281 INVITED

Phase I set up and running: the fellow point of view

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Phase I clinical trials represent the initial stage of drug development to reach testing in humans. Traditionally they differ substantially from the more advanced phase studies, although in the modern era the distinction between phase I and II is becoming increasingly blurred. The primary objectives focus on safety and toxicity of the new agent under evaluation in order to define the safety profile, dose-limiting toxicities (DLT), maximum tolerated dose (MTD) and recommended phase II dose (RP2D). Secondary study endpoints often include characterisation of pharmacokinetic (PK) and pharmacodynamic (PD) profiles, as well as assessing for early evidence of anti-tumour effects. Biomarker evaluation is also frequently incorporated.
Initial requirements for setting up a phase I protocol include expertise, knowledge of the target, the signal transduction pathway, and the mechanism of action of the selected drug, as well as close relationships with the pharmaceutical industry, dedicated staff and adequate in-house resources and facilities. Open, honest two-way communication with the sponsor is imperative from the outset if the needs and desires of all parties are to be met. A thorough understanding of the protocol and resolution of any queries need to precede trial initiation. Due to the intensive requirements of these studies in terms of number of patient visits and tests, the centre needs to ensure that all members of the team – doctors, nurses, study coordinators, pathologists, radiologists and others – are well prepared and devoted to the conduction of the study and there is adequate space for patients.
Running a phase I trial is a dynamic process. Identifying and screening patients requires attention to detail and a systematic approach to ensure protocol criteria are met. Treatment through the first cycle, typically defining the DLT period, must be followed closely and patients listened to carefully. Early identification of toxicities with prompt treatment is of utmost importance to ensure patient safety. Ongoing discussion with the sponsor and co-investigators will aid the successful running of the trial and facilitate any major changes that may be required in light of emerging information. Such data may derive from clinical parameters, from PK or PD data interpretation, or from emerging preclinical data in the true spirit of translational oncology.
It must never be forgotten that the patients and their families are enduring difficult times when they agree to participate in phase I studies. Without them we could not proceed. So though we seek to meet our own objectives, we must remain sensitive to their needs.
With an ever-expanding plethora of targeted therapies emerging from preclinical studies, participation in phase I clinical trials presents an exciting opportunity to be at the forefront of this development process that we hope will ultimately translate into potentially practice-changing findings.

282 INVITED

Novel tools for drug efficacy testing

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Only 1 in 20 new oncologic drugs that are tested in human subjects are ultimately shown to be efficacious and approved for widespread clinical use. The process of drug development in oncology is expensive and inefficient since the vast majority of novel agents fail in advanced stages of clinical testing. These failures may be due to ineffective drugs, poor patient selection (i.e., lack of accurate predictive markers for response to therapy), and lack of innovation in clinical trial design. The above represent major bottlenecks in improving patient outcome in solid tumor oncology.
To address the above issues, Phase 0 or tumor specific phase I trials with extensive translational research to understand the pharmacokinetics and pharmacodynamics of novel agents are increasingly being conducted.
Neoadjuvant/short window preoperative trials targeting a patient population with a specific molecular abnormality or a specific phenotypic/genotypic profile have been proposed as another way to address the inefficient drug development. These trials evaluate short-term surrogate endpoints, such as pathological complete response rate or changes in anatomic or functional imaging. The early assessment of tissue biomarkers after a brief exposure to targeted therapy, (single markers such as Ki67 or integrated gene expression profiles) are also being investigated as a surrogate endpoint of clinical activity. By using the pre-operative setting, signals of drug activity or inactivity can be detected much earlier to assist in go/no-go decisions, prioritizing novel therapies that should be taken forward in the adjuvant setting.
Circulating tumor cells have been also suggested as an experimental tool for an early read-out of drug activity. In an EORTC randomized phase II study, women with detectable HER2-positive CTCs and a HER2-negative primary tumor will be randomized between a short course of trastuzumab versus a placebo to determine if trastuzumab can clear HER2-positive CTCs. If this trial is positive, a phase III trial will further evaluate this hypothesis having disease-free survival as a primary endpoint. Detection and characterization of circulating tumor cells or detection of other blood-based biomarkers (circulating DNA, circulating microRNAs) may offer the possibility for real time-monitoring of a tumor phenotype/genotype after exposure to a targeted agent. Blood based biomarkers may be particularly useful since serial tumor biopsies are difficult to obtain.
The ongoing revolution with the deep sequencing DNA technology may allow for the design of clinical trials in which the administration of targeted agents will be selected based on the driver mutations/pathway alterations that characterize the tumor of each individual patient.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
Advances in leukaemia

283 INVITED

Delineating the cellular pathways and molecular determinants of normal and leukemic hematopoiesis

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The classical model for hematopoiesis predicted that the commitment to a single hematopoietic lineage requires that HSCs pass through defined restriction sites that eventually result in a strict separation between the lymphoid and myelo-erythroid lineages. This model has been strongly supported by the identification and characterisation of the common lymphoid progenitor (CLP) and common myeloid progenitor (CMP). However, over the last years we and others have presented evidence in support of the existence of a progenitor cell population in adult mouse bone marrow as well as in fetal liver, the lymphoid primed multipotent progenitor (LMPP, $Lin^{-}SCA1^{+}KIT^{+}Flt3^{hi}$), with combined lymphoid and granulocyte/macrophage (GM) potential, however little or no megakaryocyte/erythroid (MkE) potential (Adolfsson et al., Cell, 2005). Using global and single cell-analyses a hierarchical organization of transcriptional lineage programs was established, with downregulation of MkE genes from HSCs to LMPPs, sustained GM lineage priming, and up-regulation of common lymphoid (but not B and T cell-specific) genes (Mansson et al., Immunity, 2007). Furthermore, (Luc et al., Blood, 2008) we have found that the minimal residual MkE potential within LMPPs segregates with LMPPs expressing the thrombopoietin (THPO) receptor MPL, whereas the $LSKFlt3^{hi}MPL^{-}$ LMPPs lack significant MkE potential while sustaining combined GM and lymphoid potentials, and co-expressing the GM and lymphoid but not the MkE transcriptional lineage programs. These functional and molecular findings reinforce the existence of GM/lymphoid restricted progenitors with little or no ability to commit to the MkE lineage, with potential implications for normal and leukemic human hematopoiesis.
The existence of leukemic stem cells (LSCs) as distinct and rare populations of cells capable of reconstituting leukemia has recently been questioned. A related but distinct question, is whether there exists rare populations of LSCs which are uniquely resistant to conventional therapeutic targeting, and therefore also the likely source of relapses following such treatments. In a subgroup of myelodysplastic syndromes (MDS), 5q- syndrome, we have pinpointed the primary cellular target for the 5q deletion to be a rare population (typically less than 0.1% of all BM cells) of multipotent (lympho-myeloid) stem or progenitor cells, which displays phenotypic and functional stem cell properties, and efficiently displaces the normal HSC compartment. Notably, a high fraction of transfusion-dependent 5q- MDS patients go into complete clinical, morphological and molecular remission in response to Lenalidomide treatment. Whereas our investigation of the bone marrow of these 5q- patients before and after treatment with Lenalidomide, confirm that Lenalidomide efficiently eliminates the 5q- clone at the progenitor level, we can in all patients demonstrate that the 5q- MDS stem cell compartment is highly resistant to Lenalidomide.