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Preclinical and clinical toxicity correlations for cancer drugs developed by the NCI

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The development of therapeutic agents for the effective treatment of cancer has proven to be a challenging and difficult process. Currently, anticancer drugs are used clinically at or near the maximum tolerated dose (MTD) and, frequently, with significant toxicity. Therefore, preclinical toxicity studies are extremely important to establish the safety of the clinical starting dose and to identify the spectrum of drug-induced toxicities in appropriate animal models. In the US, the clinical starting dose for Phase I studies for cancer drugs is based on the MTD determined in the most sensitive of two preclinical animal models (one rodent and one non-rodent). The purpose of this analysis was to: 1) evaluate the "safety" of the clinical starting dose based on preclinical data; 2) to compare the resultant clinical and preclinical MTDs; and 3) to evaluate the accuracy of the dose-limiting toxicity (DLT) prediction based on preclinical animal models. This study includes the evaluation of the results for 38 small molecular weight compounds that the NCI has been involved in the preclinical and clinical development between 1983 and 2002. Biological modifying agents were not included in this analysis. This group of compounds included various mechanisms of action and dosing schedules. The clinical starting doses for all the compounds included in this analysis were safe, except for one clinical trial (fazarabine). Therefore, clinical starting doses based on the most sensitive of two species were safe for 98% of the clinical trials. However, for 49% of the clinical trials included on this study, the starting dose was too low resulting in an excessive number of dose escalations in the clinic. When the clinical and the preclinical MTDs were compared, neither rodents nor non-rodents predicted the MTD more accurately. However, the clinical DLT was predicted in at least one preclinical animal model for 70% of the drugs evaluated. The most common DLT was myelotoxicity (43%) followed by gastrointestinal toxicity (24%). Some types of toxicities weren't well predicted in either of the two preclinical animal models. In conclusion, preclinical toxicology studies provide a very high level of safety for cancer drugs entering clinical trials. However, this analysis suggests that additional types of studies may be necessary in order to balance safety and predictability while minimizing the length of clinical studies.

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WORKSHOP

Molecular imaging

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Measuring response to therapy with molecular imaging

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Molecular Imaging in oncology is defined as the non-invasive imaging of the key biomolecules that are important to cancer biology. Cancer researchers have discovered diverse genes and gene products, critical to cancer development and maintenance, and many of these have now been selectively imaged. Some of these molecules are themselves targets for the action of specific anti-cancer drugs, whereas other imaged molecules reflect more general biologic features of the cancer cell phenotype.
Molecular imaging is being used to monitor the response of prostate cancer to specific anti-cancer therapies. Androgen receptor (AR) is a key biomolecule that is important to the biology of the cancer. We have begun to study the expression of AR using 16b-[18F] fluoro-5a-dihydrotestosterone (FDHT). In a group of patients with progressive androgen independent prostate cancer, we have discovered that the majority of active lesions can be visualized with FDHT using PET imaging. The impact of the expression of the androgen receptor on response of individual lesions to AR targeted anti-cancer drug therapies is being explored. Most cancer cells have an accelerated glycolysis in comparison to the tissues from which they arise. The activity of hexokinase in the cancer cell is a rate-controlling enzyme in glycolysis. [18F] 2-fluoro-2-deoxy-D-glucose (FDG), is a tracer that is widely use to image the activity of hexokinase enzyme. We have found that FDG uptake, and by inference, glycolysis, is greatly increased in androgen independent prostate cancer. We are currently using FDG and PET imaging, to monitor the effect of hormono-chemotherapies on glycolysis of individual metastatic lesions in advanced patients with prostate cancer. Technical features of the imaging methods used includes measures of regional metabolism such as Standardized uptake values or SUV, as well as combinations of SUV with volume differences, a new functional imaging parameter which we have dubbed the "total lesion glycolysis" or TLG. Work performed to date supports the hypothesis that changes in FDG uptake are an early indicator of clinical response to anti-cancer regimens.
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What new pharmacokinetic information can molecular imaging provide us

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Poor pharmacokinetics is a major cause of drug failure and thus early assessment in the drug development process can reduce cost. Drugs labelled with long-lived isotopes such as carbon-14 have been used in the past to provide toxicokinetic information on new drugs in animals and humans. Such studies are based almost exclusively on analysis of blood and urine samples. Isotopic substitution with a positron emitting atom enables the pharmacokinetics in tumours and normal tissues to be studied by positron emission tomography (PET).
PET studies can be performed prior to conventional Phase I clinical trial of a compound. Chemical identity and purity of the labelled compound, as well as animal safety and dosimetry have to be established prior to these 'microdosing' studies in humans. The PET studies can also be performed at other phases of drug development. The following information can be obtained:

- First proof of hitting intended target
- First proof of intended mechanism of action
- Effect of biochemical & physiological modulators
- Early opportunity to change pharmacophore and evaluate selective accumulation of drugs into tumours (SAR)

PET has been used within the Cancer Research UK PET oncology group to study the tissue pharmacokinetics of temozolomide, DACA and 5-fluorouracil. In the case of temozolomide, drug delivery to brain tumours has been established and proof of mechanism of ring opening has been provided. A number of translational research questions were investigated during the Pre-Phase I trial of carbon-II-radiolabelled DACA. Tumour drug delivery and delivery to normal brain, myocardium and bone marrow were assessed. PET studies have also been performed during two Phase I trials to assess the effect of different schedules on tissue pharmacokinetics. PET has been used to demonstrate proof of principle of mechanism of action of eniluracil, an inactivator of dihydropyrimidine dehydrogenase. Eniluracil decreased hepatic and renal exposure of fluorine-18-radiolabelled 5-fluorouracil, and increased tumour exposure. Modulation of 5-fluorouracil tissue pharmacokinetics by biochemical modulators (interferon, PALA and folinic acid) and physiological modulators (carbogen/nicotinamide) have been studied in cancer patients.
PET pharmacokinetic studies can provide scientific feedback on the delivery and mechanism of action of new compounds, and thus, provide an early indication of weather a drug may be ineffective in tumours. Such studies can also predict for normal tissue toxicity.

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Molecular imaging of endogenous gene expression

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Molecular imaging has its roots in molecular and cell biology, as well as in imaging technology. These disciplines have now converged to provide a well-established foundation for exciting new research opportunities and for translation into clinical applications. The development of sensitive imaging-based assays to monitor molecular-genetic and cellular processes in vivo will be of value in the study of animal models of human disease (including transgenic animals), as well as for studies in human subjects.Three different noninvasive imaging technologies developed more or less in parallel: 1) magnetic resonance imaging; 2) nuclear imaging (QAR, gamma camera and PET); 3) in vivo optical imaging of small animals. Two imaging strategies - "direct" and "indirect" – are currently most widely used. "Direct molecular imaging" can be defined in terms of a probe-target interaction, whereby