success. Targeting a single pathway may prove ineffective or only transiently effective if parallel signaling pathways remain active or are upregulated, downstream pathway activation occurs or feedback loops overcome target inhibition. Both scientific and regulatory challenges exist in the efficient development of targeted therapy combinations. The foremost requirement is a strong scientific rationale to develop the combination coupled with non-clinical experimental data that supports that rationale and a thorough understanding of the consequences of pathway inhibition by the agents being combined. Evidence of synergy of the combination in *in vitro* cell lines and enhancement of the activity of the combination compared to the activity of either agent alone in *in vivo* nonclinical models should be sought. It is also desirable to identify biological indicators for likely responders in a patient population. The clinical development of targeted therapy combinations first requires characterization of the toxicity profile of each drug when given as a single agent as well as knowledge of potential pharmacokinetic interactions. Perhaps the most challenging clinical scenario is the development of a combination when one or both drugs in the combination has little or no anti-tumor activity as a single agent but the combination is expected to produce significant anti-tumor effects, the so-called synthetic lethality model. Co-enhancement refers to scenarios in which each agent is modestly active as a single agent in model systems, but the combination is highly active in the exact same model systems. Factorial clinical trial designs may be necessary to optimally evaluate drug combinations in these scenarios.

Few clinical examples of success in development of targeted therapy combinations exist at present although some pitfalls have been identified, most notably the lack of improved efficacy and increased toxicity observed when combining anti-EGFR antibodies with bevacizumab and chemotherapy in treatment of advanced colorectal cancer. Modest successes have been reported for the combination of EGFR-directed therapies in breast cancer (e.g., trastuzumab plus lapatinib superior to lapatinib in previously treated Her2 positive patients) as well as for adding arsenic trioxide to ATRA-based therapy in APL and combinatorial approaches are currently being evaluated in many other disease settings with agents hypothesized to produce more than additive anti-tumor activity. Well designed clinical trials will be necessary to clearly demonstrate the clinical benefit of such approaches and incorporation of biomarker studies will be essential in an attempt to explain both therapeutic successes and, more importantly, therapeutic failures.

23 INVITED

Targeted agents combined with radiation

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Combination of chemotherapy and radiotherapy is a mainstay in the management of patients with locally advanced tumors. Our increased knowledge of cancer at the molecular level has transformed our understanding of tumor radiation response. Preclinical models have shown that several biologic agents designed to target specifically these molecular processes can increase tumor response to ionising radiation. Many of these agents are in the process of clinical evaluation with radiotherapy. In contrast to the preclinical findings, clinical results from clinical trials combining radiotherapy to targeted therapies such as anti EGFR or anti VEGF has been sometimes associated to an increase in toxicities underscoring the need for appropriate models of tumor versus normal tissue response assessment in vivo. The challenging concept of tumor addiction and the increasing pharmacological tools available to reverse these signals may represent a novel step in the concept of tumor radiosensitization. We have developed a strategy for the treatment of HPV related tumors: the use of antiviral agents to modulate the radiosensitivity. However, in lung tumors, some data suggest that inhibition of cancer 'addiction' pathways may not necessarily translate in better response to IR into the clinic.

These data justify the importance of evaluating new agents in combination with irradiation with an appropriate methodology at the preclinical stage in order to avoid unnecessary exposure of patients to potentially ineffective or detrimental combinations.

This preclinical evaluation needs to be able to answer the following questions:

- What is the toxicity profile, is there a differential effect?
- How to compare the antitumor efficacy observed with other anticancer agents?
- What is the optimal tumor profile?
- What is the sequence adapted to the optimal antitumor effect?

An important aspect is also to take into account the mechanisms of action of ionizing radiation such as DNA damage and cell cycle check-point induction during repeated DNA daily fractions. These aspects can be used to increase tumor response to irradiation. In particular, induction of mitotic catastrophe, one key mechanism of tumor cell death after irradiation can be increased by the use of agents that override the radiation induced G2/M arrest such as CHK1/2 and aurora inhibitors. Of interest, this latter approach exploits differences in radiation response of p53 deficient versus p53 wild type cells which could eventually provide exploitable differential effect in the clinic.

Finally, one of the major issues preclinical evaluations is to minimize exposure to excessive risks for patients during phase I. The development of more relevant preclinical models of drugs-radiotherapy toxicities will be illustrated through the evaluation of the impact of new strategies on the response of non-tumor tissues developed at our lab.

Wednesday, 17 November 2010 10:15–12:10

WORKSHOP 5

Pharmacokinetics/pharmacodynamics in cancer

24 INVITED

Factors affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of nanoparticle and nanosomal anticancer agents

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Carrier-mediated agents (CMA) are classified as nanoparticles, nanosomes and conjugates. Anticancer CMA offer many unique advantages over their traditional counterparts, including improved solubility, longer duration of exposure, tumor-selective delivery, increased antitumor response and reduced toxicity. The PK of nanoparticle agents, such as nanosomes, is dependent upon the carrier and not the parent-drug until the drug is released from the carrier. The drug that remains encapsulated in the nanocarrier is an inactive-prodrug and thus the drug must be released from the carrier to be active. The PK variability associated with nanoparticles is greater compared with small molecules. The factors affecting the PK and PD variability of these agents remain unclear, but most likely include the monocytes, macrophages and dendritic cells of the RES. Thus, we evaluated the factors affecting the PK and PD of PEGylated liposomal formulations of doxorubicin (Doxil, PLD) and CKD-602 (S-CKD602) in patients (pts). The inter-patient variability in the PK and PD of these agents was associated with age, body composition, monocytes and presence of tumors in the liver. There was an inverse relationship between pts age and % decrease in monocytes at nadir with younger pts having a higher % decrease in monocytes. Pts with a higher % decrease in monocytes at nadir have an increased clearance of encapsulated drug and increased release of drug from the liposome. These results suggest that monocytes engulf PEGylated liposomal agents which causes the release of drug from the liposome and toxicity to the monocytes, and that the effects are more prominent in pts <60 years old. The development of phenotypic probes of RES function may be used to individualize the therapy of nanoparticles as a mechanism to reduce the PK and PD variability.

25 INVITED

Role of pharmacokinetics/Pharmcodynamics in dose selection of molecular targeted therapies

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Pharmacokinetics (PK) and pharmacodynamics (PD) are basic pharmacological principles that serve many purposes during drug development and daily clinical therapeutic practice. Increasingly the power of PK and PD is being recognized in the early phase of drug development, especially at the transition of preclinical to clinical development. In addition, PK–PD modeling is being explored of biomarkers that may enable safer drug development of drugs that do not show classical bone marrow toxicity and/or mucositis as dose-limiting toxicity (DLT). This is especially the case in the development of tyrosine kinase inhibitors that show hypertension and/or proteinuria as DLTs.

In the case of the transition of preclinical to clinical development often a wealth of PK and PD data exist that is more or less being ignored in the

design of a phase I study and in the selection of the dosing strategy and treatment schedule. Optimal use of the preclinical PK−PD database may improve the selection of dose and schedule in early clinical studies and facilitate the execution of these studies, thereby reducing the length of the studies, number of patients needed and patients that are being exposed to sub-therapeutic doses. An example of the implementation of such strategy is the clinical development of the a2-integrin inhibitor E7820 whereby the expression of a2-integrin on platelets and tumor cells served as a biomarker. Another example is the PK−PD modeling of the multitargeted tyrosine kinase inhibitor E7080 (HOPE). By applying PK−PD and modeling the magnitude of the effect of antihypertensive therapy could be predicted on the dose-limiting hypertension and proteinuria upon treatment with E7080, demonstrating the usefulness of the outlined methodology.

References

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26 INVITED

Is a side effect of molecular targeted therapy a marker of efficacy?

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The target of signal transduction inhibitors may be present on normal as well as tumor cells, what explains the side effects in addition to antitumor activity of molecular targeted therapy. Some toxicities may be a pharmacodynamic effect of pathway inhibition (mechanism-based toxicities) and, in tumours that depend on the inhibited pathway for proliferation, a biomarker of efficacy. Hypertension, a recognized adverse event of angiogenesis inhibitors, may be a potential biomarker of VEGF pathway inhibition and, in some occasions, of efficacy. Retrospective analyses of various studies with bevacizumab, sorafenib, sunitinib, and axitinib have verified that early development of hypertension correlates with clinical outcome in patients with different tumour types, including advanced colorectal, breast and renal cell carcinoma. In addition, several studies have suggested that development of rash with treatment with tyrosine kinase inhibitors or monoclonal antibodies against EGFR is associated with improved outcomes in patients with non-small-cell lung cancer, head and neck, colorectal and pancreatic cancer. Response rates as well as progression-free and overall survivals have improved in patients that develop skin toxicity with anti-EGFR targeted agents, such as erlotinib, gefitinib, cetuximab and panitumumab. The development of hypertriglyceridemia with mTOR inhibitors and hyperglycemia with PI3K/AKT inhibitors are pharmacodynamic effects of pathway inhibition and the potential value as markers of efficacy is under evaluation. However, the predictive value of a side effect requires validation in prospective trials, like the "dosing-to-rash" studies that are currently underway. Oncogene addiction on a specific pathway that is targeted with the therapy may be the possible link between a mechanism-based adverse event and efficacy. In addition, biological basis for this association may be pharmacological, with subjects with higher plasma levels of the drug attaining greater toxicity and antitumor response, and also genetic, as single nucleotide polymorphisms play a role in drug pharmacokinetics and pharmacodynamic processes. Additional studies are of utmost importance for further clarifications of this correlation.

27 INVITED

Drug response in a genetically engineered mouse: clinical implications

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The progress in the development of new anticancer agent's remains rather slow. One of the bottlenecks in anticancer drug development is the lack of predictive preclinical models. Conventional cancer models, based on cultured cell lines and xenograft derived from these cell lines are poor predictors of clinical outcome. In addition, as these models do not represent well the full heterogeneity of the disease have not been very useful as platforms for biomarker discovery. Recently, there has been interest in the newer models for anticancer drug development including genetically engineered mouse models and as well as freshly generated xenograft obtained directly from cancer patients. These models have several biological features that suggest may be predictors of clinical outcome. These included a more diverse and close to human cancer spectrum of genomic alterations, and the presence of stroma and cancer stem cells. A series of recent studies demonstrate that these preclinical models are suitable for biomarkers discovery and, in fact, some of the biomarkers currently in clinical use could had been discovered in preclinical models. Emerging data also suggest that these models are better predictors of the outcome of clinical trials indicating that could be useful for drug screening and design of clinical trials. Indeed, it is expected that these models will be progressively used in drug development in lieu of extensive clinical programs as it will permit a much focused clinical plan. Finally, these models look promising as platform for personalized cancer treatment. However, additional data is needed to fully determine their role in this setting.

Current representative preclinical models. drugs in patients with pancreatic cancer. Multiple clinical trials conducted in this disease have been negative. While the ultimate progress in pancreatic cancer will come from the discovery of new drugs and strategies, it is also clear that a better understanding of drug mechanism of action and expected antitumor effect may help in clinical development. If could also be argue that some agents form which preclinical results are not optimal should perhaps not be developed clinically so that resources can be prioritized and focused in those compounds with a better chance. It is noteworthy that most new agents tested in the clinic are selected with very limited preclinical information. In general, studies are limited to a few conventional cell lines at the most. It is doubtful that these cell lines, which have adapted to growth in culture for prolonged periods of time maintain are predictive of pancreatic cancer clinical outcome.

More recently, two models of pancreas cancer have become available which may facilitate the clinical development of new agents. Using genetically engineering techniques several groups have developed genetically modified mouse models which faithfully recapitulate the development and clinical presentation of the disease in mice. While these models were initially used to understand the molecular biology of pancreatic cancer, more recent studies have used these models for drug testing. In parallel to this work, other groups including our own have developed personalized pancreatic cancer tumors using patient derived tumor materials obtained at the time of surgery and propagating these tumors in nude mice. We have used this platform to perform drug screening studies, biomarker development and to design personalize treatment strategies. This work has already identified interesting new targets and strategies which are been advanced to clinical development.

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27A

Targeting the PI3K/mTOR pathway in genetically engineered mouse models of advanced prostate cancer

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The PTEN and p53 tumor suppressors are among the most commonly inactivated or mutated genes in human cancer, including prostate cancer. Loss of PTEN is associated with increased pathologic Gleason score and risk of clinical recurrence, and 20–60% of human metastatic prostate cancers have loss of heterozygosity at the PTEN locus, resulting in hyperactivation of the PI3K/mTOR pathway. Mice with germline heterozygosity for PTEN have been shown to develop prostate intraepithelial neoplasia (PIN) at a high rate (>60%) and mice with prostate specific homozygous deletion of PTEN develop invasive prostate cancer, albeit with prolonged latency. Combined inactivation of PTEN and p53 in mouse prostate elicits invasive cancer by 9 weeks of age and invariable lethality by 7 months of age. We evaluated the impact of GSK48 (dual PI3K/mTOR inhibitor) in prostate-specific PTEN/p53 double knockout mice and prostate-specific PTEN mice, respectively. The mice were imaged by 18FDG-PET and T2-weighted MRI, respectively, for baseline tumor metabolic and volumetric assessment prior to drug administration. GSK458 was