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Review

Early phase clinical trials to identify optimal dosing and safety

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ABSTRACT

The purpose of early stage clinical trials is to determine the recommended dose and toxicity profile of an investigational agent or multi-drug combination. Molecularly targeted agents (MTAs) and immunotherapies have distinct toxicities from chemotherapies that are often not dose dependent and can lead to chronic and sometimes unpredictable side effects. Therefore utilizing a dose escalation method that has toxicity based endpoints may not be as appropriate for determination of recommended dose, and alternative parameters such as pharmacokinetic or pharmacodynamic outcomes are potentially appealing options. Approaches to enhance safety and optimize dosing include improved preclinical models and assessment, innovative model based design and dose escalation strategies, patient selection, the use of expansion cohorts and extended toxicity assessments. Tailoring the design of phase I trials by adopting new strategies to address the different properties of MTAs is required to enhance the development of these agents. This review will focus on the limitations to safety and dose determination that have occurred in the development of MTAs and immunotherapies. In addition, strategies are proposed to overcome these challenges to develop phase I trials that can more accurately define the recommended dose and identify adverse events.

1. Introduction

Phase I trials of anticancer therapies classically involve cytotoxic agents that alter cell replication and metabolism. The need to more specifically target tumor cells and improve toxicity has led to the advent of molecularly targeted agents (MTAs) that include small molecule inhibitors and monoclonal antibodies, as well as immune based therapeutics. These new classes of drugs have different anticancer and toxicity profiles compared to cytotoxic chemotherapies and

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consequently challenge conventional early phase clinical testing (see Table 1). The primary objective of a phase I trial is to determine the recommended phase II dose (RP2D) of a drug or drug combination and to identify relevant treatment related toxicities. Given the different biological properties of MTAs and immunotherapies, trial designs developed during the era of cytotoxic treatments may be unsuitable to correctly define RP2D or adverse events.

The fundamental elements of a phase I study are well described in several comprehensive reviews (Le Tourneau et al., 2009; LoRusso et al., 2010). Dose escalation designs influence the number of patients enrolled, the fraction of patients treated at sub-therapeutic doses and the efficiency of the study. These designs are either rule- or model-based. The former utilizes pre-specified guidelines for observed toxicity based endpoints (e.g. dose limiting toxicity (DLT)) to determine subsequent dose levels, the maximum tolerated dose (MTD) or maximum administered dose (MAD) and RP2D (Figure 1). Model-based designs estimate the dose toxicity relationship and assign dose levels by determining the statistical probability of observing a target event. Specific trial designs are listed in Table 2. The traditional 3 + 3 design is the most commonly applied rule-based method (Storer, 1989), however it has been criticized for being slow, inefficient, inaccurate and treating a high proportion of patients at suboptimal doses (Reiner et al., 1999). Newer rule-based methods have attempted to address these issues by optimizing efficiency without compromising safety, for example, by adopting an initial acceleration phase in which cohort sizes are reduced and dose increments are large (Simon et al., 1997).

Several reviews report that toxicity has been the most prevalent endpoint used to define RP2D in phase I trials (Le Tourneau et al., 2009; Parulekar and Eisenhauer, 2004). However given that MTAs and immunotherapies may not have dose dependent toxicities to identify an MTD, pharmacokinetic (PK) or pharmacodynamic (PD) parameters could be valuable tools to help determine RP2D. Establishing dosages based on the occurrence of a pre-specified biomarker threshold, such as utilization of PK, PD or functional imaging parameters, is termed optimal biological dosing (OBD). OBD can be determined as a dose of a drug that reliably inhibits a key target in tumor or surrogate tissue, achieves a certain target plasma concentration, or reaches a pre-specified immunologic parameter. Beyond escalation design and endpoints, patient selection is another important aspect of early phase clinical trials. Traditionally phase I trials enrolled all-comers. However, increasingly contemporary phase I studies are restricting patients with specific pathology within a particular tumor type (e.g. esophageal cancers with squamous cell histology), or a specific molecular profile (e.g. solid tumors with *PIK3CA* mutations). High quality preclinical data and validated clinical assays are essential to this approach. The objective of this review is to highlight limitations in current phase I trial designs and discuss strategies to improve their accuracy and efficiency, with an emphasis on optimal dosing and safety.

2. Preclinical models

2.1. *Current models*

Numerous preclinical *in vitro* and *in vivo* models exist although no single system is considered the gold standard for evaluating toxicology and biological effects of a drug. Selecting the right system will depend on the mechanism of action and PK/PD properties of the studied agent, in addition to other practicalities such as cost, resource availability and animal model expertise. Two-dimensional cell culture has typically been used to obtain mechanistic insight on new therapeutics. In recent years, various preclinical mouse model systems have become available, including autochthonous genetically engineered mouse models (GEMMs) and chemically induced tumor models, as well as ectopic models in which syngeneic or xenogeneic tumor or cells are implanted subcutaneously or orthotopically. Each of these systems has its own advantages and disadvantages with respect to biological validity, time investment and cost (Gutmann et al., 2006; Ocana et al., 2011). Toxicology studies, on the other hand, are often undertaken in non-rodent species, such as dogs and monkeys that might be more predictive of human effects, however these models are seldom used to investigate molecular mechanisms.

2.2. *Limitations and optimization*

Human tumor cell line-based xenografts are the most commonly used model system in preclinical research. Efficacy data from various xenografts were retrospectively reviewed and compared to patient data from early phase trials to assess their predictive value. Even though histology was matched in both data sets there was a low correlation in efficacy between

Table 1 – Similarities and differences in phase I trials for different drug classes.

Trial elements	Cytotoxics	MTAs and immunotherapies
Primary end point	RP2D	RP2D
Secondary end points	Toxicity (MTD, DLT), response rate	PK or PD (molecular) parameter, toxicity, response rate
Dose escalation decisions	Toxicity based	Escalate based on toxicity or to a desired on-target effect
PK parameters	C_{max} may correlate with toxicity $t_{1/2}$ may predict recovery from toxicity	PK parameter (e.g. C_{max}, C_{min}, AUC) that correlates with desired target stimulation or suppression
Reasons for selecting RP2D	Toxicity RP2D must have tolerable toxicities and may demonstrate anti-tumor activity	Combination of toxicity and PD/PK parameters RP2D may demonstrate desired target effects with anti-tumor activity and tolerable toxicity

MTA, molecular targeted agent; RP2D, recommended phase II dose; MTD, maximum tolerated dose; DLT, dose limiting toxicity; PK, pharmacokinetic; PD, pharmacodynamic; AUC, area under the curve; SD, stable disease.

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