Phase I Trial in Oncology – Theory and Practice

Fáze I klinických studií v onkologii – teorie a praxe

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Summary
Phase I trials in oncology usually enrolling patients with advanced disease who have failed standard treatment options. The primary endpoint of these studies is to establish the recommended dose and/or schedule of new drugs or drug combinations for phase II trials. The guiding principle for dose escalation in phase I trials is to avoid unnecessary exposure of patients to sub-therapeutic doses of an agent. The mission of phase I clinical trials is to accelerate the development of new anticancer drugs with the purpose of improving quality of life and survival for patients with cancer.

Key words
phase I trial – phase I unit – rule-based design – model-based-design – targeted therapy

Souhrn
Do klinických studií fází I v onkologii jsou obvykle zařazováni pacienti s vyčerpanými možnostmi standardní léčby. Primárním cílem těchto studií je stanovení doporučené dávky nebo dávkovacího schématu pro následné studie fáze II. Postupná eskalace dávek v rámci studií fáze I vychází z preklinického testování a je plánována na principu minimalizace rizika vystavení pacientů subterapeutickým hladinám léčiva. Klinické studie fáze I napomáhají vývoji nových protinádorových léčiv s cílem zlepšení kvality života a celkového přežití u pacientů s nádorovým onemocněním.

Klíčová slova
fáze I – jednotka studií fáze I – rule-based design – model-based-design – cílená léčba

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Introduction

In the drug development, phase I trials are the studies where a drug is initially given to humans. These trials are conducted mainly to evaluate the safety of new drug. The primary endpoint is to establish the recommended dose and/ /or schedule of new drugs or drug combinations for phase II trials. The guiding principle for dose escalation in phase I trials is to avoid unnecessary exposure of patients to sub-therapeutic doses of an agent. Dose escalation methods for phase I cancer clinical trials fall into two broad classes: the rule-based designs, which include the traditional 3 + 3 design and its variations, and the model--based designs [1].

The Rule-Based Design

The rule-based designs assign patients to dose levels according to pre-specified rules based on actual observations of target events (e.g. the dose-limiting toxicity) from the clinical data. The traditional 3 + 3 design remains the prevailing method for conducting phase I cancer clinical trials [2]. It requires no modelling of the dose-toxicity curve beyond the classical assumption for cytotoxic drugs that toxicity increases with dose. This rule-based design proceeds with cohorts of three patients; the first cohort is treated at a starting dose that is considered to be safe based on extrapolation from animal toxicological data and the subsequent cohorts are treated at increasing dose levels that have been fixed in advance. Historically, dose escalation has followed a modified Fibonacci sequence [2] in which the dose increments become smaller as the dose increases (e.g. the dose first increases by 100% of the preceding dose and thereafter by 67%, 50%, 40%, and 30–35% of the preceding doses). If none of the three patients in a cohort experiences a dose--limiting toxicity, another three patients will be treated at the next higher dose level. However, if one of the first three patients experiences a dose-limiting toxicity, three more patients will be treated at the same dose level. The dose escalation continues until at least two patients among a cohort of three to six patients experience dose-limiting toxicities (i.e. ≥ 33% of patients with a dose-limiting toxicity at that dose level). The recommended dose for phase II trials is conventionally defined as the dose level just below this toxic dose level.

The main advantages of the traditional 3 + 3 design are that it is simple to implement and safe. However, a disadvantage of this design is that it involves an excessive number of escalation steps, which results in a large proportion of patients who are treated at low (i.e. potentially sub-therapeutic) doses while few patients actually receive doses at or near the recommended dose for phase II trials.

Model-Based Design

On the other hand, model-based designs assign patients to dose levels and define the recommended dose for phase II trials based on the estimation of the target toxicity level by a model depicting the dose-toxicity relationship [1]. This method can be conveniently carried out using Bayesian models. The occurrence of toxicity (or not) in patients enrolled at each dose level provides additional information for the statistical model and results in an adjustment of θ (also called posterior distribution of θ) according to Bayes' theorem. The posterior distribution is then evaluated to identify the dose closest to the target toxicity level, and this dose is used to treat future patients and to set the recommended dose for phase II trials. These model-based designs use all of the available data to model the dose-toxicity curve, and they provide a confidence interval for the recommended dose for phase II trials at the end of the trial [1].

Many phase I studies are designed to investigate combinations of two or more agents. The combination of two or more agents in the clinic should be based on a strong scientific rationale rather than simple empiricism. Unfortunately, preclinical models that accurately predict synergism or even additivity are not well characterised, and existing preclinical models often focus on the antitumour effects of drug combinations while ignoring their potential for creating severe toxicities. Determining the recommended dose for phase II trials of agents to be administered in combination may appear easier than that for single agents, given that the recommended dose for phase II trials and the toxicity of each drug are already known. For this reason, phase I combination trials usually explore only a limited number of dose levels. Korn and Simon [3] developed a graphical method to define the maximum tolerated doses (MTDs) of drugs to be used in combination that relies on the organ-specific toxicities of the drugs when given as single agents. However, this method was developed using cytotoxic drugs, which have a high likelihood of overlapping toxicities (in particular haematologic toxicities). By contrast, when drugs to be administered in combination have different mechanisms of action or non-overlapping toxicities, the recommended dose for phase II trials for the drug combination is usually expected to be near the recommended dose for phase II trials of each drug given as a single agent.

All of these methods were developed in the era of true cytotoxic drugs when it was assumed that both efficacy and toxicity increase with dose. These relationships are typically represented by dose-toxicity and dose--efficacy curves in which toxicity and efficacy increase monotonically with increasing drug dose. Consequently, these methods have used toxicity as the primary endpoint. For inhibitors and therapeutic antibodies targeted agents, the dose-efficacy and dose--toxicity curves may differ from those for cytotoxic agents, and efficacy may occur at doses that do not induce clinically significant toxicity.

Phase I Trials with Targeted Therapy

Targeted agents are designed to modulate specific aberrant pathways in cancer cells while sparing normal tissues, such that the toxicity and efficacy of these novel agents may not be dose dependent. Alternative endpoints besides toxicity have been proposed for phase I trials that evaluate targeted agents, including target inhibition in tumours or surrogate tissues and/or detection of biologically relevant pharmacokinetic levels [4–7].

The emergence of targeted, so-called "non-cytotoxic" therapies as anticancer agents may challenge the traditional phase I study paradigm in a variety of ways [8–12]. Unlike cytotoxic agents, most of which act on DNA or tubulin, these new therapies have targets including membrane receptors, components of cytoplasmic signalling pathways, cell cycle regulator proteins and proteins or factors important in angiogenesis. Because the resulting antineoplastic effects may be **cytostatic** (i.e. inhibit tumour growth or prevent metastases) rather than cytotoxic, early efficacy trials may need to incorporate measures of antitumour behaviour other than changes in tumour size. In addition to different mechanisms of action and potential antitumour effects, these novel compounds may also be characterised by a lack of clinically significant organ toxicity compared with conventional chemotherapy. Thus, although determination of the recommended phase II dose using toxicity as a surrogate endpoint for activity may be unnecessary or unachievable in the phase I setting for these agents and therapies, demonstration that the agents have the desired target effect is an important aspect of their early clinical development.

Alternatives to toxicity as a surrogate endpoint for phase I dose escalation trials evaluating non-cytotoxic therapies can include measurement of target inhibition and/or pharmacokinetic analysis. Although measurement of a molecular target effect seems logical, it is associated with several challenges. First, given the complexity of cellular pathways and signalling processes, it may be difficult to define the appropriate measure of achieved target effects for a specific drug. Second, restricting patient enrolment to those with accessible disease for assessment of the drug effect on the tumour decreases the eligible population and puts an additional level of ethical and administrative burden on the conduct of the trial. Even if patients consent to tumour biopsy, serial tumour sampling is invasive and associated with sampling errors resulting from the heterogeneous tissue composition of cancers. The use of surrogate tissues such as skin, mucosa, or peripheral blood may be an appropriate solution to these problems, provided that changes in the surrogate tissue parallel those in the tumour in preclinical studies. Third, the optimal level of "target inhibition" needs to be defined. Finally, a reliable assay for measurement of the drug effect needs to be available. Pharmacokinetic endpoints, such as achieving target plasma levels of the drug, may help with phase I study dose selection of the non-cytotoxic drug. However, pharmacokinetic endpoints are appropriate only if sufficient preclinical data exist demonstrating a convincing pharmacokinetic – pharmacodynamic relationship.

Drug toxicity, however, remains an important part of phase I drug evaluation for all drugs. Drug toxicities can be determined and reported relatively easily because of the existence of standardized criteria. Furthermore, even if toxicity is not the primary endpoint of the dose escalation study, its description remains a necessary part of early testing of new agents. Although the use of toxicity for dose selection may not be appropriate for agents that have maximal target inhibition at nontoxic doses, this method of dose selection minimizes the possibility that a sub-therapeutic dose will be chosen.

Ethical Issues with Conducting Phase I Trial

Phase I clinical trials in oncology are typically small, single-arm, open-label, sequential studies that include patients with a good performance status whose cancers have progressed despite standard treatments. The use of a vulnerable population with high expectations of benefit in a scientific experiment creates challenges for the protection of human research subjects. Once a well designed study has been established, the primary challenge is to ensure the voluntary informed consent of research participants [13]. This process involves an explanation of the rationale for the study and details of what study participation actually involves in terms of schedules, drug administration, tests and procedures, and predicted toxicities. It also involves an explanation of the nature of phase I clinical trials with a focus on the nature of uncertainty in terms of risks and benefits, differences between trial care and prior care outside a trial.

Understanding of all these ethical issues, endpoints and principles of phase I design is a crucial step not only for the patients, but also for the physicians and investigators.

Clinical Trials at Masaryk Memorial Cancer Institute (MMCI)

The tradition of conducting clinical trials at MMCI dates back to the 1970's, when the institute was an important research partner of the pharmaceutical company Lachema in the area of the development of new cytostatic drugs. However, since the last decade of the 20th century the possibility of clinical research and the number of clinical trials have significantly increased which has led to the establishment of the new Clinical Trials Unit (CTU) in 2000. Since 2000, already for more than a decade, the CTU has been providing unique professional and administrative support to clinical research at MMCI. In the last ten years, the Institute has contributed to more than 250 clinical trials, in particular phase II and III.

The department is directed by an experienced clinical pharmacologist. The team consists of 9 study coordinators/ /nurses, a data manager and an administrative coordinator. The unit provides complete pre-study procedures and after the initiation of a clinical trial coordinates its implementation under the protocol. It also provides data management and communication with the sponsor. The most common sponsors of clinical trials in the MMCI are pharmaceutical companies, as well as European research organizations (EORTC, CEECOG) and increasingly more often also academic institutions (investigator initiated trials). The preparation of a new clinical trial and pre-study procedures, i.e. the approvals of the State Institute for Drug Control (SIDC) as well as Ethics Committees and the contract signature, takes approximately 3 months. The CRU is the main partner of principal investigators (PI). The team dedicated to every clinical trial consists of a PI, co-in-

vestigators, study coordinator/nurse, radiologist, pharmacist and a pharmaceutical assistant. In 2010, there were 19 new clinical trials initiated at MMCI and 246 patients enrolled. However, the total number of patients undergoing the treatment in the clinical trials was 877 that year. In some clinical trials we have achieved a leading global position in the number of enrolled subjects.

Phase I Unit

However, since 2010 the spectrum of clinical trials has been moving towards the earlier phases of the development of a new drug. The trials of phase I and II, which are often "first in men", have greater demands on the professional, technical and organizational aspects of its realization. For this reason, Phase I Unit was established at Masaryk Memorial Cancer Institute in February 2012. The Unit provides complete implementation of the clinical trials of early phases in accordance with all legislative requirements, good clinical practice (ICH GCP) and international standards. It is made up of two triple rooms within the Department of Complex Oncology Care. Our unit is a semi-intensive care unit with facilities for close patient surveillance, including continuous cardiac monitoring. There are six full-time beds with staff seven days a week and an outpatient clinic for therapy and follow-up. Our own staff of trained and GCP-examined research nurses obtain and handle blood samples for PK and PD in the laboratory facilities in the phase I unit. Tissue sampling and processing for further analysis including snap-freeze technique can be undertaken through our collaboration with the department of diagnostic radiology/pathology and the surgical departments. Extensive pharmacokinetic measures can be analysed at the Department of Laboratory Medicine.

Mainly proof-of-concept studies typically require genomics, proteomics, metabolomics, advanced imaging and other sophisticated research tools that rarely exist in a clinical setting but can be accessed through the RECAMO (Regional Centre for Applied Molecular Oncology, www.recamo.cz) [14]. The purpose of RECAMO is to bring together research scientists and clinicians with a common aim – to translate the advances in our increasing ability to study cancer into real advances in patient care. By augmenting these resources with the scientific and operational capabilities of MMCI we create a new paradigm that incorporates the exhaustive study of new compounds into standard practice in early phase research.

Our **ambition** is to become a part of the European network of phase I units and to participate in phase I clinical trials conducted in Europe and overseas.

Conclusion

Phase I trials are the cornerstone for advancement of new therapies and also represent the clinical starting point for all new drugs undergoing clinical evaluation in patients. Although traditional scientific goals – such as defining the phase II dose, toxicity, and pharmacokinetic profile assessment – will remain, other parameters will need to be expanded and refined, including incorporating novel trial endpoints and designs. Several recent phase I studies have changed the landscape of cancer therapeutics and have suggested that early biomarker identification can substantially increase therapeutic benefit and shorten the drug development timeline [15]. Early biomarker identification and matching patients based on their personal molecular profiles are the cornerstones of a critical paradigm shift needed to improve the outcome for patients with advanced, refractory cancers. Therefore, the goals of properly performed phase I trials should clearly be scientific as well as therapeutic. The mission of phase I clinical trials is to accelerate the development of new anticancer drugs with the purpose of improving quality of life and survival for patients with cancer.

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