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TRIAL WATCH

Phase 0 trials for anticancer drug development

The results of the first 'Phase 0' clinical trial in oncology of a therapeutic agent under the Exploratory Investigational New Drug Guidance of the US FDA have recently been reported (*J. Clin. Oncol.* 13 Apr 2009; doi:10.1200/JCO.2008.19.7681).

"Phase 0 trials allow the rapid determination of proof of mechanism in human tumours, the rapid evaluation of the relative bioavailability of a series of analogues in a single human trial, or the determination of the optimal biodistribution of a series of imaging agents (such as monoclonal antibodies) in the course of a single study," says James Doroshow, Director of the National Cancer Institute, Bethesda, Maryland, USA, and corresponding author of the study. "This enhances the possibility that useful molecules move forward to further development, and could accelerate the overall process."

Guidelines for Phase 0 trials, which aim to establish at a very early stage whether an agent behaves in human subjects as would be expected on the basis of preclinical studies, were issued by the FDA in 2006. Distinctive features of Phase 0 trials include the administration of a limited number of subtherapeutic doses to a small number of subjects for short periods of time to obtain preliminary data on the action and bioavailability of the drug. Owing to these features, less preclinical safety data may be required to support such trials than standard Phase I trials, and thus they can be initiated more rapidly.

Doroshow and colleagues carried out a first-in-human study of the poly(ADP–ribose) polymerase (PARP) inhibitor ABT-888 (discovered by Abbott) in patients with advanced malignancies. The activity of PARPs, which are DNA repair enzymes, can lead to resistance to cytotoxic chemotherapy and radiotherapy, and preclinical studies have indicated that PARP inhibitors potentiate the effects of currently available DNA-damaging anticancer agents.

Administration of a single dose of ABT-888 (25 mg or 50 mg) was found to decrease levels of poly(ADP–ribose) by more than 90% in tumour biopsies of 4 out of 6 patients 3–6 hours after administration. These findings are similar to those found in xenograft models and were also reflected in the patients' samples of peripheral blood mononuclear cells (PBMCs), suggesting that PBMCs could be used as surrogate biomarkers for tumours.

This trial, which was completed within 5 months, "…allowed Abbott to avoid a formal Phase I study of ABT-888 alone, and move directly from Phase 0 to Phase I combination trials of ABT-888 plus DNA-damaging agents, probably decreasing the drug development timeline by at least a year," says Doroshow. "This was possible because the study demonstrated the dose required for complete inhibition of the target and the duration of inhibition."

Doroshow notes that there are several key challenges for the achievement of such goals to be possible for Phase 0 trials in general. The therapeutic indices of the molecules should be high so that low doses will be bioactive over a short time course. Sensitive biomarker assays are needed to measure drug effects, as well as a multidisciplinary team of researchers and clinicians to develop assays and tissue-handling protocols, which may be unique for each compound. "It will therefore require several years to determine the ultimate role of Phase 0 trials in anticancer drug development," concludes Doroshow.