Letter to the Editor

Molecular Cancer Therapeutics

Sorafenib Inhibits ABCG2 and Overcomes Irinotecan Resistance—Letter

Malcolm A. Smith

Mazard and colleagues present results providing evidence that sorafenib favors irinotecan intracellular accumulation and enhances irinotecan toxicity via inhibition of the drug-efflux pump ABCG2 (1). They conclude that sorafenib is a promising option for the treatment of irinotecan-resistant colorectal cancer and that continued investigation of the clinical effects of the sorafenib–irinotecan combination in colorectal cancer is warranted.

The authors test sorafenib *in vitro* using 10% serum conditions, but do not take into account that sorafenib is highly protein bound (99.7%) such that sorafenib concentrations that are effective in 10% FBS are ineffective in plasma conditions (2). For example, FLT3-ITD–driven cell lines have an IC_{50} of 3 nmol/L to sorafenib in 10% serum but require greater than 100-fold higher sorafenib concentrations (approximately 500 nmol/L) in plasma for a comparable level of inhibition (3). The *in vitro* cytotoxicity testing performed by Mazard and colleagues using 10% serum conditions focused on sorafenib concentrations in the 0.5 to 2.0 μmol/L range, whereas the irinotecan intracellular concentration assays used sorafenib concentrations of 50 μmol/L. Sorafenib effects observed *in vitro* in 10% serum at 0.5 to 50 μmol/L concentrations lack plausibility for successful clinical translation, as sorafenib achieves drug levels in humans that are only in the 10 μmol/L range.

The authors do perform *in vivo* testing studies and document significantly longer time to event for the combination of sorafenib and irinotecan compared with either agent alone. However, these results are consistent with an additive effect of the single-agent activities of each agent and do not require a drug interaction to explain the greater time to event for the combination. Had the results actually shown evidence of a supra-additive effect, then the authors would have needed pharmacokinetic data to rule out the trivial explanation of sorafenib increasing systemic exposure to irinotecan.

Continued publication of articles that make claims for clinical prioritization based on *in vitro* testing results utilizing clinically irrelevant concentrations of sorafenib and other anticancer agents does not contribute to the cancer research enterprise. It encourages clinical investigation of lines of research that are almost certain to end in failure, and it directs time and effort and patients away from lines of research that are more likely to lead to improved treatments for patients with cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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