and the means of tailoring a targeted and effective therapy to the select patients who benefit most from chemotherapy.
The use of pharmacogenetic profiling in CRC to predict clinical response and identify those patients susceptible to increased toxicity is still a developing field. To make progress, there must be more complete evaluation of these markers before genetic information can become a routine part of clinical practice. Retrospective analyses have clearly demonstrated the proof of principle in this approach. However, the design of new prospective trials must encompass a more comprehensive and disciplined approach with defined protocols, primary end points and increased statistical power. Only when this approach is adopted will the ambiguity be replaced with more definitive answers in regards to the predictive and prognostic value of these markers and their clinical implementation. Follow-up studies are also required to identify the functional significance of the many mutations and polymorphic variants that exist in the patient population, such functional information will inevitably assist in unraveling the complex and multi-faceted mechanisms of drug metabolism and cytotoxicity. Markers of response to the novel therapeutic drugs including bevacizumab, cetuximab and panitumumab must also be identified and rigorously validated so that the use of these agents can be targeted to those who will derive greatest benefit.

Presence and Future:

1. To identify patients that could benefit the most from chemotherapies (chance of cure, response).
2. Molecular Markers should be in included in all clinical trials to establish predictive and prognostic markers, as well as surrogate markers and validate target inhibition.
3. The selection of new combinations should be based on molecular targets identified in tumor.
4. Pharmacogenomis should be early in drug development to understand drug metabolisms and avoid life threatening toxicities.

Challenges:

1. The validation of the association of molecular markers with clinical outcome in prospective trials. It is encouraging to note that these efforts are already underway.
2. The refining of technologies and statistical methods in order to accommodate the complexity of the molecular map that may determine outcome.
3. The standardization of testing methods and results' interpretation.
4. The adaptation of these findings and methods to every day practice, especially in the community.

19 INVITED

High throughput genotyping and its possible applications in pharmacoepidemiology

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Over the last decade, the capacity to quickly, accurately, and cost-effectively genotype single nucleotide polymorphisms (SNPs) in large scale studies (thousands to tens of thousands of individuals) on high throughput platforms (hundreds of thousands to millions of SNPs) has exploded. The trigger for this explosion was the sequencing of the human genome in the late 1990s, followed by the description of "block" structure of the genome and the human HapMap. These milestones allowed us to estimate the number of "common" polymorphisms (minor allele frequency $\gtrsim$5%), and how many of these polymorphisms need to be genotyped to capture the majority (>80%) of the SNP variation in the genome.
Today, it is possible to genotype over one million polymorphisms in tens of thousands of subjects, known as "genome wide association studies" (GWAS). Much as the technology leading to GWAS has exploded, the number of GWAS publications has also exploded. However, the vast majority of these studies have focused on either dichotomous disease outcomes or anthropomorphic and/or clinically important measures. Additionally, the results presented to date have been limited to associations between single SNPs and the outcome of interest, ignoring the possible interaction between multiple SNPs and environmental factors.
In this presentation, I will provide a brief history of genome scans, followed by a description of the two major GWAS platforms (Affymetrix and Illumina) and their respective strengths and limitations. We will then discuss the main points to consider when planning and designing a genome wide scan. This will include discussion on sample selection and handling, budgetary considerations, statistical power and replication, and analysis plans. Finally, we will be able to expand our discussion into possible applications of genome scans in pharmacoepidemiology.

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

WORKSHOP 4

Phase 0 trials – are they necessary?

20 INVITED

Phase 0 microdosing studies as part of the learn/confirm approach to drug development

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Failure to predict human drug metabolism and pharmacokinetics (PK) from laboratory animal, in silico and in vitro models may mean that promising new candidate drugs are dropped sometimes quite late in the development path. Over the past 10 years a new approach to gaining human drug metabolism information has been developed known as human Phase 0 or microdose studies. In these studies, a small sub-pharmacological dose of drug is administered to humans to obtain basic ADME/PK data. The approach is reliant on having available very sensitive analytical methods such as accelerator mass spectrometry (AMS) so that trace plasma concentrations of drug and metabolites can be measured. Typically Phase 0 studies can be conducted rapidly and cheaply such that it is possible to progress from bench to bedside within a six months timeframe. Phase 0 studies are most effective when used to examine the PK of a number of drug candidates in order that a lead molecule can be selected to take on to a full Phase I study. In addition to human PK information, Phase 0 studies can establish if the drug reaches the relevant target tissue through removal of a small surgical or biopsy sample followed by drug and metabolite analysis by AMS. Concerns have been expressed that Phase 0 PK data will not be dose proportional to that seen at therapeutic doses. We have been examining this relationship over the past few years and have found an approximate 80% correlation between the dose levels. Some of this data will be presented together with examples of how Phase 0 PK data impacted on drug development.

References

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21 INVITED

Use of phase 0-changes in cancer drug development

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Change is a continuous element in the design for first-in-human studies. Some changes are mostly incremental; others are major shifts in goals and approaches. The most important change over the last decade has been the type of compound entering the clinic. The contemporary emphasis upon molecularly-targeted agents has accelerated the trend towards correlative studies, but the results of these investigations remain as secondary findings behind the classic endpoints of toxicity and occasional tumor shrinkage. The term "Phase Zero" is intended to signify a major change in the structure of first-in-human studies of anticancer drugs. It is not simply an extension of the trend towards more biomarker studies. The enormous difference for Phase Zero is that pharmacodynamic or biomarker studies are not simply correlative. Evaluation of target modulation is now the primary goal, and is intended to inform decision-making regarding further compound development. There is always some blurring of the end of discovery and the beginning of development. For many investigators, the first-in-human experience is viewed as the end of discovery and the beginning of development. Phase Zero studies are explicitly designed to extend the process of discovery into first-in-human studies, obtaining information that will shape the beginning of the development process that will follow next.
The key to decision-making is the identification of the pivotal information for a "stop-or-go" decision. The design of the first clinical study must be customized to obtain that information. Because each compound and target is different, the most important information for each trial will vary. For some cases, choosing among analogs might be the goal, and the key information might be pharmacokinetic, such as extent of absorption or half-life in the body. For most target-oriented programs, pharmacodynamic measures are most important. If the compound is intended to inhibit an enzyme in the tumor, determination of inhibition is the primary objective. For receptor blockage strategies, the occupancy of the receptor by the compound is the desired information. For imaging studies, receptor and/or compound biodistribution is likely to be the most useful information.

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

J.H.M. Schellens[1]. [1]*The Netherlands Cancer Institute, Medical Oncology, Amsterdam, The Netherlands*

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