Cancer Therapy: Clinical

Tipifarnib Plus Tamoxifen in Tamoxifen-Resistant Metastatic Breast Cancer: A Negative Phase II and Screening of Potential Therapeutic Markers by Proteomic Analysis

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Abstract

Purpose: Tipifarnib, a farnesyltransferase inhibitor, has antitumor activity in heavily pretreated metastatic breast cancer patients. Preclinical data suggest that FTIs could restore tamoxifen responsiveness in tamoxifen-resistant disease. Thus, combining FTIs and tamoxifen may be a promising clinical approach after relapse or progression on tamoxifen.

Experimental Design: Postmenopausal patients with measurable estrogen receptor– and/or progesterone receptor–expressing metastatic breast cancers were enrolled. Only patients with disease progression on tamoxifen were eligible, but there was no limitation regarding prior chemotherapy or hormone therapy regimens. Patients were immediately treated with 300 mg (n = 12) or 200 mg (n = 10) tipifarnib twice daily for 21 of 28-day cycles plus tamoxifen once daily. Serum was collected at baseline and after 8 weeks of treatment to enable proteomic comparison and identify possible predictive response markers.

Results: Twenty patients were enrolled and evaluated for efficacy: one patient had an objective response (liver metastasis) and nine had stable disease after 6 months for a clinical benefit rate of 50%; median duration of benefit was 10.3 (range, 7.4-20.2) months. The proteomic analysis by SELDI-TOF and LTQ-FT-Orbitrap identified a known peptide of fibrinogen α, the intensity of which was significantly increased in patients with progression compared with patients who benefited from the combined treatment after 8 weeks.

Conclusions: Because the primary end point of efficacy (three objective responses) was not achieved, the study is negative. Nevertheless, the identified peptide could be of interest in discriminating, at 8 weeks of treatment, responders from nonresponders. Clin Cancer Res; 16(4); 1264–71. ©2010 AACR.

The use of antihormone therapies has improved the survival of women with breast carcinoma and causes minimal side effects. However, for patients with metastatic disease, resistance to treatment, especially to tamoxifen, eventually occurs. Multiple mechanisms have been identified to explain this resistance in preclinical and in clinical studies. A major mechanism is the alteration of the cross-talk between growth factor and estrogen (E2) signaling pathways. The activation of tyrosine kinase receptors has multiple consequences that may cause tamoxifen resistance. Ras and some Rho proteins are overexpressed in human tumors, including breast carcinoma, with possible correlations with clinical outcome. Major components of the growth factor receptor pathways are GTPase proteins, such as Ras or Rho, which require posttranslational prenylation with farnesyl or geranylgeranyl lipids. A farnesyltransferase catalyzes the covalent attachment of a farnesyl group to the carboxy-terminal cysteine of prenylated proteins in E2 actions, with contrasting effects; indeed, prenylation inhibitors on the one hand block E2-mediated proliferation and on the other hand stimulate the transcriptional activity of estrogen receptor (ER)α in MCF-7 cells.

Tipifarnib (Zarnestra, R115777) is an orally bioavailable, potent, selective farnesyltransferase inhibitor (FTI; ref. 9). It inhibits the growth of several human breast tumor cell lines in vitro and in xenografts. It has been recently published that tipifarnib significantly enhances the breast pathologic complete response rate associated with standard...
Translational Relevance

Farnesyl transferase inhibitors have been initially developed to block the development of the numerous human tumors presenting an activation of the Ras pathway. Nonetheless, these compounds also exhibit antiproliferative effects on wild-type ras tumors and especially in breast tumors. It seems that they clearly can lead to additive or synergistic effects with other cancer treatments and have to be considered to avoid the resistance to hormone therapies of breast cancers. At present, another major issue is to identify biological markers that may predict which subpopulations of patients may benefit from treatment.

Based on preclinical data, we conducted a phase II clinical trial with combined tipifarnib/tamoxifen as a rescue therapy for acquired tamoxifen resistance in metastatic breast cancers. In parallel, we performed a serum profiling. The trial was negative with only one objective response. Nonetheless, one of the secondary objectives of the study was met: the combination resulted in a clinical benefit rate of 50%. In addition, we identified a peptide of fibrinogen α peptide as a possible therapeutic response marker.

Patients and Methods

Study design

This phase II, single-arm, open-label, multicenter study was conducted through the Grand Sud Ouest (GSO) cancéropole in France (Toulouse, Bordeaux, and Limoges). The protocol was approved by the French Ethics Committee (Comité Consultatif de Protection des Personnes se Prêtant à des Recherches BioMédicales). Patients provided written informed consent.

Initial assessment of patients included a medical history, physical examination, biological tests, and imaging of disease sites with tumor measurements within 4 wk of starting therapy. During the first 2 mo, complete blood counts were done weekly. Patients were reassessed every 4 wk for adverse events, and a physical exam and metabolic panel was done. Tumor lesions were measured using the Response Evaluation Criteria in Solid Tumors (17) at baseline and every 8 wk thereafter. Adverse events were graded according to the WHO scale.

The primary end point was to determine the OR rate [complete response + partial response (PR)] produced by the tipifarnib/tamoxifen combination. Secondary end points included the estimation of CB [defined as the OR plus stable disease (SD) for at least 6 mo], median duration of benefit, median time to progression (time from enrollment until progression of disease or death due to disease progression), and determination of biological predictive factors of efficacy.

Patient population

Women with histologically proven, metastatic, or locally advanced inoperable breast cancer were eligible. Tumors were considered potentially hormone sensitive if they expressed ER and/or progesterone receptor in >10% of the primary tumor cells or at a metastatic site by immunohistochemistry. Tipifarnib was given to patients when progression, according to Response Evaluation Criteria in Solid Tumors criteria, was observed on tamoxifen treatment, given either as an adjuvant treatment or for advanced/metastatic disease. There was no limit on the number of prior chemotherapy regimens, with one line for two patients, two lines for one patient, and three lines for one patient. At least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors criteria was required at study entry. For patients who had only bone metastases, a detectable nonirradiated lytic lesion was required. Other eligibility criteria included age ≥18 y, performance status (WHO) of ≤2, adequate bone marrow (absolute neutrophil count of ≥2 × 10^9 cells/L, platelets of ≥100 × 10^9 cells/L, hemoglobin of ≥10 g/dL), and adequate hepatic (aspartate amino transferase and alanine amino transferase of ≤2.5 times the upper limit of normal or 5 times in cases of liver metastasis) and renal (serum creatinine of ≤1.5 times the upper limit of normal) function. Patients were excluded if they were pregnant, taking cytochrome P450–inducing drugs, presented with a sensory neuropathy ≥grade 1, a contraindication to antiestrogens, had life-threatening lesions (such as hepatic lesion of ≥1/3 of liver volume, pulmonary lymphangitis, uncontrolled cerebral metastases, and carcinomatous meningitis), or any other malignancy within the past 5 y.

Drug delivery and dose adjustments

Tipifarnib was taken immediately after a meal twice daily at 12-h intervals in 28-d cycles consisting of 21 d...
of treatment followed by a 7-d rest period. When the study was initiated, before publication of the results of the phase I studies (16) and according to Ortho-Biotech recommendation, preliminary data indicated that 300 mg tipifarnib twice daily (level 0) was a tolerable. However, during the study, it became clear that the maximum tolerated dose was 200 mg twice daily (level 1) in combination with tamoxifen. Thus, after inclusion of 12 patients, the protocol was amended to prescribe 200 mg tipifarnib twice daily. Tamoxifen (20 mg) was given once daily in the morning. In case of toxicity, tipifarnib dose adjustments were allowed by the protocol (Supplementary Table S1). Study treatment was continued until progression or unacceptable toxicity.

Statistical considerations
Patients in this study had progressed on tamoxifen therapy. The response rate of tipifarnib alone in hormone-resistant, advanced breast carcinoma is ~14% (12). To evaluate the benefit for the combination, the response rate should be greater than that of tipifarnib alone and should be at least equivalent to that of aromatase inhibitors after antiestrogen therapy (10-24%). As per Simon, the study had an optimal two-stage design with a significance level of 0.05, had a power of 0.80, and assumes a target response rate of 25% and a lowest level of interest of 10%. The study plan was to include 40 patients, with 22 patients in stage 1 with an interim analysis; if 3 or more OR were observed, an additional 18 patients would be enrolled in stage 2.

Pharmacokinetic assessment
A volume of 5 mL of blood was collected at baseline, before the first tipifarnib dose was administered (i.e., tamoxifen only), and on day 14, before tipifarnib was administered (i.e., tamoxifen and tipifarnib), and 1 h after tipifarnib administration (i.e., tipifarnib only).

Tipifarnib serum levels were measured with a validated liquid chromatography tandem mass spectrometry (MS) assay developed by Ortho-Biotech Oncology Research and Development (18). Serum levels of tamoxifen and its metabolites were measured by high performance liquid chromatography with fluorescence detection (19).

A Wilcoxon test was used to compare the paired data of initial versus final measurements.

Serum proteomic analysis
Protein profiling. A volume of 10 mL of blood was collected before the first tipifarnib dose, again at 8 wk (first disease evaluation of each patient), and at the time of OR or progression. Serum aliquots were frozen and stored at −80°C within 60 min of blood withdrawal. We followed best experimental design practices, specifically, uniform blood sample collection, processing, and freezing.

Samples were fractionated on an anion exchange fractionation kit according to the manufacturer’s instructions (Bio-Rad). A volume of 5 μL of each serum fraction was applied and incubated with a metal affinity ProteinChip array (IMAC30) loaded with copper sulfate and washed as described by the supplier (Bio-Rad). Then, 1 μL of sinalpinic acid solution (50% v/v) was applied twice to each spot as an energy-absorbing matrix. Arrays were read on a Protein Biological System IIC ProteinChip reader (SELDI-TOF, Bio-Rad) and the spectra were analyzed using the Ciphergen Express software.

Statistics and bioinformatics. Peaks were detected automatically and the clusters’ P values were calculated using the Mann-Whitney Test on the Ciphergen Express Cluster Wizard. Then, a more advanced statistical analysis was done using a Wilcoxon-Rank test.

Biomarker enrichment. Purification was done on an anion exchange column (Bio-Rad) followed by 10-then 3-kDa cutoff ultrafiltration columns (Millipore) and followed through the SELDI-TOF profiling.

Biomarker identification. The fraction containing the protein of interest was analyzed by nanoliquid chromatography tandem MS using an Ultimate3000 system (Dionex) coupled to an LTQ-Orbitrap mass spectrometer (Thermo Fisher Scientific) as previously described (20). The tandem MS data were searched against human sequences in the public database UniProt version 13.4, which consists of Swiss-Prot Protein Knowledgebase Release 55 and TrEMBL Protein Database Release 38.4 (72 400 entries), using the Mascot search engine (Mascot Daemon, version 2.2.0; Matrix Science). The search was done with no enzyme specificity; mass tolerances in MS and tandem MS was set to 10 ppm and 1 Da, respectively; and oxidation of methionines, histidines, tryptophans, and protein NH2-terminal acetylation was set as variable modifications. Protein identification was confirmed by the manual interpretation of corresponding tandem MS data. Protein mass was determined by raw data deconvolution using the integrated Xcalibur Extract software (Thermo Electron).

Results
Patient characteristics. From September 2003 to June 2005, 22 patients were enrolled. Patient and main tumor characteristics are reported in Table 1. The median age was 64 years, with 14 patients with a performance status of 0 and 8 patients with a performance status of 1. One patient had breast carcinoma with HER2 overexpression, 82% of patients had visceral metastases (liver and/or lung), and 17 (77%) and 2 patients (9%) had received tamoxifen or aromatase inhibitors, respectively, in the adjuvant setting. Two patients (9%) received aromatase inhibitors for metastatic disease. They all had disease progression while receiving tamoxifen in either the adjuvant (n = 11) or metastatic setting (n = 11), with median times of non-progression of 48 months (range, 16-60) and 18 months (range, 7-54), respectively. The overall median time of non-progression (n = 22) was 30.5 months (range, 9-60).

Moreover, 14 patients (64%) received chemotherapy as adjuvant treatment, one of whom received high-dose chemotherapy and stem cell transplantation, and 4 (18%) received chemotherapy for metastatic disease.
Safety profile. All patients were assessable for toxicity. At the 300 mg tipifarnib twice daily dose, 6 of 12 patients required dose reductions due to hematologic or nonhematologic toxicities (Table 2). Four patients had grade 3 or 4 neutropenia or thrombocytopenia, one had grade 3 mucositis, and two developed a venous thrombosis. Moreover, one patient experienced grade 3 sensitive and painful neurotoxicity requiring her removal from the study at 6 months. This patient had received neurotoxic agents in the adjuvant and metastatic settings, including vinorelbine, and had grade 1 neurotoxicity upon entry to the trial. She rapidly recovered to grade 1 neuropathy and could be treated with docetaxel after this study. The marker analysis at 8 weeks could therefore have been influenced by the dose reduction at 4 weeks for the first two patients and by the difference of dose (300 mg versus 200 mg twice daily) for all six of them.

The initial tipifarnib dose was decreased to 200 mg twice daily for the next 10 patients and was well tolerated, except for one case of venous thrombosis leading to the patient’s removal from the study after 6 months (with SD). The most common nonhematologic grade 1 toxicities were diarrhea, asthenia, and nausea. One patient presented with a cutaneous rash and was discontinued from the study after a few days. One patient developed an acute myeloblastic leukemia a few months after the end of treatment, with no apparent correlation with any previous treatment. No analysis of the results could include the toxicity because of the low number of events for each type of toxicity.

Efficacy results. From the 22 patients, those 2 with cutaneous rash or venous thrombosis at 4 months were excluded after a few days and at 4 months, respectively, because this toxicity appeared very early in the treatment. Moreover, at 4 months, the patient was considered neither as being in progression nor having an OR. Twenty patients were then assessed for efficacy (Table 3). At the end of the first step, only one patient (5%) had a partial response at 6 months in a liver metastasis, but she was discontinued from the trial because of neurotoxicity. Because the primary end point of at least three OR was not achieved at the end of the first step, the study was discontinued. The CB rate was 50% (n = 10) with a median duration of benefit of 10.3 months (range, 7.4-20.2). The median time of CB; months (range) 10.3 (7.4-20.2), PD at 6 mo or before 10 (50%), TTP median; mo (range) 5.7 (1.9-20.2).

Pharmacokinetic results. We observed an expected significant accumulation of tipifarnib in plasma 1 hour after administration on day 14. This showed the variation in tipifarnib concentration after repeated daily dosing (Table 4). The statistical analysis from 16 patient sera showed a significant but modest increase in the median tamoxifen concentration (from 108-124.5 nmol/L) after 14 days of tipifarnib treatment (P < 0.02). This suggested that the effect of tipifarnib on tamoxifen pharmacokinetics may be biased because of the small number of patients evaluated, or is not relevant.
because neither the tamoxifen metabolites (especially endoxifen; refs. 21, 22) nor the sum of tamoxifen and of its metabolites showed any significant difference.

The early identification of any therapeutic response biomarker would be very valuable as it is likely to be detected much earlier than clinical symptoms. Due to the very short half-life of tipifarnib (estimated 2.8 hours; ref. 16) and the twice daily administration, the steady-state concentrations are already reached at day 14. However, no statistically significant difference was found in tipifarnib or tamoxifen concentrations between the patients who progressed and those who achieved CB (data not shown).

Proteomic results. Detection of biomarkers was expected at either at the initiation of treatment or after 8 weeks. Sera from 19 patients were analyzed. Among several protein peaks, three had statistically significant differential expression (Supplementary Fig. S1). One of these was detected at baseline (before administration of tipifarnib) and two were detected after 8 weeks of treatment. In a multivariate Cox regression model taking into account the three proteins, only one was strongly and statistically significantly associated with clinical outcome (area under receiver operating characteristic, curve 0.88; 95% confidence interval, 0.70-1.00). The molecular mass of this protein was determined at \( \sim 5,900 \) Da. After 8 weeks of treatment, the immediate risk of progression at 6 months for patients whose p5900 intensity was higher than a threshold value of 0.84 (chosen as the value on the receiver operating characteristic curve closest to the upper left-hand corner of the graph) was 8.2-fold higher (95% confidence interval, 1.0-66.4; \( P < 0.05 \)) than the risk for patients whose p5900 intensity was <0.84.

Two profile examples are shown in patients who either benefited or progressed at 6 months (Fig. 1A). Finally, a Kaplan-Meier plot of the probability according to the expression of p5900 at 8 weeks is shown in Fig. 1B, clearly illustrating the significantly different immediate risk of progression after 8 weeks of treatment between the two populations.

To identify this proteomic signature, and after several enrichment protocols, the fraction was analyzed by the LTQ-Orbitrap MS (Supplementary Fig. S2). We identified the peptide with a high probability score as a COOH-terminal

Table 4. Tipifarnib (ng/mL) and tamoxifen or metabolites (nmol/L) sera concentrations (\( n = 16 \))

<table>
<thead>
<tr>
<th></th>
<th>Serum sample 1</th>
<th>Serum sample 2</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>Trough concentration before day 14 tipifarnib administration (cycle 1)</td>
<td>55.8 (13.1; 222)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>551 (137; 1,980)</td>
</tr>
<tr>
<td>Trough concentration before day 0 tipifarnib administration (cycle 1)</td>
<td>108 (0; 215)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>124.5 (66; 275)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1,999.5 (165; 4,607)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>2,043.5 (977; 6,669)</td>
</tr>
<tr>
<td>Endoxifen</td>
<td>6.5 (0; 190)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>4 (0; 215)</td>
</tr>
<tr>
<td>NDDT</td>
<td>276.5 (76; 664)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>306 (118; 550)</td>
</tr>
<tr>
<td>Sum</td>
<td>2,404 (247; 5,159)</td>
<td>14 tipifarnib administration (cycle 1)</td>
<td>2,464.5 (1,376; 7,534)</td>
</tr>
</tbody>
</table>

NOTE: The sum is the addition of the tamoxifen concentration and of its three metabolite concentrations (NDT or N-desmethyl-tamoxifen, endoxifen, or 4-hydroxy-N-desmethyl-tamoxifen, and NDDT or N-desdimethyl-tamoxifen).
peptide (amino acid residues 576-629) of fibrinogen α chain precursor (Fig. 2).

**Discussion**

Signal transduction pathways involving prenylated proteins may be activated in endocrine-resistant tumors. Tipifarnib monotherapy in pretreated advanced breast cancer patients never produced a >25% CB rate (12). In our study, the primary end point of at least three OR before proceeding to stage 2 was set too high and was not met, as only one OR was observed. A 50% CB rate (10 patients) was found with minimal toxicity with 200 mg tipifarnib twice daily. A larger, randomized study is then needed to confirm the CB observed in this study with the tamoxifen/tipifarnib combination with that of tipifarnib alone. The CB rate or the progression-free survival, and not the OR rate, should be the primary objective in future nonrandomized phase II studies that combine endocrine therapy and tailored treatments because the trial had to be discontinued despite the achievement of a 50% CB rate.

A phase II trial of tipifarnib plus fulvestrant was conducted in women with hormone receptor–positive, inoperable, and locally advanced or metastatic breast cancer after first-line endocrine therapy (23). Preliminary results in 31 patients showed a 47.6% CB rate and a median time to progression of 7.2 months.

On the contrary, another recently reported phase II randomized trial of letrozole with or without tipifarnib in 121 patients with tamoxifen-resistant, advanced breast cancers did not show an increased response rate with the combination compared with letrozole alone (24). The absence of an additive effect for tipifarnib in this trial could be because tamoxifen, like fulvestrant, acts through an ER intracellular signaling pathway, whereas letrozole inhibits E2 synthesis. Moreover, we are in the situation of patients who are in progression on tamoxifen therapy at the initiation of the combination treatment, whereas the patients of the former study already showed resistance to tamoxifen but could respond to letrozole alone. We and others previously showed the additive or synergistic action of a combination of tamoxifen with a FTI to inhibit proliferation and promote apoptosis in vitro and in vivo (9, 13–15).

If preliminary results from studies combining hormone therapy and FTIs or other signal transduction inhibitors failed to show high potency, it may be due to the inability to identify the target population who would best benefit from this treatment (25). The challenge for future therapeutic development is to identify those patients who will benefit from a specific treatment combination. The median time to progression of the 20 progressing metastatic patients in the present study is 5.7 months with the tipifarnib/tamoxifen combination. The absence of modification of
tipifarnib pharmacokinetics and pharmacodynamic in the presence of tamoxifen was reported previously (16). We observed that the concentration of endoxifen, the active metabolite of tamoxifen present at concentrations 10-fold higher than 4-OH-tamoxifen (22), are maintained in the presence of tipifarnib. However, none of these concentrations correlated with the risk of progression.

No valuable peptide could be identified as a therapeutic-response marker in the pretreatment sera, but we found that high expression of p5900 was associated with an 8.2-fold higher risk of progression at 6 months after 8 weeks of treatment. This 8-week period might be relevant to stop the combination treatment before a clinical progression is observed. In breast cancers, the SELDI-TOF technique has identified serum biomarkers (e.g., ubiquitin, ferritin light chain, fibrinogen α peptide) that discriminate those with breast cancer from those with benign disease or healthy patients (26, 27).

We identified p5900 as a new 54-amino acid fibrinogen α peptide (576-629, COOH terminal end). We expected p5900 to be a protein or a peptide degradation product, whose concentration increases before clinical progression and therefore expected it to be associated with either invasion and/or the inflammation and/or the action of tipifarnib. Indeed, fibrinogen is a circulating multidomain protein consisting of two pairs of three polypeptide chains, α, β, and γ. After formation of a fibrin clot, plasmin degrades the clot into many peptides with various biological activities, including a protumorigenic one in breast cancer. The presence of smaller fibrinogen α peptides in plasma, but not sera, has been associated with the absence of breast cancer (27, 28). One of them, a 25-amino acid peptide identified as declining in HER2-positive breast cancer patients (encompassing residues 605-629, COOH terminal end; ref. 27) overlaps the 54 amino acids of the fibrinogen α peptide we identified. On the contrary, a serum profile identified one of those 25-amino acid peptides as a breast cancer-specific marker that increases in cancer patients’ sera, unselected for HER-2 status (29). The specificity of either sera or plasma profiling is of high importance and we have to be aware that those markers may not be directly related to the therapeutic targets but to the pathology signature. Scientifically, our data set is small with no independent validation of the fibrinogen peptide as a pharmacodynamic response marker. After this first step of screening, further work includes the development of specific monoclonal antibodies to analyze the benefit of p5900 in larger cohorts of patients and determining if an increased concentration of this peptide in sera determines which patients benefit from combination therapy.

The role of FTIs in breast cancer continues to be explored in four ongoing studies of tipifarnib or lonafarnib alone or in combination with chemotherapy or hereceptin.

In conclusion, this study is negative regarding the primary end point. An interesting finding of the exploratory analysis was to identify a potential pharmacodynamic, therapeutic-response biomarker in breast cancer. Translational studies should become an integral part of future clinical trial designs by analyzing the tumor and blood genotypes and/or phenotypes at the initiation of the treatment using proteomic serum profiling or other approaches.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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