The Importance of PK/PD Data—Key Biological Answers Needed to Evaluate the Success of Potential Cancer Therapeutics

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Commentary on:

The preclinical pharmacokinetic (PK)-pharmacodynamic (PD) data generated for pazopanib identified in vivo concentrations resulting in the inhibition of target receptors and pharmacological effects consistent with inhibition of the target receptors (1). We established that sustained inhibition of vascular endothelial growth factor receptor (VEGFR) 2 in vivo was required for maximum anti-angiogenic and anti-tumor effects and, as such, trough plasma concentration will be the key driver for biological activity of pazopanib and other VEGFR inhibitors. Based on preclinical experiments, we proposed that trough concentration (C24h) of ~40 μM pazopanib is required for optimal biological effects. The relationship between trough plasma pazopanib concentrations and clinical PD markers was confirmed in the first clinical trial, showing steady-state C24h ≥15 μg/ml (34 μM) was associated with increased blood pressure, an effect consistent with VEGFR2 inhibition. Further, renal cell carcinoma (RCC) patients achieving steady-state C24h ≥15 μg/ml showed a clinical benefit (2). Subsequent analyses have confirmed this relationship as progression-free survival was significantly increased in RCC patients when the steady-state trough plasma pazopanib concentrations at 4 weeks was maintained above 20.7 μg/mL (3). Pazopanib is currently approved for the treatment of patients with advanced RCC.

The role of preclinical discovery in support of drug discovery and development is not limited to the initial identification of the small molecule or biological for evaluation in humans. Research to identify and answer key questions unique to the molecule/biology is an important contribution to the success of the agent in the clinic. Lack of success of early VEGFR inhibitors may be associated with poor drug-like properties, suboptimal PK, dosing schedule, off-target activities, etc. However, in most cases, we do not fully understand the failures of these earlier studies because key experimental data is not available. Sustained target inhibition has been associated with clinical benefit with a number of signaling inhibitors, whereas acute- or short-term inhibition has been the primary driver for cytotoxics and pro-apoptotic agents. Our article focused on the relationship between circulating drug concentrations and inhibition of primary target (VEGFR2), as well as functional effect on angiogenesis and tumor growth using mouse models. Understanding how long and how much target inhibition is required for biological effect was critical in selecting a molecule with appropriate PK properties and to choose an appropriate dosing schedule.

In summary, the endpoints of PK-PD analysis conducted with preclinical models differed from the clinical endpoints. However, the concordance of the plasma pazopanib concentrations required for biologic effects in animals and humans provided confidence that the relationships were robust. The relationships between markers of VEGFR2 inhibition and pazopanib pharmacokinetics observed in preclinical models informed the analysis conducted with clinical data and supported efficient dose selection for pivotal clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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