

**IMPACT OF PHASE ZERO TRIALS (MICRO-DOSING)
IN CLINICAL TRIAL RESEARCH**

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ABSTRACT : Currently, pre-clinical trials using animal models, cell culture methods and bio-informatics takes up to 18 months and the typical development for investigational new drugs takes between ten to fifteen years and associated with high cost and low rate of approval. Phase 0 trials are attractive approach and in future would require only few pre-clinical studies, phase I trial and a reduced amount of the investigational new experimental drug on human. FDA supports the conduct of phase 0 trials in oncology related studies. The negative points pertaining to phase 0 trials is that the drug and dose is too small and reliable biomarkers are too thin on the ground despite great sum of money being spent to find and validate them. Phase 0 clinical trials can decrease the cost and time and could improve the process of drug development in future. In this review, we try to provide the recent developments and impact of phase zero trials in clinical trial research.

Abbreviations

FDA (Food and Drug Administration:USA), NOAEL (No Observed Adverse Effect Level)ADME(Absorption,Distribution,MetabolismandExcretion)

INTRODUCTION

The concept of micro-dosing in human subjects has long been an experimental technique that has promised much but has not quite lived up to its potential. The advantages of human micro-dosing are clear. Clinical trial industry sponsored by bio-pharmaceutical companies, research institutions, has clear potential for strong growth in the economy is driven by technological and scientific advances in the field of bio-medical, bio-pharmaceutical sciences (Joel, 2004; Fabio et al, 2008). Pre-clinical trials of human drugs are tested on suitable animal models for investigating the toxicology and adverse reactions which certainly permits effective and safe dose of investigational new drugs (IND) which is going to be tested on humans (Vijayaraghavan, 2009).

By using only a very tiny amount of active substance, one can establish the likely pharmacological dose and thereby determine the first dose for the subsequent Phase I study. In addition, micro-dosing can elect the best animal species for long-term toxicological studies from micro-dose metabolite profiling data. Currently, the typical development for investigational new drugs takes between ten to fifteen years and associated with high cost and low rate of approval. In the years to come, research methods and technology involved in phase 0 trials become more sophisticated and human micro-dosing may be employed to a number of drugs that could potentially be administered consecutively (Kummar et al, 2009). The major objectives of phase 0 trials is to interrogate and refine a target or biomarker assay for drug effect in human samples implementing procedures developed and validated in preclinical models. Data gleaned from a phase 0 trial are beneficial not only in prioritizing promising compounds but also in allowing the modification of phase I study design before initiation. Phase 0 trials provide an opportunity to generate essential human pharmacokinetic and pharmacodynamic data earlier in the drug development process, which could be a major advantage in the design and decision making concerning further clinical development of an agent. *In recent years*, human micro-dosing (phase 0 trials) clearly holds significant promise as an analytical tool (Twombly, 2006). It will also help in the drug repurposing and pharmacogenomics activity by expediting the initial work. This review focuses on the purpose as well as the potential merits of phase 0 trials from the perspective of a pharmaceutical company.

Role of FDA in phase 0 trials

According to the FDA a phase 0 is designed to take place very early in phase I, involves very limited human exposure receiving only sub-therapeutic dose and this means the patients (study subjects enrolled) produce a pharmacologic response than the toxic effect, and the risk involved is less than conventional phase I trials in which administration continues if there is a evidence of clinical benefit and thus phase 0 trials lack even therapeutic intent (Marchetti and Schellens, 2007). Ultra-sensitive AMS (accelerator mass spectrometry) has made it possible to undertake clinical studies in man using extremely low drug doses to obtain early PK and ADME data.

Designing Phase 0 trials

By design, phase 0 trials portend lower risks to human subject than traditional phase I trials. As such, fewer preclinical supporting data are required prior to conducting a phase 0 trial. The initial agent dose depends in part on the stated trial objectives, but should not be greater than 1/50th of the no-observed-adverse-effect level (NOAEL) estimated from animal toxicology testing. Validated pharmacodynamic assays, ideally with low variability in the molecular target, are suitable for application to phase 0 trials if the investigational agent can reasonably be expected to demonstrate target modulation at a non-toxic dose. Standard operating procedures for tissue collection and bio-specimen handling should be defined in advance and revised as necessary based on results of the phase 0 trial. Chemoprevention agent development is uniquely challenged by the need to identify widely acceptable, minimally toxic compounds (even when chronically administered) that favorably affect carcinogenesis when measured against surrogate biomarkers, rather than direct cancer endpoints.

Methods to identify bio-available, pharmacodynamically active candidates earlier in the drug development cycle would offer clear advantages with respect to process efficiency, resource utilization and other parameters. Natural products (or derivatives thereof) represent an attractive source for chemoprevention agent discovery and, given their oftentimes demonstrated favorable safety profile at standard doses, provide an excellent opportunity to explore potential benefits gained through the phase 0 trial paradigm (Paul,2010). Phase 0 trials are designed primarily to evaluate the pharmacodynamic and/or pharmacokinetic properties of selected investigational agents prior to initiating more traditional phase 1 testing. One of the major objectives of phase 0 trials is to interrogate and refine a target or biomarker assay for drug effect in human samples implementing procedures developed and validated in preclinical models. Thus, close collaboration between laboratory scientists and clinical investigators is essential to the design and conduct of phase 0 trials.

Given the relatively small number of patients and tissue samples, demonstrating a significant drug effect in phase 0 trials, requires precise and reproducible assay procedures and innovative statistical methodology. Because of the very limited drug exposure, phase 0 trials offer no chance of therapeutic benefit, which can impede an increased participation of the study subjects. A well vivid example for a well established phase 0 trial was conducted by Kummar et al., in recent years on oral poly (ADP-ribose) polymerase inhibitor, ABT-888. The information obtained as a result of this study reveal that ABT-888 was able to move quickly into combination studies, bypassing the traditional monotherapy phase I clinical trial (Kummar et al., 2009). This interesting finding provides the advantage of phase 0 trials in clinical research.

Furthermore, phase 0 trials involving limited exposure of a study agent administered at low doses and/or for a short period allow them to be initiated under the Food and Drug Administration exploratory investigational new drug guidance with less preclinical toxicity data than usually required for traditional first-in-human studies. Because of the very limited drug exposure, phase 0 trials offer no chance of therapeutic benefit, which can impede patient enrollment, particularly if invasive tumor biopsies are required. The challenges to accrual are not insurmountable, however, and well-designed and executed phase 0 trials are feasible and have great potential for improving the efficiency and success of subsequent trials, particularly those evaluating molecularly targeted agents (Anthony et al, 2008).

Ethics

FDA supports the conduct of phase 0 trials. Phase 0 trials in oncology related studies raise important ethical concerns that have received little attention in recent years. The question arises it is ethical to enroll a subject in human micro-dosing that offers them no potential clinical benefit and further concern focuses on the inclusion of terminally ill and the consequently vulnerable cancer subjects in this type of trial .The aspect was discussed in recent years by Abdoler et al, 2009.

Benefits

By incorporating the innovative idea of phase zero trials the main beneficiary will eventually be the patient population at large. If the phase zero trial study reports identifies a investigational new drug as not being of therapeutic worth, the patient population may certainly benefited through the minimization of the study participants recruited to subsequent trials on the critical path. So the sponsoring authority of the investigational new drug can realize the benefits of phase zero trials the most.

In theory, phase zero trials can enable the sponsors and manufacturing pharmaceutical companies to reduce costs by identifying the most promising of similar agents in their pipeline. Phase 0 trials will not replace the traditional dose escalation, safety and tolerance studies and they will not indicate whether a candidate drug has a positive impact on the targeted disease.

Demerits of phase 0 trials

Patients in a phase zero trial get only too small portion of the investigational new drug and such small doses could give results there are not relevant to the later real-world one. The laboratory and other parameters are very limited and very expensive hence many phase 0 trial researchers have to depend on BA/BE labs involved in use sensitive instrument in detecting the test articles at micro-dose level in the matrix of the study subjects (Chandra Prakash et al, 2007).

Discussion

Phase 0 trials serves as a good tool for clinical researchers in testing the safety and efficacy of drugs at micro level before the onset of phase I trial. Hence they serve as a very useful tool in understanding the ADME of drugs used in Cancer. Sensitive bio-analytical tools like HPLC, LC-MS/MS which can detect the drug in the matrix even at a very low level can serve as a very useful tool for phase 0 trials. In recent years drugs specific to organs and organelle are under investigation and if a new strategy is designed for understanding the levels of organ or organelle specific enzyme or protein in molar and milli molar range in response to micro-dosing of a test article (investigational new drug) such an approach will certainly galvanize and ensure wide spread application of phase 0 trials and could revolutionize the clinical research and could certainly find a new solution to adverse drug reactions and exacerbations encountered in the participants of clinical trials. Detailed discussions, seminars, workshops and continuous flow of information from different clinical research scientist is needed for the betterment and wide spread application of phase 0 trials.

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