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Overview

Early Phase Clinical Trial Designs – State of Play and Adapting for the Future

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Abstract

The process of anti-cancer drug development is complex, with high attrition rates. Factors that may optimise this process include well-constructed and relevant pre-clinical testing and use of biomarkers for patient selection. However, the design of early phase clinical trials will probably play a vital role in both the robust clinical investigation of new targeted therapies and in streamlining drug development. In this overview, we assess current concepts in phase I clinical trials, highlighting issues and opportunities to improve their meaningfulness. The particular challenge of how to design combination trials is addressed, with focus on the potential of new adaptive and model-based designs.

Key words: Adaptive design; biomarker; dose escalation methods; early phase clinical trials; phase I trials

Statement of Search Strategies and Sources of Information

Pubmed was searched for the terms 'early phase clinical trial design' and articles of relevance were individually reviewed.

Introduction

The development of anti-cancer drugs generally follows a conventional stepwise progression between phases of trials, each with different objectives but aiming to find signals that allow advancement to the next stage of clinical testing (Table 1). This process is widely recognised to be slow and inefficient, and ultimately less than 10% of new therapeutic agents are approved [1,2]. Because of these high failure rates, there has been increased focus on strengthening the underlying pre-clinical work required to generate valid hypotheses [3] and use of biomarkers to identify the most appropriate patients for treatment, particularly in the era of molecular targeted agents (MTA) [4]. Alongside this it is important to consider the design of early phase clinical trials, to ensure they incorporate rigorous stop–go signals and streamline drug development to enable new agents to fail promptly if they are not destined to be tolerable or active.

Increasingly, pre-clinical work amasses data on pharmacodynamic, pharmacokinetic and toxicological profiles, dose or exposure/effect relationships and potential interactions. There are several examples of drug development where a pharmacokinetic/pharmacodynamic model has been used to predict the therapeutic window and design the dosing schedule, with multiple trial designs assessed *in silico* before patients are treated [5]. Window of opportunity studies, with short durations of drug administration, are becoming increasingly popular, encouraging insight into novel therapeutic mechanisms of action at an early stage of a drug's development.

Early phase clinical trials are generally defined as phase I and non-randomised phase II trials. This review focuses on

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Table 1
Phases of clinical trials during drug development

Phase 0	Very small exploratory trials carried out to determine the preliminary pharmacokinetic and pharmacodynamic characteristics of the new compound after administering limited doses, as a preliminary investigation before taking it to further evaluation (not routinely undertaken).
Phase I	Small trials, non-randomised. Primary objectives to assess safety and tolerability and to identify a recommended phase II dose. They evaluate pharmacokinetic and pharmacodynamic biomarkers obtained with the different dose schedule combinations.
Phase II	Larger trials. Usually non-randomised. Main objective to assess anti-tumour activity in a specific setting (usually measure response rates as the primary end point).
Phase III	Very large trials. Mostly randomised. Primary objective is usually determining efficacy of the drug as compared with placebo/standard of care (if any). The primary end points are generally overall survival/progression-free survival.
Phase IV	'Real life patients'. Post-marketing trials, testing long-term safety in patient population.

phase I trials, which include the first-in-human study of a new investigational medicinal product (IMP) as monotherapy, a combination of approved standard drugs, a combination of approved drugs and a new IMP, combination of IMPs or combinations of new or approved drugs with radiation. Phase I trials aim to establish the optimal dose and schedule of a novel drug or combination of drugs, while determining the toxicity profile. The key end point is to determine the recommended phase II dose (RP2D) based on the determination of the maximum tolerated dose (MTD) of the IMP under investigation. The most common phase I study end points are summarised below:

- Primary
  - Identify MTD and RP2D
  - Identify dose-limiting toxicities (DLTs)
- Secondary
  - Pharmacokinetics
  - Pharmacodynamics (molecular and clinical)
  - Target modulation
  - Efficacy

Traditionally, phase I trials do not feature anti-tumour efficacy as a primary objective, and historically there has been a low probability of response (<10%) in early phase studies [1]. Therefore, patient motivation for entering such clinical trials must be considered, particularly in patients who have no standard treatment options available and may have limited life expectancy. The informed consent process should explore the intensity of the required trial interventions, significant time commitment, potential for serious toxicity and low chance of achieving benefit for the individual concerned.

For many decades, these trials have assumed that a higher dose will be the most efficacious and that the probability of toxicity will increase with increasing dose. Although these assumptions may be valid with conventional cytotoxic agents, in the era of MTA and immunotherapies and with the increasing use of combinations of therapies, there is recognition that new designs should aim to identify the most active dose with the fewest adverse events rather than the MTD. In this review, we discuss early phase clinical trial designs, both as single agents and in combination, identifying the issues with conventional designs and the potential of alternatives.

Current Concepts in Phase I Trial Design

The main principle guiding dose escalation in phase I trials is to treat as many patients as possible within the therapeutic dose range, avoiding unnecessary exposure of patients to sub-therapeutic doses of an agent, while preserving safety and maintaining rapid accrual [6]. During the escalation stage, patients are recruited into the trial sequentially in cohorts to receive a dose equal to or higher than the previous patient, with appropriate intervals between cohorts to carry out safety reviews before opening the next higher dose cohort. Based upon the occurrence of severe toxicity, DLT may be identified. DLT is defined prospectively as unacceptable adverse events, either due to severity (e.g. grade 3 or 4, determined by Common Terminology Criteria for Adverse Events [CTCAE]) or duration, which limits further dose escalation, and this is classically based on toxicity emerging in cycle 1 of treatment administration. More recent DLT definitions, however, may be more nuanced, such as grade 3 gastrointestinal adverse events despite adequate concomitant preventative medicine, or grade 2 chronic and unremitting toxicity. If the MTD is confirmed within a particular dose cohort, the RP2D may be defined based on pre-agreed criteria [7–9].

Starting Dose

Historically, the initial starting dose was selected based on rodent (mouse/rat) and non-rodent (dog/non-human primate) toxicology. Although myelosuppression and gastrointestinal toxicity in humans may be reflected using rodents, hepatic and renal toxicity is less reliably predicted, making the use of a second species frequently necessary. For about 20% of new drugs, mouse data alone are insufficient to safely predict the human MTD [10]. The dose (defined in mg/m^2 of body surface area) associated with 10% lethality in mice ($MELD_{10}$) can be predicted to be about equivalent to the human MTD [11], with the initial phase I trial dose 1/10 of the $MELD_{10}$ or, if lower, 1/3 to 1/6 of the lowest dose that causes any toxicity (toxic dose low) in non-rodents [12]. Another method to select the starting dose is use of the 'no observed adverse effect level' (NOAEL). The starting dose for phase I trials with a pharmacokinetic or pharmacodynamic end point is generally 1/50 of the rat NOAEL [13]. Allometric scaling is used to calculate the equivalent surface area dose across species.

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