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PROBLEMS IN EVALUATION OF COMPOUNDS INVOLVED IN SIGNAL TRANSDUCTION IN PHASE I STUDIES

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The phase I evaluation of "standard" cytotoxic drugs, where myelosuppression is the major dose limiting toxicity, is relatively straightforward, and the use of pharmacokinetically directed dose escalation procedures have proven great benefit. The development of novel cytotoxic agents has, however, led to many potential difficulties including identification of the best schedule of administration. In addition the dose limiting toxicity may not be myelosuppression, and for many products drug doses are very low making classical pharmacokinetics impossible.

One class of compounds of great interest as potential anti cancer agents are compounds targetted as inhibitors of signal transduction. The lead compound in this area is bryostatin I, a protein kinase C partial agonist. This compound showed potent activity in pre clinical in vitro and in vivo models. This compound has been evaluated in 2 phase I studies in the UK where weekly infusions were the best tolerated. Maximum tolerated doses were very low (25μg/m2), with dose limiting toxicity myalgia. A variety of biological parameters were assessed, with significant changes in IL-6 and TNFαc detected which may be useful for biological monitoring of this agent. Biological monitoring may prove to be a valuable approach for the assessment of this exciting new class of agents.

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WHAT IS MTD?

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Maximal tolerated dose (MTD) has been the goal and hallmark of Phase I chemotherapy trials since their inception. Since treatment in maximal doses has been felt to be equated with maximal response when using antineoplastic chemotherapy drugs, the concept was universally accepted and included in the testing of new immunomodulating agents in all phase I studies. Higher chemotherapy doses have usually correlated with increased response rates; higher immunomodulator doses, however, have not in general corresponded to "optimal" dose response or scheduling.

Ammonium-trichloro (dioxyethylene-0,0') tellurate, AS101, is a new agent found to have potent immunostimulatory actions both in vitro and in vivo. A standard phase I study in humans was completed showing AS101to have a wide safety margin with minimal toxicity up to 14 mg/m^2 IV three times a week. Dose escalation per modified Fibonacci method was terminated when grade III-IV nausea and vomiting developed. The latter, classicaly, has not been a standard for toxicity necessitating termination of dose escalation. Optimal immunostimulatory action of AS101, however, was found to be 3 mg/m^2 IV three times a week with doses higher than 5 mg/m^2 IV three times a week showing significant decrease and depression of all stimulatory effects.

We will present our final phase I results of AS101 with emphasis on reaching MTD and will propose changes for the future where optimal stimulatory doses and not MTD will be the primary goals when testing new immunomodulating agents.

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BIOREDUCTIVE DRUGS IN PHASE I - HOW TO EVALUATE

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SUPPRESSION OF PHILADELPHIA[1] LEUKEMIA CELL GROWTH IN MICE BY bcr-abl ANTISENSE OLIGODEOXYNUCLEOTIDES

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Injection of Philadelphia chromosome-positive leukemic cells into SCID mice induces a disease process closely resembling that in leukemia patients. In leukemic mice treated with an antisense oligodeoxynucleotide complementary to the bcr-abl junction, no leukemic cells expressing the cALL antigen were detected nor did leukemic colonies form in semisolid medium. Bcr-abl transcripts were not detected in most tissue samples from four antisense-treated mice up to 8 weeks after injection of leukemic cells. Untreated mice and mice treated with a 6-base mismatched bcr-abl antisense oligodeoxynucleotide or a bcr-abl sense oligodeoxynucleotides were dead 8 to 13 weeks after leukemia cell injection (median survival time 9.7 ± 0.9) where as mice treated with bcr-abl antisense oligodeoxynucleotides died of leukemia 18 to 23 weeks after injection (median survival time 19.4 ± 1.3). These findings provide evidence for the in vivo effectiveness of an anti-cancer therapy based on antisense oligodeoxynucleotides targeted to a tumor-specific gene.

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PHASE I STUDIES WITH BIOLOGICAL RESPONSE MODIFIERS (BRM).

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Phase I studies of chemotherapeutic agents are based on the principle that tumour cell kill is positively correlated with dose of drug. Patients in phase II studies will, therefore, be treated near to the maximum tolerated dose (MTD). Starting doses are based on studies in laboratory animals and ensure that the first dose level is non-toxic (usually 1/10th of the LD_{10} in mice or 1/10th of the toxic dose low in dogs). Dose escalation usually follows a modified Fibonacci series or is pharmacokinetically guided.

These principals do not apply for phase I studies with BRMs. Starting doses are usually chosen empirically due to lack of pre-clinical models which predict toxicity. Further heaviliy pre-treated patients with advanced cancer are inappropriate for such phase I studies due to suppressed/damaged biological responses. Biological Responses are not always positively correlated with dose and the optimum biologically active dose is usually less than the MTD. Measurement of biological responses such as NK or LAK activity often show large interpatient or temporal variations. Larger patient cohorts at each dose level are therefore necessary to allow accurate determination of dose response effects. Finally the mechanism of antitumour activity in vivo is often unclear and parameters predicative of response are often difficult to determine. All these points continue to make phase I studies with BRMs problematic.

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POLYMER-DRUG CONJUGATES : CHALLENGES FOR PHASE I

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During the last decade soluble synthetic copolymers of N-(2-hydroxypropyl)methacrylamide (HPMA) have been developed as carriers of anti-tumour agents (eg.daunorubicin, doxorubicin, melphalan) [1], and HPMA copolymer conjugates containing doxorubicin will shortly enter Phase I under the auspices of the British Cancer Research Campaign's Phase I/II Clinical Trial Committee. Drug is covalently bound to the polymeric carrier via peptidyl spacers that are designed for intra-tumoural cleavage by lysosomal thiol-dependent proteases, and it has been shown that drug conjugation alters markedly its whole-body, and cellular pharmacokinetics, leading to reduced toxicity and improved therapeutic index. These complex macromolecular prodrugs offer certain challenges in their development towards clinical evaluation, not only in terms of pharmaceutical development, but also in respect of their novel mechanism of action. With the progress of other types of chemo-delivery system into the clinic (liposomes, immunoconjugates, particles for embolisation etc.), it has become increasingly obvious that there is a fundamental need to consider the clinical protocol very carefully, on a case by case, basis if optimal evaluation is to be achieved.

[1] R. Duncan (1992) Drug-polymer conjugates : potential for improved chemotherapy. *Anti-Cancer Drugs*, **3**, 175-210.

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