A Pharmacodynamic Study of the P-glycoprotein Antagonist CBT-1® in Combination With Paclitaxel in Solid Tumors

RONAN J. KELLY,* ROBERT W. ROBY,* CLARA C. CHEN,* DEBORAH DRAPER,* VICTORIA LUCHENKO,* DARYL BARNETT,* ROBERT K. OLDHAM,* ZINNAH CALUAG,* A. ROBIN FRYE,* SETH M. STEINBERG,* TITO FOJO,* SUSAN E. BATES*

*Medical Oncology Branch and †Biostatistics and Data Management Section, Center for Cancer Research, and ‡Departments of Nuclear Medicine and Radiology, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, USA; CBA Research, Lexington, Kentucky, USA

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Abstract

Background: This pharmacodynamic trial evaluated the effect of CBT-1® on efflux by the ATP binding cassette (ABC) multidrug transporter P-glycoprotein (Pgp/MDR1/ABCB1) in normal human cells and tissues. CBT-1® is an orally administered bisbenzylisoquinoline Pgp inhibitor being evaluated clinically. Laboratory studies showed potent and durable inhibition of Pgp, and in phase I studies CBT-1® did not alter the pharmacokinetics of paclitaxel or doxorubicin.

Methods: CBT-1® was dosed at 500 mg/m² for 7 days; a 3-hour infusion of paclitaxel at 135 mg/m² was administered on day 6. Peripheral blood mononuclear cells (PBMCs) were obtained prior to CBT-1® administration and on day 6 prior to the paclitaxel infusion. 99mTc-sestamibi imaging was performed on the same schedule. The area under the concentration–time curve from 0–3 hours (AUC0–3) was determined for 99mTc-sestamibi. The same schedule. The area under the concentration–time curve from 0–3 hours (AUC0–3) was determined for 99mTc-sestamibi. Lung uptake was not changed.

Results: Twelve patients were planned and enrolled. Toxicities were minimal and related to paclitaxel (grade 3 or 4 neutropenia in 18% of cycles). Rhodamine efflux from CD56+ PBMCs was a statistically significant 51%–100% lower (p < .0001) with CBT-1®. Among 10 patients who completed imaging, the 99mTc-sestamibi AUC0–3 for liver (normalized to the AUC0–3 of the heart) increased from 34.7% to 100.8% (median, 71.9%; p < .0001) after CBT-1® administration. Lung uptake was not changed.

Conclusion: CBT-1® is able to inhibit Pgp-mediated efflux from PBMCs and normal liver to a degree observed with Pgp inhibitors studied in earlier clinical trials. Combined with its ease of administration and lack of toxicity, the data showing inhibition of normal tissue Pgp support further studies with CBT-1® to evaluate its ability to modulate drug uptake in tumor tissue.

Discussion: Although overexpression of ABCB1 and other ABC transporters has been linked with poor outcome following chemotherapy efforts to negate that through pharmacologic inhibition have generally failed. This is thought to be a result of several factors, including (a) failure to select patients with tumors in which ABCB1 is a dominant resistance mechanism; (b) inhibitors that were not potent, or that impaired drug clearance; and (c) the existence of other mechanisms of drug resistance, including other ABC transporters. Although results in this animal model support a new look at Pgp as a target, in this era of “targeted therapies,” trials designed that directly assess modulation of drug uptake, including quantitative nuclear imaging, should be pursued before clinical efficacy assessments are undertaken. Such assessment should be performed with compounds that inhibit tissue Pgp without altering the pharmacokinetics of chemotherapeutic agents. This pharmacodynamic study demonstrated that CBT-1®, inhibits Pgp-mediated efflux from PBMCs and normal liver.

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Correspondence: Susan E. Bates, M.D., 9000 Rockville Pike, Building 10 Room 12N226, Bethesda, Maryland 20892, USA. Telephone: 301-402-1357; Fax: 301-402-1608; e-mail: sebates@helix.nih.gov; first published online in The Oncologist Express on March 16, 2012. http://dx.doi.org/10.1634/theoncologist.2012-0080