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