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Current issues in dose-finding designs: A response to the US Food and Drug Adminstrations's Oncology Center of Excellence Project Optimus

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Abstract

With the advent of targeted agents and immunological therapies, the medical research community has become increasingly aware that conventional methods for determining the best dose or schedule of a new agent are inadequate. It has been well established that conventional phase I designs cannot reliably identify safe and effective doses. This problem applies, generally, for cytotoxic agents, radiation therapy, targeted agents, and immunotherapies. To address this, the US Food and Drug Administration's Oncology Center of Excellence initiated Project Optimus, with the goal "to reform the dose optimization and dose selection paradigm in oncology drug development." As a response to Project Optimus, the articles in this special issue of *Clinical Trials* review recent advances in methods for choosing the dose or schedule of a new agent with an overall objective of informing clinical trialists of these innovative designs. This introductory article briefly reviews problems with conventional methods, the regulatory changes that encourage better dose optimization designs, and provides brief summaries of the articles that follow in this special issue.

Keywords

Dose finding, dose optimization, phase I, drug development, trial design

Introduction

The emergence of designed molecules, biological agents, and radioligands engineered to treat cancers and other diseases by attacking specific targets has led to a new era in cancer treatment. Following the success of the tyrosine kinase inhibitor imatinib for treating chronic myelogenous leukemia,[1,2] there has been intensive research aimed at engineering novel targeted agents and biotherapies to treat a wide variety of diseases. Natural killer cells, modified to express an anti-CD19 chimeric antigen receptor, have been used successfully to treat B cell hematologic malignancies.[3] Allogeneic cord blood-derived T-regulatory cells have been used to treat COVID-19-induced acute respiratory distress syndrome.[4] The nonsteroidal aromatase inhibitor letrozole, combined with the monoclonal antibody bevacizumab, have increased progression-free survival time in patients with advanced breast cancer.[5,6] Prostate cancer patients with homologous recombination repair genes have been shown to have prolonged survival following treatment with poly-ADP (adenosine diphosphate) ribose polymerase inhibitors.[7] Radioligand therapy with 177Lu-PSMA-617 has prolonged progression-free and overall survival when added to standard of care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer.[8] There are many more examples of promising new targeted agents and biotherapies in patient populations with specific somatic or germline mutations.

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Ongoing preclinical research to develop targeted agents and immunotherapies has created a pressing need for clinical trials to evaluate new treatments. While successes like those noted above have provided promising efficacy as new agents emerge, safety remains a major concern. Although biologically targeted agents have reduced the risks of toxicities, such as nausea/vomiting and neutropenia associated with cytotoxic chemotherapy, a variety of new adverse events have been seen. These include cytokine release syndrome, neurotoxicity, and graft-versus-host disease with cellular therapies, as well as cardiac or thyroid dysfunction, hypertension, ototoxicity, and bleeding with targeted molecules and immunotherapies.

Conventional dose-finding designs

Historically, conventional clinical evaluation of a new agent has begun by fixing a schedule and identifying a maximum tolerated dose (MTD) having an acceptable level of dose-limiting toxicity (DLT) in a phase I trial. This is followed by evaluation of efficacy in terms of an early anti-disease effect, "response," in a phase II trial or expansion cohort of the agent given at the MTD. For logistical convenience, DLT and response are defined over relatively short follow-up periods, often one or two cycles of therapy. In phase I, doses are chosen adaptively for successive cohorts of one, two, or three patients based on the (dose, DLT) data of previous patients. The most commonly used methods include a variety of 3 + 3 algorithms,[9] versions of the continual reassessment method (CRM),[10,11] interval-finding designs, and other model-based designs. Most versions of the 3 + 3 implicitly target doses having toxicity probability, p_{tox}, either 16% or 33%. A CRM design is based on a model assuming that p_{tox} increases with dose, and it chooses a dose having estimated p_{tox} closest to a specified fixed target, typically 20%, 25%, 30%, or 33%. Both methods ignore response, instead implicitly assuming that the probability of response, p_{res}, increases with dose. In many trials, an "expansion cohort" of additional patients is treated at the MTD.

Problems with conventional designs

There is an extensive literature explaining why conventional methods are likely to do a poor job of identifying a safe and effective dose of a new agent;[12–14] 3 + 3 algorithms and the CRM are based on toxicity alone, while ignoring efficacy or mechanistic biological outcomes like target modulation. Consequently, conventional methods have high risks of performing poorly for chemotherapy, radiation therapy, stem cell transplantation, cellular therapy, immunotherapy, and targeted agents. Flaws with conventional dose-finding methods have been identified by computer simulations that estimate average behavior, by specific examples of dose-toxicity and dose-response curves that illustrate logical flaws, and by many completed trials where the conventional dose-finding design failed to identify a safe and effective dose. Shah et al.[15] gave examples of several new agents with MTDs determined in conventional early-phase trials that later were found to have unacceptably high adverse event rates, based on post-marketing data observed after US Food and Drug Administration (FDA) approval. Thall et al.[16] described a phase I trial for an agent in the preparative regimen for allogeneic stem cell transplantation where a dose was selected using the time-to-event CRM, followed by an expansion cohort, but longer follow-up showed that the selected dose was associated with the shortest survival time.[17]

Conventional phase I methods rely on the implicit assumption that p_{tox} and p_{res} both increase with dose. These assumptions may be valid for cytotoxics, therapies, but may not be true for targeted agents, depending on their biological mechanisms of action. For example, as the dose of a targeted agent is increased p_{res} may increase to a point beyond which it remains constant so that the p_{res}–dose curve reaches a plateau. This may occur if an agent reaches a saturation level in systemic exposure of the metabolized agent in the patient's blood. In such settings, because it is likely that p_{tox} still will increase with dose, a conventional method is likely to recommend an overly toxic MTD. Since monotonicity assumptions imply that it would not be ethical to randomize patients among doses, they have motivated the convention of adaptively choosing doses for successive patient cohorts. However, for many targeted agents or immunotherapies, there is no biological or medical reason to assume that p_{tox} and p_{res} increase with dose. In such settings, randomization is ethical and is more appropriate because it provides unbiased comparisons between doses.[4] Small sample sizes are used conventionally in early-phase trials mainly to accelerate the treatment evaluation process. This convention is a false economy, however, because it ignores the elementary statistical principle that small sample sizes give unreliable inferences, which often lead to selection of unsafe and/or ineffective doses. A logical problem with choosing an MTD based on toxicity alone is that an MTD always will be identified, unless the lowest dose is overly toxic. If a new agent has no anti-disease effect at all but p_{tox} increases with dose, an MTD still will be chosen. In this case, the agent given at the MTD does harm without benefit. If an agent has no effect at all, and produces neither toxicity nor response, the highest dose will be chosen as the MTD, producing a completely useless treatment. A CRM design with target toxicity rate 30% considers a dose with toxicity rate 40% more desirable than a dose with toxicity rate 1%, which only makes sense if it is assumed implicitly that p_{res} must increase with dose. Because these problems

are due to the fact that efficacy is ignored, a first step to a solution is accounting for both toxicity and response, that is, conducting a phase I–II trial.

A different problem is that many targeted agents are administered repeatedly over long periods of time. For example, in an analysis of real-world data from patients with metastatic non-small cell lung cancer, patients treated with single agent immunotherapy, such as a programmed death-ligand 1 (PD-L1) directed immune checkpoint inhibitor, stayed on therapy for about twice as long as those treated with doublet chemotherapy.[18] In such settings, it is important for dose-finding designs to use long-term toxicity data to adjust doses adaptively so that cancer treatments given over longer time periods are tolerable. This is essential to ensure that patients do not have unacceptable risks of high-grade adverse events, cumulative toxicity, or persistent lower grade adverse events. With long-term therapy, the traditional paradigm for determining a MTD is very unrealistic because it focuses on high-grade toxicities seen within the first one or two cycles of treatment. If 20%–30% of patients experience grade 3 or higher toxicities within the first cycle of treatment at a selected MTD, insisting that patients continue therapy at this dose for months or years is disconnected from reality, and it does not adequately protect patients. Rather, evaluation of long-term toxicities is necessary. While several efficient phase I designs that account for late onset toxicities are available,[19–22] unfortunately, these still have seen limited use in practice.

Despite increasing awareness in the medical research community of severe problems with conventional dose-finding methods, and the availability of superior designs with freely available, user-friendly software, conventional designs currently are used in the great majority of dose-finding trials.

Changing the paradigm

In 2021, the Oncology Center of Excellence in the US FDA launched Project Optimus, with the mission of reforming the dose-finding paradigm in oncology drug development, recognizing that optimizing dose is essential for safe and effective anti-cancer treatment.[23] Project Optimus aims to

> educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well.

As part of the Project Optimus effort, in 2023, the FDA released draft guidance for industry for optimizing doses of oncologic drugs, with an emphasis on the importance of dose optimization prior to seeking FDA approval. The 2023 draft guidance focuses on several key points: (1) doses must have justification that is appropriate for the development stage of the agent; (2) dosage selection should depend on "the totality" of the available data, which may include safety, dynamic, pharmacokinetic, pharmaco dynamic, efficacy data, and so on; (3) randomized comparisons are encouraged to support dose selection; (4) low-grade symptomatic toxicities should be included in safety evaluation; and (5) drug developers should meet in the early stages of clinical development to discuss their plans with the FDA for dose selection methods.[24]

Another initiative established by the FDA's Oncology Center of Excellence is Project Renewal, which aims to update prescribing information, including dosing, for older oncology drugs, to ensure that information is clinically meaningful and scientifically up to date.[25] An example of Project Renewal's relabeling is capecitabine, which was initially approved in 1998 at a twice daily dose of 1250 mg/m^2 (on days 1–14 of a 21-day cycle). An American Society of Clinical Oncology (ASCO) survey published in 2022 found that 41% of oncologists who treat breast and/or gastrointestinal cancer patients with capecitabine regularly prescribed it at a starting dose level lower than 1250 mg/m^2.[26] Based on available data, in December 2022, there was a major update to the label of capecitabine which included new indications and also the addition of 1000 mg/m^2 (twice daily) as starting dose for patients with metastatic breast cancer.[27] While there was an abundance of data to support lower dosing for capecitabine, other oncology drugs that have been approved more recently and have been prescribed to a narrower patient population may not have the necessary data available. Thus, it is imperative for oncology drugs, which have demonstrated poor tolerance to be reconsidered for dosing. Unfortunately, there is little incentive for drug companies to perform re-optimization studies after approval, unless mandated by regulatory authorities.

Now that the FDA has provided guidance on dose and schedule selection for oncology drug development, it is critically important for the clinical trials community to provide reliable dose selection designs and make them available with user-friendly software for implementation. In addition, while there is still a need for re-optimization of approved agents, the oncology drug development community can do better by utilizing more appropriate designs. New designs should be tailored for the agent's type and class, and approaches for dose selection should be based on more than early safety endpoints. Ideally, dose selection should account for multiple endpoints, including pharmacokinetics and pharmacodynamics, short- and long-term tolerability and efficacy, as well as remission duration, progression-free survival time, survival time, and quality of life.

When ethically appropriate, randomized designs that include a standard of care arm are attractive because they provide unbiased comparisons of clinical outcomes, even if they are not powered for making confirmatory conclusions. These issues are addressed by the family of recently proposed "generalized phase I–II" designs, which use a phase I–II design to identify a set of candidate doses, randomize patients among the candidates, and select a best dose from the candidates based on long term therapeutic success rates.[17]

An overview of the articles in this issue

The articles in this issue of *Clinical Trials* are a response to Project Optimus. The goal is to provide non-mathematical explanations of the methods so that clinical researchers may become familiar with the designs and use them in their own dose-finding trials. The topics were chosen to cover an array of current issues, and the authors were chosen due to their expertise and their experience designing dose-finding trials.

The articles in this special issue of *Clinical Trials* may be summarized as follows:

Practical dose finding methods. Yuan et al. review practical considerations in the design and conduct of dose-finding trials, focusing on the shift from finding an MTD to identifying an optimal biological dose (OBD) of a targeted agent or immunotherapy. They review several different strategies for finding an OBD, including hybrid phase I–II and phase II–III designs, and discuss practical considerations for choosing a design and conducting a trial. They illustrate the methods with real world trials.

Accounting for risk–benefit trade-offs. Msaouel et al. discuss medical and scientific issues that underlie the conduct of phase I–II dose-finding trials. They explain how to account for risk–benefit trade-offs using utility functions tailored to individual patient prognostic covariates, and identify optimal personalized doses. They describe a utility-based phase I–II design that chooses each patient's dose to maximize their expected utility. The design is illustrated by a phase I–II trial of a targeted agent for treating metastatic clear cell renal cell carcinoma.

Selecting a dose based on both efficacy and toxicity. Zang et al. provide a review of phase I–II trials and highlight several innovative designs based on both efficacy and toxicity that identify an OBD. They classify designs into three broad categories: efficacy-driven, utility-based, and incorporating multiple efficacy endpoints. They review the dose-outcome model, definition of the OBD, and the software for each design, and provide a decision tree for selecting the most appropriate design.

Accounting for patient subgroups in dose finding. Lin et al. describe ways of integrating patient subgroups into one trial, while using Bayesian approaches that allow information to be borrowed across subgroups. Relationships between dose, toxicity and efficacy are estimated within subgroups, and a joint estimation approach yields efficient inferences.

Dose finding in the setting of late onset toxicities. Lee et al. discuss challenges in dose optimization when treatment-related adverse events occur late in the course of treatment, or after treatment is stopped. A method for incorporating late onset toxicities is provided, in addition to an illustrative example of this design.

Dose finding when you have two or more agents to optimize. Wages et al. provide methods for dose optimization in the context of two (or more) agents when both agents are escalated in the trial. A well-established method (partial order CRM) is extended to include efficacy endpoints in addition to safety endpoints.

Challenges in the setting of re-optimization. Strobehn et al. consider historical reasons for the usual "MTD" dose finding paradigm and discuss how it is untenable in the precision medicine age. They briefly address the drug development (i.e. pre-approval) setting and focus on priorities and considerations for re-optimization of anti-cancer agents that have already been FDA approved.

Limitations based on small sample sizes in dose finding trials. Chiuzan et al. discuss the strength of evidence to support dose selection when traditional designs with small sample sizes are used, and the need for sample size and precision considerations in trial designs and in reporting of results from dose finding trials.

What dose optimization means to patients. Maues et al. provide a patient perspective, advocating for a patient-centered approach for dose optimization in drug development and treatment, and presenting evidence from surveys of patients. Many patients and their advocates dismiss the "more is better" assumption and encourage dose finding approaches that maintain quality of life.

As understanding of the biological mechanisms underlying different classes of targeted agents and immunotherapies grows, ideally, dose-finding designs for clinical trials will be tailored to reflect this new knowledge. In turn, regulatory agencies may use this growing scientific understanding to refine rules and regulations to better facilitate the treatment development process, while still protecting patent safety. With better dose optimization methods, such as those considered in this issue, the clinical trials community has an opportunity to support the call for new approaches that will benefit patients, drug developers, and regulators.

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