The ethical dimension of first-in-human studies has always been carefully considered. In the standard Phase One study, there is therapeutic intent, although the probability is unfortunately low. In the phase zero setting, no therapeutic benefit is expected. Thus, the motivation of the volunteer patients is primarily altruism. Differences between Phase Zero and Phase One, including the relative risks and benefits of biopsies, will be discussed.

22 INVITED

Implementation of phase 0 trials

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An increase in the number of identified therapeutic cancer targets achieved through recent biomedical research has resulted in the generation of a large number of molecules that need to be tested further. Current development of (anticancer) drugs is a rather inefficient process that for an average new molecule takes around 10−15 years. It is also a challenging process as it is associated with high costs and a low rate of approval. It is known that less than 10% of new molecular entities entering clinical phase I testing progress beyond the investigational program and reach the market; this probability is even lower for anticancer agents. In 2003 the US FDA declared the urgent need for new toolkits to improve the critical development path that leads from scientific discovery to the patient.

In this scenario, Phase 0 (zero) trials should allow an early evaluation in humans of pharmacokinetic and pharmacodynamic profiles of test compounds through administration of sub-pharmacological doses to a low number of humans. Phase 0 trials are clinical studies conducted early in Phase I, before the traditional dose escalation, safety and tolerance studies. These first-in-man trials should involve a very limited number of normal volunteers or patients, exposed to a novel compound at a reduced dose compared to starting doses in Phase I and for a short time-period. Typically, Phase 0 studies have no therapeutic neither diagnostic intent. Due to the low doses administered and the low risk of toxicity, shorter preclinical packages to support these studies are required. Phase 0 trials have been proposed to help in making an early selection of promising candidates for further evaluation in Phase I/II/III trials, providing a potentially useful instrument for drug discovery, particularly in the field of oncology. Phase 0 studies are expected to reduce costs of drug development, and to limit preclinical in vitro and in vivo testing and the time-period of drug development. However, there are also concerns about the utility and feasibility of Phase 0 studies.

In January 2006 guidelines on exploratory investigational new drug studies in humans have been published by the US FDA, and currently a Phase 0 program is ongoing at the National Cancer Institute in order to evaluate the real impact (feasibility and utility) of Phase 0 studies on drug development. In Europe a Position Paper produced by the EMEA in 2004 raised the possibility of a reduced preclinical safety package to support early microdose clinical studies, and, as announced by a recent Concept Paper on medicinal products published by the CHMP of EMEA, EMEA's guidelines on Phase 0 studies are expected shortly. There are a number of relevant practical issues to be considerd prior to execution of Phase 0 trials.

Execution of Phase 0 trials may be hampered by ethical reasons as well as by the willingness of patients to take part in these trials that will have no therapeutic benefit to them.

Despite the opportunities provided by Phase 0 trials, it is expected that more efficient, faster and less costly drug development is achieved especially by better preclinical selection of clinical candidates based in more stringent assessment of proof of concept as well as by selection of clinical candidates with better pharmacological profiles and by better definition of the target population of patients. However, the true impact on the drug development process and especially the safety of Phase 0 studies need to be carefully explored.

References

Marchetti S & Schellens JHM. The impact of FDA and EMEA guidelines on drug development in relation to Phase 0 trials. Br J Cancer. 2007; 97: 577−81.

23 INVITED

Industry perspective

G. Gordon. *USA*

Abstract not received

Wednesday, 22 October 2008 10:15–12:00

WORKSHOP 5

Targeting the CYP pathway

24 INVITED

The evolution of CYPs from metabolising enzymes to potential targets in cancer therapy development

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Cytochromes P450 (CYP) are a superfamily of haemothiolate monoxygenases comprising at least 57 functional proteins in humans. Selective CYP subfamily members are responsible for the biosynthesis of ecosanoids and steroids. As such inhibitors of these endogenous pathways are identified as a route to therapy. Exemestane, Letrozole and Anastrozole are inhibitors of CYP19 key to the aromatisation of androgens to produce oestrogens that drive hormone dependent cancers. Inhibitors of CYP24A1 extends the half life of endogenous calcitriol and Vitamin D analogues with potential benefit in cancer treatment. Inhibitors of CYP26 could prevent deactivation of All-Trans-Retinoic-Acid used in the treatment of PML. CYPs also function to metabolise xenobiotics and conventionally are regarded as detoxification enzymes that promote the elimination and diminish the pharmacology of drugs. At least fifteen members of CYP1, 2, 3 and 4 subfamilies contribute to the fate of drugs by increasing their polarity with often profound changes to their pharmacokinetic and pharmacodynamic properties. There is growing evidence that such pathways can contribute to the deactivation of anticancer drugs and hence the presence or even over expression of drug metabolising CYPs in tumours could be considered as a resistance mechanism.

The high expression of selected CYPs in tumours creates the potential for tumour selective activation to generate either pan-cytotoxic or molecularly targeted agents. As a consequence CYPs can now be recognised as potential therapeutic targets. The activation of several classes of clinically important alkylating agent notably the oxazaphosphorines (e.g. cyclophosphamide), and nitrosoureas is known to involve selective CYPs although the liver is generally acknowledged to contribute significantly to their clinical utility. The potential for design of agents that are substratess for extrahepatic CYPs offers the promise of tumour selective prodrugs. AQ4N (banoxantrone), currently in Phase IIa trials, is a prodrug topoisomerase II inhibitor activated by CYP1A1, 2B6 and 3A4 specifically under hypoxic conditions and for which clinical proof of concept as a hypoxia targeted agent is shown. Other agents, including Prodrax, based on the concept of N-oxide reduction pioneered by the discovery of AQ4N are also under development. Other developments include, the aminobenzothioazole, Phortress, a CYP1A1 inducer effective in AhR competent tumours. The design of chloromethylpyrolloindolines as prodrugs of ultrapotent minor groove alkylating agents that are specifically activated by selective CYP isoforms is also currently underway. The increasing interest in the CYP expression of clinical tumours alongside the development of relevant preclinical models should provide a rich seam of opportunity for the discovery CYP-activated drugs.

25 INVITED

CYP-activated prodrugs as chemotherapeutics

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Background: Increasing tumour specificity and reducing toxicity by the use of inactive systemic prodrugs which are preferentially metabolised within the tumour cells to cytotoxic agents is an attractive therapeutic strategy. Many drugs in clinical use induce, inhibit or are metabolised by the cytochrome P450 group of enzymes (CYPs), which are present in many tissues, including tumour cells.

Three agents are being investigated in early clinical trials which attempt to utilise tumour CYPs to convert prodrugs to active metabolites within the target tissue.

Methods/Results: The first agent to enter the clinic, AQ4N, is selectively activated within hypoxic tissues by CYPs 3A4, 1A1 and 2B6 to AQ4, a topoisomerase II inhibitor and DNA intercalator. This agent has completed phase I evaluation in a dose escalation study with fractionated radiotherapy in oesophageal cancer [1]. Additionally a proof of principle study where a single of AQ4N was given prior to surgery demonstrated that tumour levels of AQ4 were higher than adjacent tissues with selective activation in hypoxic regions of the tumour [2]. Drug related adverse events include