includes engagement with patient advocacy groups (Box 4). An example of this is the RadCom program in the United Kingdom (26), which is a formal collaboration across multiple disciplines with the primary aim of improving the development of...
Box 4: Consumer Advocacy—Key Messages from the Workshop

- The one-size-fits-all approach is not good enough—the promise of combining drugs with radiotherapy in specific circumstances is obvious.
- When used properly, patient-reported outcomes can empower patients; however, data entry can be arduous, and it is hard to remain engaged given other competing pressures on time and attention.
- The coordination of care with drug–radiotherapy combinations is important—need to identify local champions to drive this agenda forward.
- Ensuring that side effects are managed effectively is important to all patients.
- Ensuring that patients understand the science driving the trial, to the best of their abilities, helps foster resilience and dealing with uncertainty.
- Patients will go online—it is essential to provide reliable resources and means to engage with digital health.

References


Disclosures of Potential Conflicts of Interest

M.R. Crittenden reports receiving commercial research grants from Jounce Therapeutics and Nanobiotix, and is a consultant/advisory board member for Celldex, AstraZeneca, and Pfizer. P.T. Tran reports receiving commercial research grants from Astellas and Refexion, is listed as inventor on a patent regarding compounds and methods of use in ablative radiotherapy (patent filed 3/9/2012; PCT/US2012/028475, PCT/WO/2012/122471), and is a consultant/advisory board member for Dow. R.D. Baird reports receiving commercial research grants from AstraZeneca, Boehringer Ingelheim, and Genentech/Roche, and is a consultant/advisory board member for Roche, Shionogi, Boehringer Ingelheim, Genentech, and Molecular. T. Illidge reports receiving speakers bureau honoraria from Takeda, Bristol-Meyers Squibb, and Roche. S.M. Hahn holds ownership interest (including patents) in Liquid Biotech. R.A. Sharma reports receiving commercial research grants from Sirtex and BTG, speakers bureau honoraria from Bayer, Guerbet, and AstraZeneca, and is a consultant/advisory board member for Varian, Sirtex, DeepMind, Terumo, BTG, and Cancer Research UK. No potential conflicts of interest were disclosed by the other authors.

Conclusions

We have witnessed the recent approval of many systemic therapies with varied mechanisms of action leading to an unprecedented opportunity to investigate new drug–radiotherapy combinations. Perceived challenges associated with generating preclinical data and establishing trial endpoints for registration should be readily tractable. Insufficient novel drug–radiotherapy combinations have reached the clinic, and the attendees of this workshop identified several opportunities to foster development in this important cancer therapeutic space. Workshop participants felt energized to take forward the solutions proposed in this summary article to transform the landscape of translational radiation biology and significantly improve clinical outcomes for cancer patients.

Authors’ Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.S. Ahmad, H. Bulbeck, T. Illidge, T.S. Lawrence, A.J. Walker, R.A. Sharma

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.S. Ahmad, T. Illidge, A.J. Walker, R.A. Sharma

Study supervision: T. Illidge, A.J. Walker, R.A. Sharma

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