The Vascular Endothelial Growth Factor Receptor Inhibitor PTK787/ZK222584 Inhibits Aromatase

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Abstract

Endocrine therapy is well established for the treatment of breast cancer, and antiangiogenic agents are showing considerable promise. Targeting the vascular endothelial growth factor (VEGF) and estrogen receptor (ER) signaling pathways concomitantly may provide enhanced therapeutic benefit in ER-positive breast cancer. Therefore, the effects of the VEGF receptor (VEGFR) tyrosine kinase inhibitor PTK787/ZK222584 (PTK/ZK) were investigated using human breast cancer cell lines engineered to express aromatase. As expected in this system, estrogen (E2) or androstenedione induced a proliferative response and increased ER-mediated transcription in ER-positive cell lines expressing aromatase. However, surprisingly, in the presence of androstenedione, PTK/ZK suppressed both the androstenedione-stimulated proliferation and ER-mediated transcription. PTK/ZK alone and in the presence of E2 had no observable effect on proliferation or ER-mediated transcription. These effects result from PTK/ZK having previously unrecognized antiaromatase activity and PTK/ZK being a competitive aromatase inhibitor. Computer-assisted molecular modeling showed that PTK/ZK could potentially bind directly to aromatase. The demonstration that PTK/ZK inhibits aromatase and VEGFR indicates that agents cross-inhibiting two important classes of targets in breast cancer could be developed. [Cancer Res 2009;69(11):4716–23]

Introduction

Over 70% of breast carcinomas express the estrogen receptor (ER) and require estrogen stimulation for their growth. Treatment with tamoxifen, which blocks ER, has made a substantial contribution to the dramatic decrease in the mortality from breast cancer in western countries over the last two decades. More recently, clinical trials have shown that aromatase inhibitors that block estrogen production have superior efficacy to tamoxifen; significant increases in disease-free survival were seen with the third-generation aromatase inhibitors, anastrozole, letrozole, and exemestane (1–4). However, a substantial proportion of women with ER-positive breast cancer becomes resistant to endocrine treatment. Therefore, it has been suggested that combining aromatase inhibitors with agents targeting other key biochemical pathways required for tumor viability may further improve breast cancer survival (5, 6).

There is extensive evidence supporting the role of angiogenesis, the formation of new blood vessels, in breast cancer development, invasion, and metastasis. Vascular endothelial growth factor (VEGF) is a critical regulator of angiogenesis, and VEGF actions are mediated by binding to the VEGF receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2). The combination of targeted antiangiogenic therapy with conventional treatment is an attractive strategy in breast cancer (7), as malignant cells are targeted directly, as well as indirectly, through neovascularization driven by the stroma. In addition, antiangiogenic agents reduce tumor interstitial pressure and normalize the vasculature, and this may improve the delivery of systemic therapy. Resistance to hormonal therapies in breast cancer remains a significant treatment challenge (5, 8). The VEGF pathway has been implicated in this process (9), and this has led to the hypothesis that concomitantly targeting the VEGF and ER signaling pathways may provide enhanced therapeutic benefit. Targeting VEGFR with tyrosine kinase inhibitors (TKI) in breast cancer has significant potential (7). PTK787/ZK222584 (PTK/ZK) was developed as a potent and selective inhibitor of VEGFR-2 and VEGFR-1 (10) and is undergoing clinical evaluation for the treatment of breast and other cancers. Although, TKIs commonly have additional activity against other tyrosine kinases, inhibitory activity across other classes of drug targets has not been documented. Here, we show that the PTK/ZK, a VEGFR TKI, also significantly inhibits aromatase. This “multitargeting” activity could potentially contribute to the antitumor effect of PTK/ZK. The ability of a single small molecule inhibitor to inhibit two distinct biological and biochemical pathways may allow the rational development of agents designed to inhibit cross-class targets.

Materials and Methods

Materials. 17β-Estradiol (E2) and androstenedione were from Sigma. [1–3H]-Androstene-3,17-dione was from NEN Radiochemicals. Letrozole and PTK/ZK (Supplementary Fig. S1) were synthesized by Novartis Pharma AG and stored at –20°C as 10 mmol/L stocks in 100% ethanol or DMSO, respectively. Sorafenib was provided by R. Marais, and imatinib was from LKT Laboratories. Chemicals, unless otherwise stated, were of molecular grade and purchased from Sigma. Tissue culture grade plastics were purchased from Nunc.

Tissue culture. ER-positive human breast cancer cell lines MCF7 [ER+/HER2−] and BT474 [ER+/HER2+], together with the ER-negative cell line SKBR3 [ER−/HER2−], were stably transduced with a retroviral construct pBabeAROM expressing full-length human aromatase (CYP19). Clones expressing clinically relevant levels of aromatase activity were selected (MCF7 AROM 2A, BT474 AROM, and SKBR3 AROM). Target cell lines were also transduced with the pBabeNeo backbone (MCF7neo, BT474neo, and SKBR3neo). MCF7 AROM [AROM+/ER+] cells, which have a high level of aromatase activity, were generated by stable transfection of CP91 under
control of the cytomegalovirus promoter (pcDNA3AROM), as previously described (11), or the pcDNA backbone (MCF7/pcDNA3 [AROM−/ER+]). All cell lines were cultured in phenol red RPMI medium containing 10% fetal bovine serum (FBS), 10 μg/mL insulin, 2 mmol/L glutamine, and 1 mg/mL G418. Steroid-depleted medium, called DCC-FBS medium, was composed of the phenol red RPMI medium containing 10% dextran charcoal–stripped FBS, 10 μg/mL insulin, and 2 mmol/L glutamine. The characteristics of the cell lines are shown in Supplementary Table S1.

Cell proliferation assays. Cell lines were depleted of steroids for 3 d (12), seeded into 12-well plates at 1 × 10^5 per well, and allowed to acclimatize for 24 h before treatment with drug combinations indicated for 6 d with daily changes. Cell number was determined using a Z1 Coulter Counter (Beckman Coulter). Results were confirmed in a minimum of three independent experiments, and each experiment was performed in triplicate.

Transcriptional assays. Cell lines (previously stripped of steroids for 3 d) were seeded in 24-well plates at 7 × 10^4 per well in steroid-depleted (DCC) medium and transfected using FuGENE 6 (Roche) with 0.1 μg luciferase reporter construct (EREIIkluc) and pCH110 (Promega) activity were measured using a luminometer (TD20/20). Normalized luciferase activity from triplicate wells was expressed relative to vehicle-treated control. Results were confirmed in a minimum of three independent experiments, and each experiment was performed in triplicate.

Aromatase assays. Aromatase inhibition assays were performed using MCF7 AROM 1 cells ("in-cell" assay), microsomes isolated from MCF7 AROM 1 cells, and human placental microsomes. Aromatase activities were determined by the standard tritiated water release method (13) with AROM1 cells, and human placental microsomes. Aromatase activities were calculated in picomoles of tritiated water released per mg protein, and phosphate buffer (0.05 mol/L, pH 7.4). The PTK/ZK concentration was 600 nmol/L. The reaction was started by the addition of protein and stopped after 20 min by the addition of 10% trichloroacetic acid. The tubes were centrifuged at 3000 × g for 10 min. Aliquots (0.5 mL) were added to 10 mL of scintillation fluid (QuickSafe A, Zinsser Analytic) and counted in a liquid scintillation counter (LS 6500, Beckman Coulter). For calculation of \( K_i \) and \( K_m \) values, results were plotted in a double reciprocal Lineweaver Burk plot (1/\( \text{activity} \) vs 1/[substrate]), wherein the y-axis intercept corresponds to \(-1/K_m\) (in the absence of inhibitor) or \(-1/K_m'\) (in the presence of inhibitor).

Computer modeling. A homology model of aromatase (CYP19A_Human) was created based on the crystal structure of human cytochrome P450 CYP3A4 enzyme (PDB code 1W0G) as a template. Modeling was done within the Quanta™ and Insight™ programs. Docking was carried out using the genetic algorithm program GOLD (16). To dock PTK/ZK, a binding cavity of up to 10 Å within aromatase was generated around the coordinates of C10 atom of metyrapone. The docked PTK/ZK structure was then subjected to molecular dynamic simulation within YASARA. During the simulations, the heme was constrained but the protein and PTK/ZK were allowed free movement.

The pharmacophore model for aromatase inhibition is previously described (17). In the pharmacophore model, the most potent azole and steroid inhibitors of aromatase are aligned using the heme group of the enzyme as the reference anchoring point. Close analogues of the potent inhibitors devoid of aromatase inhibitory activity are also included in the model, allowing the definition of the volumes accessible and nonaccessible to ligands in the active site of the enzyme. PTK/ZK, in a low energy conformation, was positioned in the model using its pyridine moiety to chelate the iron atom of the heme group while trying to fit the rest of the molecule in the space occupied by the active molecules defining the volume accessible to ligands.

Statistical analysis. A one-way ANOVA followed by a Tukey’s multiple comparison test was performed to determine statistical significance. A P value of <0.01 was considered statistically significant.

Results

PTK/ZK has antiproliferative effects on MCF7 AROM cells. To assess the effects of the aromatase inhibitor letrozole combined
with the VEGFR inhibitor PTK/ZK, we required ER-positive, aromatase-transfected cell lines. The previously described ER-positive, aromatase-transfected cell lines MCF7 AROM 1 [AROM+/ER+] cells (11), MCF7 AROM 2A [AROM+/ER+] and BT474 AROM [AROM+/ER+/HER2+] cells were used. In this system, aromatase converts the substrate androstenedione to estradiol, the growth signal for ER-positive cells and this process is inhibited by aromatase inhibitors.

Increasing doses of 17β-estradiol (E2) stimulated growth in both MCF7 AROM 1 [AROM+/ER+] cells and MCF7 cells transfected with the empty vector MCF7/pcDNA3 [AROM−/ER+] (Fig. 1A). These results were expected as the MCF7-derived cell lines are ER positive. Increasing concentrations of E2 failed to induce proliferation in the ER-negative SKBR3 AROM [AROM+/ER−] cells (Fig. 1A), confirming that ER is necessary to mediate the effects of E2. Treatment with androstenedione also caused a dose-dependent increase in cell number compared with untreated MCF7 AROM 1 [AROM−/ER+] cells; androstenedione at 10 nmol/L stimulated growth of ∼12-fold compared with untreated cells (Fig. 1B). In contrast, unlike E2, androstenedione treatment did not increase proliferation of the MCF7/pcDNA3 [AROM−/ER−] cells. The ability of androstenedione to increase proliferation of MCF7 AROM 1 [AROM+/ER+] cells was consistent with its metabolic conversion into estrogens by the cells. The failure of androstenedione to stimulate proliferation in the MCF7/pcDNA3 [AROM−/ER+] cells suggests that aromatase activity is required for androstenedione-stimulated proliferation. This was confirmed by the inhibition of androstenedione-stimulated proliferation of MCF7 AROM 1 [AROM+/ER+] cells by the aromatase inhibitor letrozole. Almost 60% suppression of androstenedione-stimulated proliferation was achieved with 100 nmol/L letrozole (Fig. 1C). To investigate whether this was a general phenomenon of ER-positive breast cancer cells, these results were confirmed in MCF7 AROM 2A cells [AROM+/ER+] and another ER-positive cell line, BT474-aromatase-transfected cells (BT474 AROM [AROM+/ER+/HER2+]; data not shown). Furthermore, androstenedione treatment did not lead to proliferation in SKBR3 AROM [AROM+/ER−] cells, suggesting that both aromatase and ER are required to mediate androstenedione-stimulated effects.

Having validated the cell lines to be used, we then investigated whether PTK/ZK could affect the proliferation of ER-positive breast cancer cells. In view of the lack of vasculature and microenvironment in this in vitro model, PTK/ZK was not expected to affect proliferation. MCF7 AROM 1 [AROM+/ER+] cells were cultured in steroid-depleted media (DCC) and subsequently treated over 6 days with 10, 100, and 1,000 nmol/L of PTK/ZK alone and in combination with a standard dose of androstenedione (10 nmol/L). As expected, treatment with androstenedione resulted in an increase (12-fold) in proliferation compared with untreated cells. Unexpectedly, however, increasing doses of PTK/ZK inhibited cell proliferation.
proliferation with a dose of 1.000 nmol/L, resulting in a 43% decrease ($P < 0.0001$). However, PTK/ZK in the absence of aromastenedione had no effect on proliferation ($P = 0.72$; Fig. 2A). No effects of PTK/ZK were seen in MCF7/pDNA3 [AROM−/−ER+] cells, either in the presence or absence of aromastenedione (Fig. 2B). The reduction in aromastenedione-stimulated proliferation was confirmed in BT474 AROM [AROM+/ER+HER2+] cells (Fig. 2C) and MCF7 AROM 2A [AROM+/ER+] cells (Supplementary Fig. S2A). In addition, no effects were seen either in the presence or absence of aromastenedione in ER-negative SKBR3 AROM [AROM+/ER−] cells (Fig. 2D). This suggested that the antiproliferative effects observed with PTK/ZK in the presence of aromastenedione might be associated with the expression of ER and/or aromastenedione.

PTK/ZK inhibits ER-mediated transcription in MCF7 AROM cells. To investigate the mechanism of the inhibition of cell proliferation by PTK/ZK, we first assessed whether the effects of PTK/ZK involved an ER-mediated mechanism. Therefore, an estrogen response element (ERE)–linked luciferase reporter construct was transfected into MCF7 AROM 1 [AROM+/ER+] cells and the effects of various treatments on luciferase activity measured. Androstenedione (10 nmol/L) increased ER transcriptional activity at 12-fold compared with untreated cells, and PTK/ZK, in the presence of androstenedione, abrogated this effect. PTK/ZK decreased ER/ERE transactivation in MCF7 AROM cells in a dose-dependent manner; 1 μmol/L reduced activity by 76% ($P < 0.0001$). Consistent with the effects on proliferation, PTK/ZK had no effect on ER/ERE transactivation in the absence of aromastenedione ($P = 0.72$; Fig. 3A). These results suggest that PTK/ZK affects ER-mediated transcription only in the presence of aromastenedione. The effects of PTK/ZK on ER-mediated transcription were confirmed in BT474 AROM [AROM+/ER+HER2+] cells (Fig. 3B) and MCF7 AROM 2A [AROM+/ER+] cells (Supplementary Fig. S2B).

PTK/ZK has no effect on oestradiol-stimulated MCF7 AROM cells. We speculated that the unexpected effects of PTK/ZK on proliferation in the aromastenedione-stimulated cells could be due to antiamarase activity. To assess this, we provided E2 directly to the cells, thereby negating the requirement for aromastenedione activity in MCF7 AROM [AROM+/ER+] cells, and investigated whether PTK/ZK maintained inhibitory effects in this situation. Proliferative responses to increasing doses of PTK/ZK (10, 100, and 1,000 nmol/L), in combination with 1 nmol/L E2, were assessed in MCF7 AROM 1 [AROM+/ER+] cells. As expected, E2 treatment caused an increase in proliferation (~20-fold) compared with untreated cells. In contrast to the effects seen in the presence of aromastenedione, PTK/ZK had no effect on cell proliferation at a concentration of up to 1 μmol/L ($P = 0.81$; Fig. 4A). As anticipated, in the presence of E2, PTK/ZK had no effect in MCF7/pDNA3 [AROM−/−ER+] cells (Fig. 4B) or SKBR3 AROM [AROM+/ER−] cells (Fig. 4C). The inhibitory effects of PTK/ZK in the presence of aromastenedione, but not estradiol, were confirmed in BT474 AROM [AROM+/ER+/HER2+] cells (Fig. 4D) and MCF7 AROM 2A [AROM+/ER+] cells (Supplementary Fig. S4A). Similarly, no inhibitory effect of PTK/ZK was noted in the presence of E2 in ERE transactivation studies (Fig. 5A and B). These findings suggested that aromastenedione function was necessary for the antiproliferative action of PTK/ZK.

PTK/ZK is an aromastenedone inhibitor. To confirm the antiamarase activity of PTK/ZK, tritiated H2O assays monitoring aromastenedone activity were carried out in MCF7 AROM 1 [AROM+/ ER+] cells. As expected, letrozole suppressed aromastenedone activity.

![Figure 3. PTK/ZK inhibits the ER/ERE-mediated transactivation of aromastenedone expressing ER cells. To assess the effect of PTK/ZK on ER/ERE transactivation MCF7 AROM 1 [AROM+/ER+] cells (A) and BT474 AROM [AROM+/ER+/HER2+] cells (B) were transiently transfected with an ERE-linked luciferase reporter construct followed by 24 h of treatment with vehicle (0.01% v/v ethanol), aromastenedone (10 nmol/L), or estradiol (1 nmol/L) and increasing concentrations of PTK/ZK. Luciferase activity was normalized by ß-galactosidase from cotransfected pCH110. Normalized luciferase activity from quadruplicate wells was expressed relative to the vehicle-treated control. Bar, SE. Effects were confirmed in three independent experiments. *, $P < 0.01$ compared with controls.](image-url)
that PTK/ZK might be inhibiting a kinase that regulates aromatase activity. We, therefore, addressed the possibility that the antiaromatase activity of PTK/ZK might be acting through tyrosine kinase inhibition. However, neither sorafenib (VEGFR and platelet-derived growth factor receptor inhibitor) nor imatinib (c-KIT and c-FMS inhibitor) inhibited aromatase (Fig. 6A), suggesting that the ability of PTK/ZK to suppress aromatase activity is likely to be independent of the tyrosine kinases VEGFRs, c-KIT, or c-FMS.

Computer modeling supports novel aromatase inhibitory action of PTK/ZK. To provide a structural explanation for the novel aromatase inhibitory activity of PTK/ZK, we carried out computer-assisted molecular modeling studies. We used two independent models to investigate this. Both suggest that PTK/ZK binds favorably with aromatase, providing further support for our data showing that PTK/ZK is an aromatase inhibitor (Fig. 6C and D). From a pharmacophore model (17), it can be concluded that PTK/ZK presents two structural characteristics consistent with its ability to inhibit aromatase: a heme-binding group and a hydrophobic moiety fitting in the sterically allowed region of the active site (Fig. 6C). However, according to the model, the most potent azole inhibitors of aromatase, such as letrozole, possess a chemical moiety able to mimic rings C and D of androstenedione, the enzyme natural substrate. This is not the case for PTK/ZK. Although the compound can be fitted in the accessible volume above the plane of the steroid substrate, it does not overlap with the latter, in particular with rings C and D or equivalently with the cyanophenyl ring of letrozole mimicking these features. This is likely the reason why the compound does not show the very high inhibitory potency achieved with letrozole.

In the second model, PTK/ZK was docked into a homology model of aromatase using the GOLD program (Fig. 6D). To verify the docking results, the aromatase substrate metyrapone was docked using the same parameters and compared with the X-ray structure of cytochrome P450CYP3A4. The docked structure of PTK/ZK with aromatase showed that the pyridine moiety of PTK/ZK superimposes onto the pyridine moiety of metyrapone, enabling the nitrogen atom to make electrostatic interactions with the heme. We also modeled other small molecule inhibitors to test whether the aromatase inhibitory activity of PTK/ZK could be a universal property of TKIs. A range of small molecule inhibitors and known aromatase inhibitors were docked into the model of aromatase [lapatinib (GW572016), lonafarnib (SCH66336), tipifarnib (RI15777), sorafenib (BAY439006), vandetanib (ZD6474), everolimus (RAD001)]. Only letrozole, anastrozole, and PTK/ZK docked in the favored orientation with a ring nitrogen pointing toward the heme iron.

Discussion

The development of dual target inhibitors for the treatment of breast cancer has generated much interest. For example, lapatinib targets the tyrosine kinases EGFR and HER2 (18) and is showing some success in the clinic (19). Recently, dual aromatase and sulfatase inhibitors have shown potential in preclinical breast cancer models (20). However, these approaches have been limited, thus far, to the inhibition of similar classes of targets, for example, either tyrosine kinases or E2 synthesis. Here, we show for the first time that a single chemical entity, a TKI developed to target
Targeting VEGFR with TKIs in breast cancer is believed to have great potential. Patients have already been recruited to phase II clinical trials of PTK/ZK in breast cancer (PTK/ZK/docetaxel, PTK/ZK/trastuzumab, and PTK/ZK and letrozole).

Our early experiments in MCF7 AROM [AROM+/ER+] cells were suggestive of angiogenesis-independent effects of PTK/ZK. PTK/ZK inhibited androstenedione-stimulated proliferation and decreased androstenedione-induced ER-mediated transcription. Of importance, no vasculature or stroma was present in this cell culture system. These effects were abrogated in the presence of estrogen and led us to investigate the effects of PTK/ZK on aromatase activity. Both in-cell and microsomal aromatase assays confirmed the previously unknown aromatase inhibitory action of PTK/ZK. The in vitro potency of PTK/ZK as an aromatase inhibitor is in a similar range as anastrozole but is less than letrozole. The lack of aromatase inhibition with sorafenib and imatinib suggests that aromatase inhibition is a direct effect of PTK/ZK. Structural studies of PTK/ZK provided further support for aromatase inhibition and suggested that other common TKIs do not have this activity. However, the identification of this dual activity in PTK/ZK provides a potential opportunity to achieve enhanced aromatase inhibitory capability in related compounds. Following, the submission of this manuscript, the crystal structure of human aromatase (3EQM) was published (22). Modeling studies using this structure verified the ability of PTK787 to dock into the heme site of human aromatase.

Data from phase I trials of PTK/ZK have shown that at a dose of 1,000 mg/day, a C\text{max} of 18 \mu M, a C\text{min} of 0.41 \mu M, and an AUC of 88 \mu M h are achieved, and over a 24-hour period, the concentration of PTK/ZK is above 1 \mu M for the majority of the time (23). Our findings indicate that the IC\text{50} of PTK/ZK for aromatase activity is submicromolar and the \text{Ki} of 101nmol/L is significantly lower than the circulating concentrations achieved in patients. Although the dose and scheduling of PTK/ZK has been controversial (24), of clinical relevance, the pharmacokinetic properties of PTK/ZK at doses commonly used in clinical trials suggest that the systemic exposure is likely to be sufficient to provide clinically relevant aromatase inhibition. Our findings suggest the clinical potency of PTK/ZK is likely to be inferior to letrozole but similar to that of anastrozole. Adverse effects known to be associated with aromatase inhibitors have been reported in phase I/phase II clinical trials of PTK/ZK. Arthralgia was documented in 35% of patients with hormone refractory prostate cancer (25), and 7% of patients with gastrointestinal stromal tumors treated with PTK/ZK reported hot flushes (26). However, the mentioned adverse effects are nonspecific and could be due to other factors. Clinical studies of PTK/ZK specifically designed to measure changes in estradiol levels are necessary to establish the full clinical implications of our finding.

These results are provocative and suggest that there are novel mechanisms of PTK/ZK action in ER+ breast cancer. PTK/ZK was developed as a VEGFR inhibitor and may therefore affect angiogenesis. Our data suggests that PTK/ZK also inhibits aromatase, and this may lead to a reduction in tumor cell proliferation. The dual pronged attack of a single agent on both angiogenesis (stroma) and cell proliferation (tumor) has the potential to reduce breast cancer growth and metastases. In addition, if the antiaromatase activity clinically is relevant, then this may have serious implications when treating premenopausal women or indeed men with this agent in a variety of malignant and nonmalignant conditions, because there are significant consequences of aromatase inhibition in these groups. Finally, by studying the structure and properties of PTK/ZK, currently under clinical evaluation, was developed as a potent and selective TKI of VEGFR-2 and VEGFR-1. Kinase inhibitor selectivity studies indicate that PTK/ZK is a relatively selective kinase inhibitor (21). Several preclinical studies have confirmed VEGFR inhibition of endothelial cells and resulting antiangiogenic effects in in vitro and in vivo tumor models.
PTK/ZK, it may be possible for drugs to be intentionally designed to target two distinct biological pathways with greater potency.

Disclosure of Potential Conflicts of Interest

M. Dowsett: Consultant, Novartis and AstraZeneca; commercial research grant, Novartis. The other authors declared no potential conflicts of interest.

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