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Randomized Study of Paclitaxel and Tamoxifen Deposition into Human Brain Tumors: Implications for the Treatment of Metastatic Brain Tumors

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Purpose: Drug resistance in brain tumors is partially mediated by the blood-brain barrier of which a key component is P-glycoprotein, which is highly expressed in cerebral capillaries. Tamoxifen is a nontoxic inhibitor of P-glycoprotein. This trial assessed, in primary and metastatic brain tumors, the differential deposition of paclitaxel and whether tamoxifen could increase paclitaxel deposition.

Experimental Design: Patients for surgical resection of their primary or metastatic brain tumors were prospectively randomized to prior paclitaxel alone (175 mg/m²/i.v.) or tamoxifen for 5 days followed by paclitaxel. Central and peripheral tumor, surrounding normal brain and plasma, were analyzed for paclitaxel and tamoxifen.

Results: Twenty-seven patients completed the study. Based on a multivariate linear regression model, no significant differences in paclitaxel concentrations between the two study arms were found after adjusting for treatment group (tamoxifen versus control). However, in analysis for tumor type, metastatic brain tumors had higher paclitaxel concentrations in the tumor center (1.93-fold, $P = 0.10$) and in the tumor periphery (2.46-fold, $P = 0.039$) compared with primary brain tumors. Pharmacokinetic analyses showed comparable paclitaxel areas under the serum concentration between treatment arms.

Conclusions: Paclitaxel deposition was not increased with this tamoxifen schedule as the low plasma concentrations were likely secondary to concurrent use of P-450-inducing medications. However, the statistically higher paclitaxel deposition in the periphery of metastatic brain tumors provides functional evidence corroborating reports of decreased P-glycoprotein expression in metastatic versus primary brain tumors. This suggests that metastatic brain tumors may respond to paclitaxel if it has proven clinical efficacy for the primary tumor's histopathology.