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Editorial Comment

Phase 0 (zero) clinical trials: More than zero benefit?

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Drug development is a long, complex and expensive process. The conventional sequence of processes involved in drug development usually comprises a preclinical phase and three clinical phases, i.e. phases I–III. Currently, the typical development for investigational new drugs takes between 10 and 15 years and is associated with high costs and low rate of approval.[1] Owing to the fast progress in biomedical and pharmaceutical research, the number of new molecular entities starting the development process has increased significantly since about 1990; however, the rate of approval for marketing is declining.[2] It has been estimated that currently a novel compound entering clinical phase I testing has only an 8% chance of reaching the market, and the probability is even lower for an anticancer drug (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf).[3] This low success rate has been ascribed to the high number of new molecular entities with diverse mechanisms of action to be tested for activity and efficacy combined with the lack of predictive preclinical models and inadequate and complex clinical trial designs. Overall, 75% of the costs of drug development are associated with failures mainly in the early stages of development.[4] Often the toxicity is severe and poorly predictable. Furthermore, as high as 40% of exits from phase I trials are caused by inappropriate pharmacokinetics of the test compound.[5,6] A number of investigational new drugs fail in clinical testing because they do not behave pharmacologically as predicted in animal studies. Consequently, there is a need for additional methods to evaluate potential new drugs and to optimise existing development strategies. This is particularly true for the field of oncology where the increased understanding of genetic and molecular mechanisms involved in malignant cellular transformation has led to major changes in therapeutic approaches.

Phase 0 clinical trials have no therapeutic or diagnostic purpose for the volunteer; in principle, they should allow researchers to quickly establish whether a novel compound has appropriate pharmacokinetic and pharmacodynamic profiles in humans. 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. However, owing to the low doses administered, the limited number of humans treated and the reduced risk of toxicity, the phase 0 strategy would require fewer preclinical *in vitro* and *in vivo* studies than a typical phase I trial and a reduced amount of the experimental drug. Potentially, phase 0 clinical studies could help in eliminating candidate drugs before they reach phase I testing, thus reducing costs and time and improving the efficiency of drug development.[7]

There are, however, a number of limitations and challenges associated with the execution of phase 0 trials and these have been well addressed in the paper by Kummar et al. (in this issue).[8] The paper is the result of a Task Force consisting of knowledgeable investigators in this field representing academia, the pharmaceutical industry and the FDA, the US regulatory authority. However, it is not clear

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whether the authors report on personal title or whether they publish on behalf of their affiliated institutes. In the latter case it might have been of interest to also include a representative of the European Medicines Agency (EMEA). Despite the opportunity of performing phase 0 trials in oncology the authors conclude that only a few studies have been published employing this trial type. In addition, they rightfully address a number of key questions including whether the phase 0 study will improve the efficacy of subsequent trials, whether patients will take part in a trial that is of no benefit to them and whether phase 0 trials are needed to demonstrate pharmacodynamic (PD) effects of the compound under investigation or whether this could simply be implemented in traditional phase I studies. The future will tell us under which circumstances and for which types of drugs phase 0 studies may be beneficial for the drug development process and whether the ethical dilemma will or will not limit swift execution of these trials. Concerning the latter issue, the experience at the US National Cancer Institute with the poly-ADP ribose polymerase inhibitor (PARP) inhibitor ABT-888 appears to be encouraging.[9] However, there are a number of potential advantages associated with the execution of phase 0 studies and possibly the pharmaceutical industry needs a little more time to implement these trials in their drug development process. Clearly, the preclinical toxicology package can be limited significantly thereby speeding up first-in-man studies of (a range of) new anticancer drugs (http://www.emea.europa.eu/pdfs/human/swp/259902en.pdf – Position paper on the non-clinical safety studies to support clinical trials with a single microdose (CPMP/SWP/2599/02/Rev 1)). In addition, much lower quantities of test drug need to be synthesised prior to this phase 0 first-in-man study, which is a big advantage in view of time and costs. Furthermore, the test drug does not formally need to be produced according to GMP, although of course the test batch needs to pass all necessary quality tests prior to phase 0 testing. However, the industry will also need to make a strategic change as executing a phase 0 trial needs to be considered early on in the drug development process starting preclinically. Limiting the initial toxicology package, sufficient to embark on a phase 0 trial, needs to be considered prior to the execution of a full scale toxicology programme to make optimal use of this advantage. In addition, if a non invasive study is planned with a PET readout then this has immediate consequences for drug synthesis. Of course, PET tracer synthesis generates additional costs that should be weighed against the potential advantages of performing PET studies in phase 0. In addition, and also extensively addressed by Kummar et al., is the need for a validated PD assay in tumour and/or normal tissue, in which validation needs to be part of the preclinical phase of drug development.

Ideally, by performing phase 0 studies, the optimal clinical candidate is identified more swiftly and at lower costs than in the current rather traditional drug development process and uncertainty as to whether the drug of interest reaches its defined target is eliminated. It is important to understand that a phase 0 trial cannot substitute poorly determined PD/proof of principle in the preclinic setting. Kummar et al. are to be complemented for contributing to our understanding of when and when not phase 0 studies may be of benefit in the anticancer drug development process.

Conflict of interest statement

None declared.

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