Cancer Concepts and Principles: Primer for the Interventional Oncologist—Part I

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ABSTRACT

A sophisticated understanding of the rapidly changing field of oncology, including a broad knowledge of oncologic disease and the therapies available to treat them, is fundamental to the interventional radiologist providing oncologic therapies, and is necessary to affirm interventional oncology as one of the four pillars of cancer care alongside medical, surgical, and radiation oncology. The first part of this review intends to provide a concise overview of the fundamentals of oncologic clinical trials, including trial design, methods to assess therapeutic response, common statistical analyses, and the levels of evidence provided by clinical trials.

ABBREVIATIONS

CR = complete response, DCR = disease control rate, EASL = European Association for the Study of the Liver, FDA = Food and Drug Administration, HCC = hepatocellular carcinoma, mRECIST = modified Response Evaluation Criteria in Solid Tumors, NCCN = National Comprehensive Cancer Network, ORR = overall response rate, PFS = progression-free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, WHO = World Health Organization, TTP = time to progression

Interventional oncology offers undeniable benefits to cancer patients in collaboration with medical, surgical, and radiation oncology. In order to affirm our place among these oncologic specialties, interventional radiologists must not only continually contribute to and stay abreast of the ever-evolving treatments available to cancer patients but must also understand the fundamental principles that guide cancer care. Historically, interventional oncology procedures were first performed for palliative treatment or in exceptional cases. Now supported by robust evidence, this discipline is gaining major importance in the management of cancer and is becoming incorporated in therapeutic algorithms as first-line therapies. An interventional oncologist must understand the intricacies of clinical trials not only to critically assess evidence for new and evolving treatments, but also to design and carry out the clinical studies that will continue to define the role of interventional oncology. Just as fluency of expression and understanding in a language requires more than simple familiarity with its vocabulary, assuming a confident and informed role as

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an interventional oncologist requires proficiency with the tools and metrics of oncology.

The first part of this review intends to provide a concise overview of the fundamentals of oncologic clinical trials, including trial design, methods to assess therapeutic response, common statistical analyses, and the levels of evidence provided by clinical trials. The second part of this review will focus on methods of tumor characterization; the principles of medical, surgical, radiation, and interventional oncology; and the current treatment paradigms, including the levels of evidence behind the treatments, for cancers most commonly encountered in interventional oncology. Terms of particular importance will be italicized to highlight their importance in the interventional oncologist's lexicon.

CLINICAL TRIAL DESIGN

Cancer treatment trials are designed to evaluate new therapies and are divided into different phases of evaluation for anticancer agents according to the United States Food and Drug Administration (FDA) (1). *Phase I* trials evaluate the safety and toxicity of a compound and are typically performed in a dose-escalation format. Progressively higher doses are administered to determine the maximum tolerated dose and dose-related toxicities to establish a safe dose for the subsequent phase of the trial. *Phase II* trials focus on determining the efficacy of an agent at its maximum tolerated dose. Because response rates and duration of response are the typical endpoints, patients must have measurable disease at baseline, which, according to most criteria, must be at least 1 cm (2,3). *Phase III* clinical trials are conducted when the maximum tolerated dose of an agent has been tested in phase II study and has demonstrated a reasonable response. Phase III trials typically compare the test agent versus standard-of-care therapy. Although phase III trials are the definitive studies to demonstrate superiority of a new therapy versus the previous standard, many new cancer agents are FDA-approved after successful phase II studies. *Phase IV* clinical trials, often referred to as postmarketing or postapproval studies, are conducted to gather more information about the real-life clinical applicability of a therapy after it has been approved in order to evaluate its clinical implementation, expand labeling and approval, or meet requirements established by a regulatory authority.

Randomized controlled trials are the gold standard of clinical studies. *Comparative trials* (ie, nonrandomized) are vulnerable to various sources of bias and, therefore study conclusions must be interpreted with caution. Propensity scores and match-pairing can help minimize the effects of bias on this type of study. Although randomization produces comparable groups by eliminating selection and allocation biases, on average, one should confirm that factors affecting prognosis and outcome are evenly balanced between the control and intervention groups. The lack of selection and allocation bias and reliable comparability of randomized groups is also required for accurate use and interpretation of tests of statistical significance (4).

Blinding is another important factor in determining the validity of clinical trial results and conclusions. In *unblinded* studies, the participant and the investigator know the intervention to which the participant has been assigned. Although this model more accurately reflects clinical practice, it opens the results to bias. For example, participant reporting of side effects or investigator treatments may be affected and change the course of therapy and results. However, certain treatments do not lend themselves to complete blinding. In a *single-blind* study, only the investigator knows to which group the participant has been assigned. It eliminates participant reporting bias but does not eliminate bias with regard to investigator behavior and data assessment. *Double-blind* clinical trials eliminate investigator knowledge and therefore investigator bias. Unfortunately, knowledge of specific drug side effects often prevents the complete blinding of a treatment arm. As an example, sorafenib produces specific toxicities that would be clearly recognized by investigators during the management process. In *triple-blind* studies, the individuals evaluating data and results are not aware of the participant treatment groups (5).

Intent-to-treat analysis is a critical component of clinical trials. It indicates that all patients assigned to a study arm at the time of randomization are analyzed regardless of subsequent events, such as noncompliance with treatment, receiving no treatment, *crossover*, loss to follow-up, and dropping out of the study. It eliminates bias that might overestimate the clinical benefit of the therapy and ensures that "real-world" effects of the treatment or control are reflected in data analysis. In contrast, in a *per-protocol* analysis, only patients who complete the clinical trial according to the trial protocol are evaluated (6).

ASSESSMENT OF RESPONSE

The outcomes of oncologic therapies can be measured according to several different criteria, each of which reflects a different clinical value that can help determine the applicability of statistically significant results.

Tumor Response Assessment

The *World Health Organization (WHO)* criteria for reporting results of cancer treatment were the first standardized approach to report degrees of tumor response, recurrence, and disease-free interval (2). In a bidimensional approach, maximal tumor cross-sectional area is approximated by measuring the mathematical product of the longest diameter and longest perpendicular of each