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

Robert L. Fine,1 Johnson Chen,1 Casilda Balmaceda,2 Jeffrey N. Bruce,3 May Huang,4 Manisha Desai,5 Michael B. Sisti,3 Guy M. McKhann,3 Robert R. Goodman,3 Joseph S. Bertino, Jr.,6 Anne N. Nafziger,6 and Michael R. Fetell2

Abstract

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.

There are ~ 150,000 cases per year of metastatic brain tumors (MBT) in the United States. Yet, there is no established consensus for their treatment with chemotherapy. The majority of natural product chemotherapy (NPC) agents do not substantially cross the intact blood-brain barrier (BBB), contributing to resistance to these agents (1). Approximately half of all chemotherapy drugs are NPC agents; yet, only CPT-11 and topotecan have modest clinical efficacy for primary brain tumors (PBT). NPC agents may have more use if their accumulation into brain tumors could be increased. A major constituent of the BBB that blocks traversement of NPC is P-glycoprotein, which is highly expressed at the apical surface of cerebral capillaries (2–4). P-glycoprotein pumps NPC across the BBB back into the vascular lumen and is also responsible for the multidrug resistance (MDR) phenotype. Thus, inhibition of P-glycoprotein may improve deposition of NPC agents, such as paclitaxel, in brain tumors.

Inhibition of the MDR phenotype by tamoxifen has been reported in various human cancer lines (5–7). Our group showed that incubation of 6 μmol/L tamoxifen or its major metabolite, N-desmethyltamoxifen (N-DESTAM), increased intracellular vinblastine 5-fold in human cancer lines (7). We found that [3H]tamoxifen aziridine bound to P-glycoprotein and was competitively inhibited by cold tamoxifen, N-DESTAM, and NPC drugs, but not by antimetabolites (8). Our group showed that tamoxifen or N-DESTAM induced potent stimulation of P-glycoprotein ATPase function in Sf9 cells stably...
transfected with the human MDRI gene (9). Callaghan and Higgins also showed that tamoxifen inhibited vinblastine transport by direct binding to P-glycoprotein (10).

The development of P-glycoprotein inhibitors has been limited by toxicities from concentrations required to modulate P-glycoprotein activity and from alterations in the pharmacokinetics of the NPC agents. Our phase I trial (11) of high-dose limited by toxicities from concentrations required to modulate transport by direct binding to P-glycoprotein (10).

Higgins also showed that tamoxifen inhibited vinblastine. Paclitaxel was given 2 hours following the last dose of tamoxifen in intact BBB may account in part for paclitaxel's poor efficacy. Adequate paclitaxel deposition in a glioma with a partially tissue have been shown (15). Thus, the failure to achieve inhuman PBT samples and undetectable levels in normal brain humangliomalines (12–14), low concentrations of paclitaxel cells without other drug resistance mechanisms commonly found in cancer cells.

Although paclitaxel has shown potent in vitro activity in human glioma lines (12–14), low concentrations of paclitaxel in human PBT samples and undetectable levels in normal brain tissue have been shown (15). Thus, the failure to achieve adequate paclitaxel deposition in a glioma with a partially intact BBB may account in part for paclitaxel's poor efficacy for PBT (16, 17).

Materials and Methods

The Institutional Review Board at Columbia approved this protocol, and written consent was obtained from all patients following Health Insurance Portability and Accountability Act guidelines.

Patients. Patients, ages 18 to 80, between 1998 and 2004 were eligible if they had a histologically documented PBT, which was completed. Patients ages 18 to 80, between 1998 and 2004 were eligible if they had a histologically documented PBT, which was completed.

Randomization. The randomization was into either a paclitaxel or a tamoxifen + paclitaxel arm and was not stratified for PBT or MBT.

Treatment plan. Patients received either paclitaxel (175 mg/m²/ i.v. over 3 hours) or tamoxifen (160 mg/m² bid p.o. on days 1-5) followed by paclitaxel over 3 hours (175 mg/m²/i.v.) on day 5. Paclitaxel was given 2 hours following the last dose of tamoxifen in the tumor or any other tissue. Paclitaxel concentrations were determined by the laboratory and were adjusted for potential confounders and for control of any imbalances in patient characteristics that occurred by chance despite randomization. A confounder was defined as a variable associated with both the study arm and the outcome.

Results

Patient characteristics. Figure 1 shows the trial profile. Of the 29 patients enrolled to the trial, 27 were assessable. Patient characteristics are listed in Table 2. Only one of the nine MBT patients was randomized to tamoxifen + paclitaxel, and the remaining eight patients received paclitaxel alone. This distribution of MBT patients resulted from using a simple randomization algorithm without stratifying for tumor origin. All the PBT and none of the MBT patients had prior brain surgery. Thus, 92% of patients in the tamoxifen + paclitaxel group had prior surgery compared with 47% of patients in the paclitaxel group. Most patients had received prior brain radiation therapy (87% and 91% for the paclitaxel and the tamoxifen + paclitaxel groups, respectively). However, more...
PBT patients received prior brain radiation than MBT patients (94% versus 56%, respectively; data not shown).

The most commonly represented histology was glioblastoma multiforme: five patients in the paclitaxel arm and seven in the tamoxifen + paclitaxel arm. Other PBT types included anaplastic astrocytoma, anaplastic oligodendroglioma, and primitive neuroectodermal tumor. In the paclitaxel arm, MBT included: non–small cell lung (NSCLC), melanoma, and small cell lung (SCLC). One patient in the tamoxifen + paclitaxel arm had metastatic renal cell.

Toxicity of paclitaxel and tamoxifen. The single dose of paclitaxel resulted in no toxicities above grade 2. For tamoxifen, grade 1 to 2 cerebellar ataxia occurred in 33%, which spontaneously resolved, and one patient had grade 2 thrombocytopenia while on tamoxifen alone.

Effect of paclitaxel and tamoxifen. The single dose of paclitaxel resulted in no toxicities above grade 2. For tamoxifen, grade 1 to 2 cerebellar ataxia occurred in 33%, which spontaneously resolved, and one patient had grade 2 thrombocytopenia while on tamoxifen alone.

Effect of tamoxifen on tissue concentrations of paclitaxel. Median paclitaxel deposition in all PBT and MBT patients irrespective of study arms is presented in Fig. 2. Although no significant differences were observed between the two study arms, marginal differences in concentrations were seen between the two tumor types after adjusting for study arm in the tumor center and periphery, where it was significant (P = 0.10; Table 4). Figures 3 and 4 graphically depicts these differences with box plots for each treatment group. The horizontal line that lies within the box indicates the median paclitaxel concentration for each tumor type. Note that for the MBT group in the tamoxifen + paclitaxel arm, there is only a horizontal line and no box because there was only one patient in this group.

Median tamoxifen concentrations in PBT and plasma. Among the PBT patients, there was no significant difference in median tissue concentrations of tamoxifen in the center and periphery of tumor and normal surrounding brain (Table 5). Peak plasma concentrations of tamoxifen ranged from 0.130 to 2.34 μmol/L, with a median of 0.54 μmol/L (Table 5).

<table>
<thead>
<tr>
<th>Table 2. Patient characteristics by study arm</th>
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<tbody>
<tr>
<td>Study arm</td>
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<tr>
<td>Tumor type</td>
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<tr>
<td>Primary brain tumors</td>
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<tr>
<td>Metastatic brain tumors</td>
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<tr>
<td>Mean age, y (SD)</td>
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<td>Age range, y</td>
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<tr>
<td>BSA in m² (SD)</td>
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<tr>
<td>Female (%)</td>
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<tr>
<td>Concurrent medications</td>
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<tr>
<td>CYP3A-inducing anticonvulsant</td>
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<tr>
<td>Daily dexamethasone</td>
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<tr>
<td>Prior therapy</td>
</tr>
<tr>
<td>Brain surgery</td>
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<tr>
<td>Brain radiation therapy</td>
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<tr>
<td>Any chemotherapy</td>
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<tr>
<td>Tamoxifen</td>
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<td>Abbreviation: AUC, area under the curve.</td>
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<tr>
<th>Table 3. Median tissue levels (interquartile range) by tumor type and by treatment group</th>
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<tr>
<td>By tumor type</td>
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<tr>
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</tr>
<tr>
<td>Tumor center (ng/g)</td>
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<tr>
<td>Tumor periphery (ng/g)</td>
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<tr>
<td>Normal surrounding brain (ng/g)</td>
</tr>
<tr>
<td>Paclitaxel plasma AUC (ng/mL h)</td>
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<tr>
<td>Abbreviation: AUC, area under the curve.</td>
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Table 4. Variable estimates from regression analysis representing differences in paclitaxel levels on log scale between study arms and tumor types together with the corresponding change fold and $P$

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Tumor center</th>
<th>Tumor periphery</th>
<th>Normal surrounding brain</th>
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<tbody>
<tr>
<td></td>
<td>Estimate (SE)*</td>
<td>$x$ Fold difference</td>
<td>$P$</td>
</tr>
<tr>
<td>Study arm (tamoxifen + paclitaxel vs paclitaxel alone)</td>
<td>–0.59 (0.37)</td>
<td>0.55</td>
<td>0.120</td>
</tr>
<tr>
<td>Tumor type (metastatic vs primary)</td>
<td>0.66 (0.39)</td>
<td>1.93</td>
<td>0.100</td>
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</table>

*Estimates are average differences in log (ng/g) concentration between groups. The SE of the estimate is provided in parentheses. Each estimate is adjusted for the other predictor.

$^1x$ fold difference is the ratio of concentration on the raw scale of one group vs the other.

Pharmacokinetic analyses. Median plasma paclitaxel area under the serum concentration over 0 to 24 hours for the tamoxifen + paclitaxel group was not significantly higher than the paclitaxel group ($P = 0.596$; Table 6). A multivariate regression model found no significant differences in plasma paclitaxel concentrations between study arms after adjusting for tumor type ($P = 0.596$) or for study arm ($P = 0.777$). Thus, tamoxifen did not affect the pharmacokinetics of paclitaxel.

Discussion

Despite the randomization process, there were inequities between the two treatment arms. In particular, 11 of 12 patients in the tamoxifen + paclitaxel group had a PBT, whereas the paclitaxel group had comparable proportions of MBT and PBT patients (53% versus 47%, respectively). To compensate for this imbalance, a multiple linear regression model was used to adjust the estimated study arm effect for tumor type. No statistically significant increase in paclitaxel accumulation in the tumor center, periphery, or surrounding normal brain tissue was found between patients who did or did not receive tamoxifen after adjusting for tumor type. Of note, the peak plasma tamoxifen concentrations ranged from 0.13 to 2.34 μmol/L, which is lower than that reported by us (6–8 μmol/L) to increase the cytotoxicity of doxorubicin in a P-glycoprotein–expressing hepatocellular carcinoma cell line and in hepatocellular carcinoma patients (20, 21).

The tamoxifen dosing regimen was based upon our phase I trial by Trump et al. (11) that determined the maximum tolerated dose of tamoxifen, when used in combination with vinblastine. The tamoxifen maximum tolerated dose regimen consisted of 13 days of tamoxifen, whereas the present study used only 5 days because of medical necessity (11). This 13-day schedule produced mean plasma concentrations of tamoxifen and N-DESTAM of ~4 and 6 μmol/L, respectively (11). N-DESTAM has similar activity, at equimolar concentrations, to tamoxifen for inhibiting P-glycoprotein in MDR cell lines (7, 11, 20) and attains plasma concentrations equal or higher than tamoxifen. Although plasma N-DESTAM concentrations were not measured, the combined total peak plasma tamoxifen and N-DESTAM concentration likely ranged from 0.26 to 4.68 μmol/L. The lower peak plasma tamoxifen concentrations in this study relative to those in Trump et al. may thus reflect, in part, lower doses of tamoxifen used in the current study (1,600 versus 4,000 mg/m$^2$ total; ref. 11).

Another factor for the lower concentrations of tamoxifen, as well as for paclitaxel, observed in the current study may be the concurrent use of CYP-inducing medications. The isoenzymes CYP2C8 and CYP3A are the major catabolic pathways for paclitaxel and tamoxifen. Patients on CYP2C8- and CYP3A-inducing anticonvulsants had paclitaxel concentrations in the tumor center that were approximately half that of patients who were not. Previous trials of paclitaxel in gliomas also found plasma paclitaxel concentrations and plasma areas under the serum concentration reduced by 50% in patients on CYP-inducing anticonvulsants (16, 22, 23). In the tamoxifen + paclitaxel arm, 83% of patients were on CYP2C8- or CYP3A-inducing anticonvulsants, and all were on dexamethasone, a known CYP3A inducer.

There was no significant difference in paclitaxel areas under the serum concentration from 0 to 24 hours between those who did or did not receive tamoxifen. This stands in contrast to other P-glycoprotein inhibitors, such as cyclosporine, valspodar (PSC 833) and biricodar (VX-710), which inhibited the CYP catabolism of NPC agents and required up to 50% dose reductions of NPC drugs (24–26). In addition, tamoxifen alone has reported anti-glioma activity (27, 28). The lack of altering the area under the serum concentration of paclitaxel, its anti-glioma properties, and the low toxicity profile suggest that tamoxifen may have advantages over other P-glycoprotein inhibitors; however, tamoxifen concentrations may not have
been high enough to affect the pharmacokinetics of paclitaxel. However, tamoxifen accumulates in tissue to concentrations >10-fold higher than plasma, as published by Lien et al. (29) and us (11). Thus, we cannot be sure of the actual BBB tamoxifen concentrations attained in our study.

The ability to discern tamoxifen’s effect on paclitaxel deposition is also affected by the patients’ treatment histories. Brain radiation disrupts the BBB (30–32) and reduces BBB-P-glycoprotein expression by 40% (33). Of PBT patients in this study, 94% had prior radiation compared with 56% in the MBT group. In spite of this, MBT versus PBT patients still had 2.46-fold higher median paclitaxel content in the growing tumor periphery. In addition, there was a statistical difference between tamoxifen + paclitaxel versus paclitaxel groups for prior surgery, which also disrupts the BBB; 92% versus 47% ($P = 0.04$), respectively, and 100% of the PBT group and 0% of the MBT group had prior surgery as stated in Patients. When assessing study arm differences, this disparity was taken into account by using a multiple linear regression model adjusting for tumor type. We were unable to clarify the effect of prior brain surgery between the tumor types as it occurred only in the PBT group. Thus, the increased paclitaxel concentrations in the center and periphery of MBT compared with PBT is probably underestimated by the current study because nearly twice as many PBT patients versus MBT patients had prior radiation, and all patients with PBT and zero MBT patients had prior surgery. Both of these prior therapies could have increased the paclitaxel deposition in the PBT group.

There is concordant data regarding the differential expression of P-glycoprotein in MBT and PBT tissues. Henson et al. (34) found low expression of P-glycoprotein by immunohistochemistry in PBT and MBT cells (2 of 22 of glioblastoma multiforme, 0 of 7 of MBT) but high expression in PBT-BBB vascular endothelial cells (17 of 22 or 77% of glioblastoma multiforme) and less in MBT (3 of 7 or 43%). Nabors et al. (35) similarly observed low immunohistochemistry P-glycoprotein staining in glioma cells (2 of 8) with high positive staining in glioma neovascularature in the same specimens (6 of 8). In normal brain specimens, 7 of 10 were positive for BBB-P-glycoprotein but none (0 of 10) in the brain parenchymal cells.

Töth et al. (36) found vascular endothelial cells from 25 of 29 of gliomas positive for P-glycoprotein (86%), whereas only 3 of 6 MBT were positive. Demeule et al. found that tumor and vasculature P-glycoprotein expression by Western blot in gliomas was similar to that in normal brain tissue, whereas P-glycoprotein levels in brain metastases from lung adenocarcinomas and melanoma were 40% and 5% of that in normal brain tissue, respectively (37). Furthermore, tumor and its neovascularure from concordant primary lung adenocarcinomas and its brain metastases had low and equal P-glycoprotein immunohistochemistry expression, suggesting the P-glycoprotein levels in MBT reflect P-glycoprotein expression in the tissue of origin (37). Together, findings suggest significantly decreased P-glycoprotein immunohistochemistry expression in MBT and its neovascularure compared with PBT (36, 37) and suggest that the BBB-MDR phenotype in PBT is mediated to a minor degree by tumor cells and predominantly at the level of tumor BBB vasculature. Conversely, MBT generally have low P-glycoprotein expression in their tumor cells and vasculature dependent upon histologic origin (34–37). Tumor tissue expression of P-glycoprotein was not directly analyzed in our study as it was prospectively designed as a pharmacologic trial, and sufficient tissue was unavailable after high-performance liquid chromatography analyses.

The significant differences in tissue concentrations of paclitaxel between PBT and MBT at the tumor periphery may also reflect differences in vasculature biology. In general,
PBT may be generalized to other agents within the NPC class.

Increased intratumoral deposition of paclitaxel in MBT versus varied degrees of affinity. Thus, it is conceivable that the P-glycoprotein will bind and efflux virtually all NPC with functional increase in paclitaxel deposition into MBT. Lower P-glycoprotein expression in MBT do translate into a that these previous immunohistochemistry studies showing differences in NPC deposition. Our study is the first to show BBB-P-glycoprotein expression between PBT and MBT but do not show whether this translates into actual pharmacologic differences in NPC deposition. Our study is the first to show that these previous immunohistochemistry studies showing lower P-glycoprotein expression in MBT do translate into a functional increase in paclitaxel deposition into MBT. P-glycoprotein will bind and efflux virtually all NPC with varied degrees of affinity. Thus, it is conceivable that the increased intratumoral deposition of paclitaxel in MBT versus PBT may be generalized to other agents within the NPC class.

In 26 untreated patients with MBT from NSCLC, a paclitaxel/cisplatin–based regimen without radiation, with either vinorelbine or gemcitabine, resulted in a 38% intracranial response rate (40). A similar study of vinorelbine, gemcitabine, and carboplatin without brain radiation for 20 untreated NSCLC-MBT patients produced a 45% intracranial response (41). These studies are notable because paclitaxel and vinorelbine are NPC substrates of P-glycoprotein. These results stand in contrast to the lack of clinical efficacy of paclitaxel for PBT even with increased doses of paclitaxel to compensate for its catalysis from anticonvulsant CYP inducers (16, 17). If BBB permeability is higher in MBT, then treatment of MBT with paclitaxel, as well as other NPC agents recommended for the specific histologic tumor, as opposed to using lipophilic alkylating agents [e.g., temozolomide, 1,3-bis(2-chloroethyl)-1-nitrosourea] for all patients, should be considered. In addition, many antimitabolites (i.e., 5-fluorouracil and gemcitabine) and some alkylators (i.e., cisplatin and carboplatin) partially cross the BBB and could be potential chemotherapies for MBT according to their efficacy for the specific histology.

Further illustration of this principle is supported by the literature on temozolomide, a lipophilic methylating agent that penetrates the BBB to 40% of its plasma concentration (42). In a phase II study of temozolomide for melanoma brain metastases, Agarwala et al. (43) found a 7% intracranial response with 29% stability rate among 117 untreated patients. However, temozolomide's activity in NSCLC with or without brain metastases varied from 0% to 10% (44–48). Temozolomide's modest efficacy in melanoma MBT and its low activity in NSCLC MBT correspond to its activity against the respective primary tumors and not to its ability to cross the BBB.

### Summary

Our ability to detect a tamoxifen effect on paclitaxel deposition in PBT was hampered by low concentrations of tamoxifen and paclitaxel secondary to CYP inducers. Further study of tamoxifen as a BBB-P-glycoprotein inhibitor should consider higher and longer dosage regimens of tamoxifen or use of an anticonvulsant that does not induce CYP, especially CYP3A (e.g., levetiracetam).

The major implication of this study is that, perhaps, the treatment of MBT by chemotherapy should not be defined by which agents best penetrate the BBB but by considering which NPC and non-NPC agents are most active for the metastatic neoplasm (i.e., paclitaxel for breast and NSCLC). Because there is concordance of P-glycoprotein expression in the vasculature of tumors and their brain metastases (36, 37), this concept may

### Table 5. Median tamoxifen tissue and plasma levels in primary brain tumor patients

<table>
<thead>
<tr>
<th>Median concentration (interquartile range)</th>
<th>Tumor center</th>
<th>Tumor periphery</th>
<th>Normal surrounding brain</th>
<th>Individual patient peak plasma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor center</td>
<td>4,297 ng/gm (2,485.5)</td>
<td>3,716 ng/gm (2,231.5)</td>
<td>3,823 ng/gm (4,596)</td>
<td>0.54 μmol/L (0.379)</td>
</tr>
</tbody>
</table>

*Individual peak plasma concentration range is 0.130 to 2.34 μmol/L.

### Table 6. Modeling of plasma paclitaxel AUC over 0 to 24 hours using study arm and tumor type as variables

<table>
<thead>
<tr>
<th>Median AUC 0 = 24 hrs (interquartile range; ng/mL h)</th>
<th>Study arm: paclitaxel alone vs tamoxifen + paclitaxel</th>
<th>Tumor type: primary vs metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel Alone (n = 10)</td>
<td>Estimate [log (ng/mL h)] P</td>
<td>Estimate [log (ng/mL h)] P</td>
</tr>
<tr>
<td>Tamoxifen + paclitaxel (n = 7)</td>
<td>3,262.5 (845.4)</td>
<td>4,933.7 (4,540.8)</td>
</tr>
<tr>
<td></td>
<td>0.202 0.596</td>
<td>−0.119 0.777</td>
</tr>
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</table>

*Individual patient peak plasma* 0.54

Abbreviation: AUC, area under the curve.
be relevant for tumors which commonly metastasize to the brain and have low intrinsic P-glycoprotein expression in its tumor cells and neovascularity, such as NSCLC, SCLC, melanoma, and NPC-sensitive breast cancers. The current treatment paradigm for MBT with chemotherapy is not well established. We believe this work forms the rationale for further investigation into the use of taxanes, such as paclitaxel, as well as other NPC agents for the treatment of MBT dependent upon their histologic origin and history of response to specific NPC agents.

Acknowledgments

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References

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