Phase 0 Clinical Trials Will Overcome Stagnation of Anticancer Drug Development?

Překonávají klinické studie fáze 0 stagnující vývoj protinádorových léčiv?

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Summary

Recent guidance from the US Food and Drug Administration supports the conduct of a new type of exploratory clinical trials, commonly called phase 0 clinical trials, on the development of innovative anticancer agents, particularly targeted agents. Phase 0 clinical trials are controversial mainly because of the lack of clinical benefit to the participant patients. However, it was recognized that Phase 0 clinical trials can provide a platform to assessing the biological effects on the targets in tumoral human samples, evaluate biomarkers for drug effects and to generate essential human pharmacokinetics and pharmacodynamics data earlier in the drug development. It is expected that such trials will became a routine part of early-phase oncological drug development in the future.

Key words

phase 0 clinical trials – targeted therapy – cancer

Souhrn

Poslední pokyny vládní agentury Food and Drug Administration v USA podporují provádění nového typu výzkumných klinických studií, obecně označovaných jako klinické studie fáze 0, které se týkají vývoje inovativních, zejména cílených, protinádorových léčiv. Klinické studie fáze 0 jsou kontroverzní zejména z důvodu nedostatečného klinického přínosu pro pacienty zapojené do těchto studií. Připouští se však, že klinické studie fáze 0 mohou poskytnout platformu pro posuzování biologických účinků na vzorky lidské nádorové tkáně, hodnocení biomarkerů z hlediska účinků léčiv a pro získávání základních humánních farmakokinetických a farmakodynamických údajů v počátečních fázích vývoje léčiv. Očekává se, že tyto studie se v budoucnu stanou rutinní součástí počátečních fází vývoje onkologických léčiv.

Klíčová slova

klinické studie fáze 0 – cílená léčba – zhoubné novotvary

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Despite important and fast advances in biomedical and pharmaceutical research, the number of new molecule entities has increased significantly since 1990. However, the rate of approval for marketing to the US Food and Drug Administration (US FDA) is declining. In 2005 only 20 new drugs were approved by the US FDA compared with 36 in 2004 and 53 in 1996 [1]. Moreover, about 10% of Investigational New Drug applications for new molecular entities submitted to the US FDA progress beyond the investigational phase [2] with a success even lower in oncology [3]. This low success rate has been related to the higher number of new molecular entities with diverse mechanisms combined with the lack of predictive preclinical systems (both *in vitro* assays and *in vivo* animal models) and inadequate and complex clinical trial designs. There are indicators that the shift away from the use of nonspecific cytotoxic agents to more specific molecular targeted entities requires the availability of reliable assays and predictive pharmacodynamic markers in early clinical trials. In 2006, the US FDA addressed some of these early development issues and introduced a new exploratory clinical trial, commonly called phase 0 clinical trial [4].

At present, after preclinical studies, the traditional dose finding phase I studies are followed by phase II and III efficacy studies. The purpose of phase 0 clinical trials is to focus on exploring phamacokinetics (such as bioavailability, metabolism, tissue distribution) and pharmacodynamics profiles of novel targeted drugs and assist in the go versus no-go decision earlier in the expensive development process using relevant human models instead of sometimes inconsistent animal models. Because phase 0 trials will involve a relatively small number of patients, about 10–15, exposed to the low dose of the test drug administered and the short time period of drug exposure, the associated risk of toxicity is lower than in phase I trials.

The European Medicines Agency and the US FDA have addressed the methodology of microdosing. The concept behind microdosing is the use of extremely low non-pharmacologically active doses of a drug. Both regulatory bodies consider microdose as "less than 1/100 of the dose calculated to yield a pharmacological effect of the test substance to a maximum dose of < 100 micrograms" [5]. The ability of microdosing studies could predict human pharmacokinetics at therapeutic dosages; however, the methodology recognizes limitations which need to be addressed (e. g. the human sampling schemes will be based on results from preliminary animal PK data, which may not accurately predict pharmacokinetic profiles in human) [6].

Different settings for phase 0 clinical trials have been proposed, for example single-agent and combination drugs, selection of a lead agent for clinical trials and early application of molecular-imaging studies [7]. The single-agent phase 0 trial brings the possibility of assessing the biological effects on the targets in tumour biopsy obtained pre and post-drug administration and evaluate the target modulation. In addition, such trials would provide the opportunity to use and refine a biomarker assay to study the effects of the drug in tumour samples, peripheral blood or other surrogate tissue and provide a closer approximation of a safe, but potentially effective starting dose with a smaller number of patients. For drugs in combination, i.e. two targeted agents or a targeted agent and a conventional cytotoxic agent, phase 0 trials would help to determine the schedule and sequence between them after assessing the modulatory effects of one drug on another. The pharmacokinetics and pharmacodynamics data for different schedules of administration would provide the basis for further studies. During a drug discovery structurally-related analogue molecules are usually generated. The lead agent selection for further clinical development is made on the basis of in vitro and animal model data but without reliable prediction about efficacy and toxicity in humans [8]. Phase 0 clinical trials would contribute importantly, providing pharmacokinetic and pharmacodynamic data in the selection of the lead agent for further development. In the universe of molecular-imaging studies, radiopharmaceuticals can be effectively evaluated using microdoses in the context phase 0 clinical trials for study of biodistribution and effect of an agent on a given target.

Phase 0 trials may bring new therapeutic agents to the bedside; however there are still concerns whether they can significantly shorten the drug development process, as they will not replace the traditional dose escalation, safety, tolerance and efficacy studies. The Phase 0 trials don't bring any therapeutic benefit to the patients whereas in phase 1 trials, despite being performed without therapeutic intent, there is still on average a low response rate of about 5% [9]. As regards this, Informed Consent for study participants in phase 0 trials must clearly document that the dose of the investigative agent will be lower than the therapeutic effect. Additional ethical concerns surrounding participation in a phase 0 trial is the need of several biopsies or even future exclusion or delays from participation in certain clinical trials which could significantly impair patient enrolment. Therefore, this issue should be discussed with the patient, and phase 0 trials should be considered only for those patients with advanced disease who do not have symptoms that require immediate therapy [10]. A French group has suggested that the most suitable target candidates for phase 0 trials, who could circumvent the majority of the ethical concerns and specially the need of repeated biopsies, should be patients with locally advanced or metastatic disease with the therapeutic option of a surgical resection [11].

The first paper about phase 0 clinical trial with a novel oral poly (ADP-ribose) polymerase inhibitor was recently published in the Journal of Clinical Oncology [12] where the data was available within 5 months after starting the trial, and allowed the ATB-888 drug to bypass the traditional monotheraphy phase I trial and move quickly into combination studies.

The answer to the question will the phase 0 clinical trials will overcome stagnation of anticancer drug development will probably remain unknown till the agents under study in phase 0 trials reach the end of their develop-

ment. There are more than 500 oncology drugs waiting to enter into clinical development within this decade. Theoretically, many of those potential anticancer agents might benefit from the phase 0 trials by an early identification of the most promising agent, reducing cost and expediting their drug development. Our courageous cancer patients who volunteer in those phase 0 trials deserve nothing less.

References

1. Twombly R. Slow start to phase 0 as researchers debate value. J Natl Cancer Inst 2006; 98(12): 804–806.

2. Guidance for industry, investigators, and reviewers. Exploratory IND studies. U.S. department of health and human services. Food and drug administration. Center for drug evaluation and research (CDER). January 2006.

3. Kola L, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004; 3(8): 711–715.

4. Kinders R, Parchment RE, Ji J et al. Phase 0 clinical trials in cancer drug development: from FDA guidance to clinical practice. Mol Interv 2007; 7(6): 325–334.

5. European Medicines Agency, Committee for medicinal products for human use. Position paper on non-clinical safety studies to support clinical trials with a single microdose. London, June 23, 2004.

6. Bertino JS Jr, Greenberg HE, Reed MD. American colleague of clinical pharmacology position statement on the use of microdosing in the drug development process. J Clin Pharmacol 2007; 47(4): 418–422.

7. Kummar S, Kinders R, Rubinstein L et al. Compressing drug development timelines in oncology using phase "0" trials. Nat Rev Cancer 2007; 7(2): 131–139.

8. Johnson JI, Decker S, Zaharevitz D et al. Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. Br J Cancer 2001; 84(10): 1424–1431

9. Von Hoff DD, Turner J. Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs 1991; 9(1): 115–122.

10. Abdoler E, Taylor H, Wendler D. The ethics of phase 0 oncology trials. Clin Cancer Res 2008; 14(12): 3692–3697.

11. Pocard M, Soria JC, Aldaz-Carroll L et al. Phase 0 clinical trials in oncology: an exploratory methodology for constructing a study with patients undergoing surgery for metastatic disease. J Clin Oncol 2010; 28(30): 4551–4553.

12. Kummar S, Kinders R, Gutierrez ME et al. Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies. J Clin Oncol 2009; 27(16): 2705–2711.