Predicting Chemotherapy Response to Paclitaxel with ^{18}F-Fluoropaclitaxel and PET

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Paclitaxel is used as a chemotherapy drug for the treatment of various malignancies, including breast, ovarian, and lung cancers. To evaluate the potential of a noninvasive prognostic tool for specifically predicting the resistance of tumors to paclitaxel therapy, we examined the tumoral uptake of ^{18}F-fluoropaclitaxel (^{18}F-FPAC) in mice bearing human breast cancer xenografts by using small-animal–dedicated PET and compared ^{18}F-FPAC uptake with the tumor response to paclitaxel treatment. **Methods:** PET data were acquired after tail vein injection of approximately 9 MBq of ^{18}F-FPAC in anesthetized nude mice bearing breast cancer xenografts. Tracer uptake in reconstructed images was quantified by region-of-interest analyses and compared with the tumor response, as measured by changes in tumor volume, after treatment with paclitaxel. **Results:** Mice with tumors that progressed demonstrated lower tumoral uptake of ^{18}F-FPAC than mice with tumors that did not progress or that regressed ($r = 0.55$, $P < 0.02$; $n = 19$), indicating that low ^{18}F-FPAC uptake was a significant predictor of chemoresistance. Conversely, high ^{18}F-FPAC uptake predicted tumor regression. This relationship was found for mice bearing xenografts from cell lines selected to be either sensitive or intrinsically resistant to paclitaxel in vitro. **Conclusion:** PET data acquired with ^{18}F-FPAC suggest that this tracer holds promise for the noninvasive quantification of its distribution in vivo in a straightforward manner. In combination with approaches for examining other aspects of resistance, such quantification could prove useful in helping to predict subsequent resistance to paclitaxel chemotherapy of breast cancer.

Key Words: breast cancer; paclitaxel; ^{18}F; PET; chemotherapy

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Resistance to chemotherapy is one of the most significant obstacles in improving the efficacy of cancer treatment. When treatment is ineffective, tumor cell proliferation continues and patients unnecessarily experience adverse effects of their chemotherapy regimens, delay in obtaining a potentially more effective regimen, and possibly diminished opportunity for ultimately achieving durable remission with therapy that might have had greater efficacy. Conventional methods of assessing the response to therapy, such as physical examination, mammography, ultrasound, or serial CT scans, depend on physical characteristics of tumors and are often slow to detect changes after chemotherapy (*1*). It may take several weeks to months to evaluate the efficacy of the treatment. Unfortunately, it is difficult to reliably predict whether paclitaxel (or most other chemotherapy agents) will be effective for a particular patient with cancer in advance of treatment, although some recent progress has been made in this regard (*2*). More accurate predictors of the response to chemotherapy in patients with cancer would clearly be valuable for guiding optimal clinical management.

Paclitaxel is currently one of the most commonly prescribed chemotherapy drugs for ovarian, breast, and lung cancers. It is a naturally occurring compound with antitumor activity that inhibits cellular proliferation through the stabilization of tubulin during cellular replication (*3*). As with many chemotherapy agents, resistance to paclitaxel remains a significant problem in the treatment of patients with cancer. Chemotherapeutic failure may be related to initial resistance intrinsic to the tumor cells, to resistance acquired by tumors during treatment, or to physiologic factors extrinsic to tumors (e.g., individual variations and pharmacokinetic behaviors of drugs). Moreover, resistance may be heterogeneous, with respect to either different tumors in the same individual or even different cells in the same tumor. Although paclitaxel has demonstrated antitumor activity against several cancers, clinical drug resistance has been a major limitation to its ultimate efficacy. Some assays with biopsy specimens in vitro are able to identify tumor cells with intrinsic resistance to certain chemotherapy agents (*4–13*). However, these assays are not as successful in predicting the response of tumors in patients with cancer in vivo, because they recapitulate neither the microenvironment of the tumor nor the physiology of the host.

PET with tracers that are not chemotherapy specific, such as ^{18}F-FDG (*14–16*) and 3-deoxy-3-^{18}F-fluorothymidine,

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has been used for the assessment of the response to chemotherapy in patients with breast cancer (*17*). Such measures can help capture in an individual patient with cancer the impact of intertumor heterogeneity and physiologic resistance that would be missed by assays with biopsy specimens in vitro. Several studies have been aimed at the development of radiolabeled chemotherapy tracers to noninvasively study the uptake of chemotherapy agents in vivo, with various results. Li et al. and Inoue et al. studied the use of ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-paclitaxel as an imaging agent for mammary tumors but did not find a predictive value for this tracer (*18,19*). In humans, tracers such as 5-^{18}F-fluorouracil (5-^{18}F-FU) and the acridine derivative ^{11}C-*N*-2(dimethylamino)ethylacridine-4-carboxamide have been studied as potential PET tracers for predicting the response of colorectal cancer and acute myelogenous leukemia to treatment with fluorouracil and amsacrine, respectively (*20–23*).

Our previous work demonstrated that small-animal PET with the novel tracer ^{18}F-fluoropaclitaxel (^{18}F-FPAC) can be used to estimate the biodistribution of paclitaxel in mice bearing human breast cancer xenografts by use of straightforward quantitative measures readily transferable to the clinical setting (*24*). Similar observations have been made for non–tumor-bearing animal models (*25,26*). The present work explores the potential use of PET as a noninvasive tool for predicting the tumor response to paclitaxel treatment by use of such measures.

MATERIALS AND METHODS

Materials

Unless otherwise noted, all chemicals were purchased from Sigma-Aldrich or Fisher Scientific and were of the highest grade available. Human breast cancer–derived cell lines MCF-7 (American Type Culture Collection) and MCF-7/AdrR (courtesy of the John Wayne Cancer Institute) were propagated for use in RPMI medium supplemented with 10% fetal bovine serum, L-glutamine at 2 mmol/L, and 1% penicillin-streptomycin (Invitrogen). All cell lines were maintained in a humidified 37°C 5% CO_2 environment.

Radiosynthesis of ^{18}F-FPAC

The radiosynthesis of ^{18}F-FPAC was performed as described by Kiesewetter et al. (*25*) in 2 steps. The first step was nucleophilic aromatic substitution by ^{18}F-fluoride in pentamethylbenzyl trimethylammoniumbenzoate followed by hydrolysis with trifluoroacetic acid to form ^{18}F-fluorobenzoic acid. The second step was the treatment of ^{18}F-fluorobenzoic acid and 3′-debenzoylpaclitaxel with diethyl cyanophosphonate and triethylamine, resulting in amide formation to the desired ^{18}F-FPAC. Total synthesis time ranged between 90 and 120 min, with a radiochemical yield of approximately 10% and a purity of ≥97%. Specific activity ranged between 37×10^{10} and 111×10^{10} Bq/mmol.

Breast Cancer Xenografts in Nude Mice

All animal studies were performed under a protocol approved by the Chancellor's Animal Research Committee of UCLA. MCF-7 or MCF-7/AdrR (*26*) cells, which form xenografts in athymic mice, were injected subcutaneously at $\sim 3.0 \times 10^7$ cells per tumor in the shoulder region of 4- to 6-wk-old female athymic mice weighing 20–30 g (Charles River Laboratories). MCF-7 human breast cancer cells express estrogen and progesterone receptors, which facilitate tumor growth and are known to be sensitive to paclitaxel treatment. The MCF-7/AdrR cell line exhibits multidrug resistance, and this line was specifically selected for resistance to paclitaxel. Before cell injection, all mice were primed with 17β-estradiol (Innovative Research of America) applied subcutaneously (1.7 mg of estradiol per pellet) to promote tumor growth.

Small-Animal PET Imaging and Predictive Value of ^{18}F-FPAC

Mouse PET images were acquired as previously described (*24*). Briefly, a 100-μL solution containing approximately 9 MBq of ^{18}F-FPAC in 100% dimethyl sulfoxide was injected via the tail vein into female nude mice (CD-1 *nu/nu*) bearing MCF-7 strains of human breast cancer tumor xenografts. We performed a time course experiment to determine the uptake time providing the optimal tumor-to-background ratio. An uptake time of 30 min was chosen for ^{18}F-FPAC imaging purposes because we found very little change in the tumor-to-background ratio of uptake after this time point, although mice were assayed to 3 h. Mice were anesthetized by inhalation of 2% isoflurane, and 5-min scans were acquired after 30 min of uptake by use of a Concorde P4 microPET instrument (Concorde Microsystems Inc.) with the mouse in the prone position. The long axis of the mouse was set parallel to the plane of the detectors, and the mouse was positioned such that the posterior extent of the field of view excluded the tail. Immediately after ^{18}F-FPAC scans were obtained, mice were treated intraperitoneally with a single dose of paclitaxel formulated in dimethyl sulfoxide (Acros Organics USA; 40 mg/kg). Treatment efficacy was monitored until any of 3 end points was reached: a tumor size of greater than 1.5 cm, complete tumor regression, or death.

All microPET images were reconstructed by filtered backprojection with a matrix size of $128 \times 128 \times 63$, a slice thickness of 1.21 mm, and a voxel size of 0.174 mm^3 and were analyzed by a standard region-of-interest (ROI) method with AMIDE (UCLA-Pharmacology) software. All tumors were monitored by serial micrometer measurements at least once a week after PET was performed. Tumor sizes were estimated by an area measurement of length × width (mm^2); volumes were calculated as $(\sqrt{\text{area}})^3$. Because survival times were quite variable (range, 24–166 d), a change in tumor volume was reported in rate-of-change units, calculated as [$\log_{10}$(end-point volume) minus $\log_{10}$(initial volume)]/(days elapsed since treatment). Quantitative data were expressed as measured standardized uptake value (mSUV) units, defined as (tumor ROI cps per pixel)/(total body anterior to tail cps per pixel). Body uptake was determined by defining a 3-dimensional isocontour ROI around the entire body present within the field of view. Because a specific direction of the relationship between ^{18}F-FPAC uptake and the tumor response was hypothesized a priori, uptake data for responder and nonresponder groups were compared by use of unpaired 1-tailed Student *t* tests, and the significance of correlations was assessed by use of a 1-sample *t* test of the associated Pearson coefficients.

RESULTS

To assess the potential value of ^{18}F-FPAC for predicting chemotherapy resistance, the rate of change in tumor

volumes after treatment was compared with the magnitude of ^{18}F-FPAC uptake before treatment. In general, mice with tumors that progressed demonstrated lower tumoral uptake of ^{18}F-FPAC than mice with tumors that did not progress or that regressed ($r = 0.55$, $P < 0.02$; $n = 19$) (Fig. 1). Among mice bearing xenografts of the intrinsically paclitaxel-resistant cell line MCF-7/AdrR, 1 tumor unexpectedly regressed 89% after treatment with paclitaxel. Although this result was not predicted on the basis of the cell type from which the tumor had been derived, this outcome was predicted by the relatively high initial ^{18}F-FPAC uptake (mSUV, 1.0) that was observed (Fig. 2B). The remaining 3 mice bearing MCF-7/AdrR tumors that failed to regress had correspondingly lower ^{18}F-FPAC uptake (average tumor volume more than doubling, increasing by +129%; average mSUV, 0.16) (Fig. 2A). Thus, by several measures, low ^{18}F-FPAC uptake was a significant predictor of chemoresistance. This relationship was a fairly consistent one, demonstrable when data were pooled across 3 consecutive independent experiments with mice bearing MCF-7 or MCF-7 AdrR tumors. However, data points from 2 of the 19 mice, both bearing MCF-7 tumors, constituted outliers to this general relationship (Fig. 1, open circles), such that when they were removed from the linear regression analysis, the correlation was strengthened substantially ($r = 0.83$, $P < 0.001$; $n = 17$). Additional analyses examined the responses of tumors in the remaining 17 mice.

Because the effects of chemotherapy are dependent not only on transport into tumor cells and other possible mechanisms of resistance but also on the availability of the drug, specifically, hepatic modulation in the case of paclitaxel, we compared tracer accumulation in the liver with tumor uptake as well as the therapeutic response. There was no correlation between tumor uptake and liver uptake of ^{18}F-FPAC; there was a slight negative correlation between liver uptake of ^{18}F-FPAC and tumor progression ($P = 0.18$), indicating that higher liver uptake did not account for decreased tumor uptake and resistance to treatment with paclitaxel.

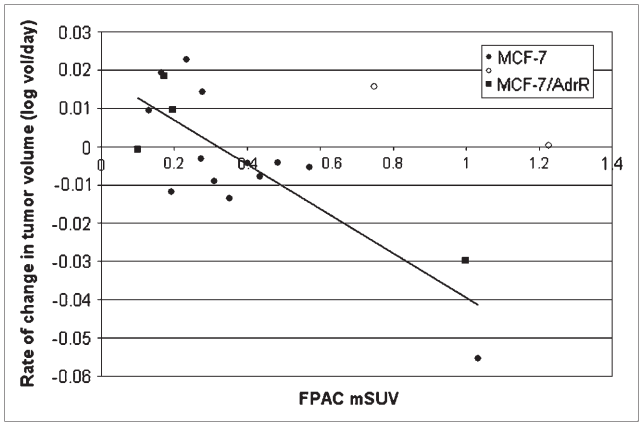

FIGURE 1. Comparison of microPET mSUVs of ^{18}F-FPAC and rate of change in tumor volume (see "Materials and Methods") in female athymic mice bearing MCF-7 tumors ($P < 0.02$; $n = 19$). ■=mice bearing MCF-7/AdrR tumors; ●=mice bearing MCF-7 tumors; ○=data points that were outliers for 2 of 19 mice bearing MCF-7 tumors.

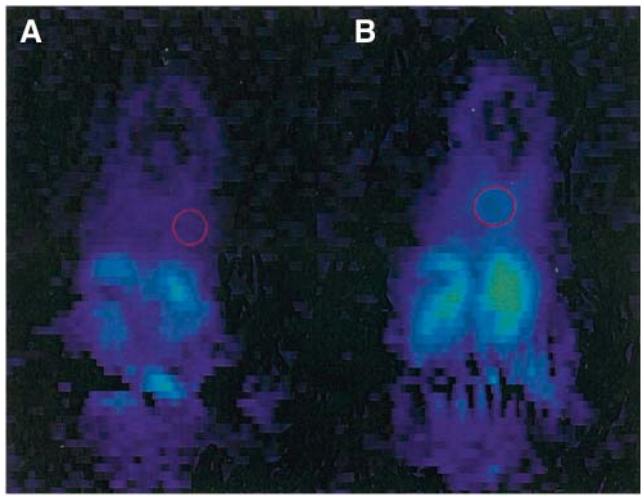

FIGURE 2. Whole-body microPET images of MCF-7/AdrR tumors subcutaneously injected in right shoulder. Images represent tomographic coronal slices of tumors (red circles) imaged after 30 min of uptake of ~9.25 MBq of ^{18}F-FPAC after tail vein injection. Animals were imaged prone so that left side of image corresponds to left side of animal. (A) Mouse bearing MCF-7/AdrR cells resistant to paclitaxel treatment (+103%) with low ^{18}F-FPAC uptake (mSUV, 0.19). (B) Mouse bearing MCF-7/AdrR cells responsive to paclitaxel treatment (−89%) with high ^{18}F-FPAC uptake (mSUV, 1.0).

With regard to examination of the potential predictive value of low ^{18}F-FPAC uptake for identifying chemoresistance in individuals before treatment, when tumors were stratified by mSUV, those with low ^{18}F-FPAC uptake demonstrated progression after treatment, whereas those with high ^{18}F-FPAC uptake tended to regress; the mean ± SD slope for $\log_{10}$(volume/d) for an ^{18}F-FPAC mSUV of less than 0.3 was $(9 \pm 4) \times 10^{-3}$, and the mean ± SD slope for $\log_{10}$(volume/d) for an ^{18}F-FPAC mSUV of greater than 0.3 was $(-20 \pm 6) \times 10^{-3}$ ($P < 0.005$) (Fig. 3). If chemoresistance was defined as any increase in tumor volume, then this pretreatment imaging criterion had an overall accuracy of 82% (14/17), a sensitivity of 100% (6/6), and a specificity of 73% (8/11) for identifying chemoresistant tumors. The data were also stratified into groups of tumors that at least doubled in volume and those that progressed less or regressed (Fig. 4). Tumors that doubled had a higher initial average ^{18}F-FPAC mSUV than those that did not; the ^{18}F-FPAC mSUV for tumors that more than doubled was 0.48 ± 0.1, and the ^{18}F-FPAC mSUV for tumors that did not was 0.22 ± 0.03 ($P < 0.025$).

DISCUSSION

Paclitaxel is a commonly prescribed therapeutic agent for patients with metastatic breast cancer and is also used in adjuvant therapy regimens. Several other structurally

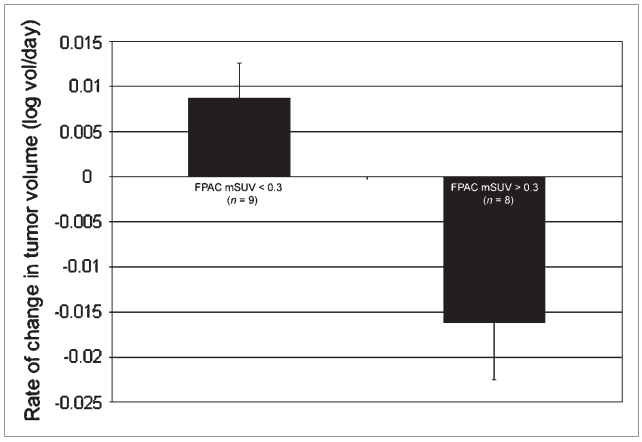

FIGURE 3. Comparison of average changes in tumor volumes after paclitaxel treatment in female athymic mice bearing MCF-7 and MCF-7/AdrR tumors stratified by ^{18}F-FPAC uptake ($P < 0.005$; $n = 17$).

diverse chemotherapy agents are used in the treatment of breast cancer. During the last 30 y, many clinical trials have established regimens that are effective for a fraction of the patients treated but to which a substantial minority of patients do not respond. Those patients are subjected to unnecessary toxicities and delay in receiving other regimens that might be more effective for certain patients with breast cancer.

Several studies have measured the efficacy of metabolic tracers as early indicators of the chemotherapy response in patients with breast carcinoma. ^{18}F-FDG PET has been the most widely studied tracer for monitoring treatment and has demonstrated utility in this regard (*27–32*). More recently, it was reported that the cellular proliferation biomarker 3-deoxy-3-^{18}F-fluorothymidine could serve as an accurate predictor of the chemotherapy response in patients with breast cancer and undergoing adjuvant therapy or treatment

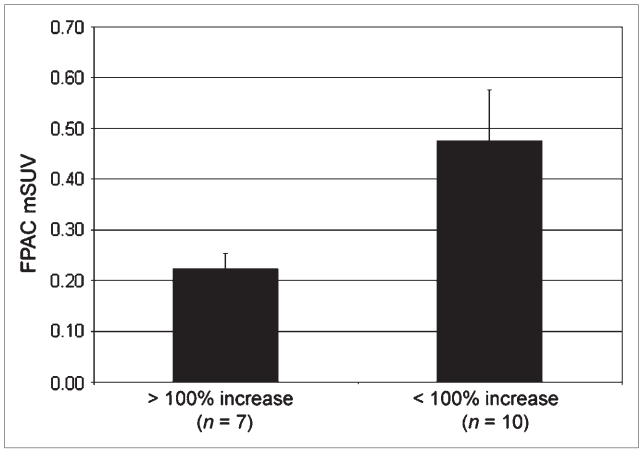

FIGURE 4. Comparison of ^{18}F-FPAC uptake in female athymic mice bearing tumors demonstrating greatest resistance to paclitaxel (at least doubling in volume after treatment) and less resistant or responsive tumors ($P < 0.025$; $n = 17$).

for metastatic breast cancer (*17*). Other tracers designed to assess the uptake of chemotherapy compounds have also been studied for their potential in predicting the therapeutic response in humans and animals in advance of the administration of the first pharmacologic dose of chemotherapy. Kesner et al. reported predictive value for the response of breast cancer xenografts by using the radiolabeled chemotherapeutic agents 5-^{18}F-FU and ^{18}F-fluorocyclophosphamide (*33,34*). Shani and Wolf studied the biodistribution of 5-^{18}F-FU in rodents; a direct relationship between the tumor response and tumor levels of 5-^{18}F-FU in different lines of tumors in mice and rats was found (*35*). Li and colleagues demonstrated a significant accumulation of ^{111}In-DTPA-paclitaxel in paclitaxel-sensitive tumors in mice by using γ-scintigraphy imaging and autoradiography (*18*). They did not identify a correlation between the response to paclitaxel treatment and the tumor uptake of the tracer, however (*19*); this inability to predict chemoresistance with ^{111}In-DTPA-paclitaxel may have been attributable to its water-soluble properties, contributing to a biodistribution different from that of the actual therapeutic drug paclitaxel, a highly hydrophobic compound. Instead of using the chelating agent DTPA to radiolabel paclitaxel, we used fluorinated paclitaxel, which was previously reported to have a biodistribution similar to that of its parent compound (*24–26*).

In the present study we explored the use of ^{18}F-FPAC as a tracer to predict the response to paclitaxel in breast cancer xenografts. Lower levels of paclitaxel uptake, as indexed by ^{18}F-FPAC mSUVs, tended to be associated with a higher risk for progression. This relationship appeared to be robust under experimental conditions, being maintained after pooling of data across multiple independent experiments involving 2 different cell lines with different previously identified levels of intrinsic chemoresistance.

CONCLUSION

The method used here for predicting chemotherapy resistance can account for physiologic resistance mechanisms, such as reduced drug penetration, or resistance attributable to multicellular interactions and the 3-dimensional shape of the tumor, which is difficult to recapitulate in vitro. It cannot account for all forms of resistance, however. With further validation in animal studies, it would be worthwhile to consider testing a clinical strategy in which intrinsic resistance is screened initially with in vitro methods, and then, for drug candidates to which tumors would appear to be intrinsically sensitive, the imaging-based tests described here could be used in vivo to assess physiologic resistance.

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