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15-0600-Dr. Fox's response to letter to the editor

Elizabeth Fox and Frank M. Balis

The Children's Hospital of Philadelphia, The Perelman School of Medicine at The University of Pennsylvania, CTRB 4016, 3501 Civic Center Blvd, Philadelphia, PA 19104, USA

We appreciate the comments to the Editor submitted by Dr. Srinivas regarding our recently published clinical trial.¹

The primary objective of the clinical trial was to determine the recommended dose, safety and tolerability of the P-glycoprotein inhibitor, tariquidar in combination with docetaxel, doxorubicin, or vinorelbine in children and adolescents with recurrent solid tumors. The primary endpoint was toxicity of a single dose of tariquidar administered up to 48 hours prior to the administration of tariquidar in combination with cytotoxic chemotherapy. No dose limiting toxicity of single agent tariquidar was observed. The design and schedule of drug administration permitted secondary objectives including evaluating the impact of tariquidar on the pharmacokinetics of cytotoxic agents, and pharmacodynamics studies including Pgp functional assays in peripheral blood mononuclear cells and in tissue and tumor using functional imaging. The study was not powered to make statistically valid comparisons. However, the correlative studies generated important preliminary data. Dr. Srinivas frames the issues as the interplay between Pgp inhibitor and the cytotoxic drugs and the distribution pattern of tariquidar to augment Pgp-mediated drug efflux from tumor. Our ability to fully assess these issues was impacted, in part, by technical considerations and necessary ethical constraints when performing research in children.

To assess pharmacokinetic interactions, detailed plasma sampling was performed and non-compartmental pharmacokinetics of total docetaxel, doxorubicin and its primary active metabolite doxorubicinol, and vinorelbine were reported. Each child had sampling for tariquidar alone and repeat sampling after tariquidar was administered in combination with the cytotoxic agent. The clearance of tariquidar overall was similar to adults and did not differ on day 1 (alone) compared to day 3 (with cytotoxic agent). Clearance of the cytotoxic agents was highly variable. The coefficient of variation for clearance of each cytotoxic agent was 40–50%. Ideally to compare the impact of tariquidar on the disposition of cytotoxic agents, the PK of the cytotoxic agent would have been studied with and without tariquidar. This could not be done because the blood volume required exceeded permissible standards in children and the schedules of docetaxel and doxorubicin administration (every 3 weeks) made this impractical in a study where the more than half of the participants received a single cycle of protocol therapy. Thus, we made a comparison of drug clearance to previously published data for the three anticancer drugs in children. We did not control for sampling strategy or analytical method. Therefore, cautious interpretation of the data is warranted. Dose limiting toxicity related to cytotoxic agents was minimal, 0/6 for docetaxel, (75 mg/m²), 1/6 for doxorubicin (50 mg/m²) and 0/6 for vinorelbine (20 mg/m² day 1 and 8), indicating that any decrease in clearance did not result in clinically significant toxicity.

The tariquidar IC_{50} for CYP3A4 is greater than 100 μM .² The maximum plasma concentration of tariquidar achieved in children and adolescents was less than 3 μM , therefore, alteration in CYP3A4 metabolism of cytotoxic agents is unlikely.

Regarding tissue distribution of tariquidar, we measured the impact of inhibition of Pgp on tissue uptake of surrogate markers rhodamine and sestamibi. We did not measure the tissue distribution of tariquidar. However, the volume of distribution of tariquidar in humans is large (approximately 7 L/kg) indicating extensive tissue distribution. Considering mass balance, it is unlikely that inhibition of Pgp mediated drug efflux of cytotoxic drug from a tumor weighing grams would result in a measurable or significant decrease in systemic exposure of the cytotoxic agent.

Differential distribution of Pgp efflux pump on tissue or tissue specific differences in Pgp inhibitor binding could impact the intratumoral concentration of the cytotoxic agent. For example, others have demonstrated that the half maximal effect concentration for functional inhibition of Pgp at the human blood brain barrier is 20 fold higher than in peripheral blood mononuclear cells.³ In our study, we were unable to find a correlation between objective tumor response and Pgp expression in archival tumors using immunohistochemistry (IHC). This could be attributed to selection of antibody for IHC staining, use of archival tissue or other factors. To date, paired tumor biopsies pre- and post therapy have not been obtained in children on research studies. In our study, no participant had a biopsy to obtain tissue for research purposes. Of 29 children enrolled, 13 (45%) had archival tumor tissue at diagnosis and relapse submitted for IHC. Therefore, we cannot adequately assess the frequency of the acquisition of Pgp expression at relapse or the impact or extent of inhibition by tariquidar in our patients.

We are encouraged by the enthusiasm for additional studies of Pgp inhibitors in oncology and neurosciences. To the query “what is missing?” we reply: a multidisciplinary approach to understanding the complexities, mechanisms, and interaction of Pgp inhibitors and anticancer therapy. Overcoming acquired and innate resistance and improving central nervous system penetration of drugs including cytotoxic and molecularly targeted anticancer agents is critical to improving outcome for our patients.

- Elizabeth Fox & Frank M. Balis

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