Effects of gefitinib (Iressa) on mammary cancers: preventive studies with varied dosages, combinations with vorozole or targetretin, and biomarker changes

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Abstract
The ability of the epidermal growth factor receptor inhibitor gefitinib (Iressa) to prevent/treat methylnitrosourea (MNU)-induced mammary cancers and to modulate biomarkers in female Sprague-Dawley rats was examined. Rats were given a single dose of MNU (75 mg/kg body weight) at 50 days of age. In the prevention studies, continual treatment with Iressa at 10, 3, or 1 mg/kg body weight per day beginning 5 days after MNU reduced tumor multiplicity by 93%, 43%, and 20%, respectively. Treatment of rats bearing small palpable cancers with Iressa (10 mg/kg body weight per day) resulted in the complete regression of 70% of the tumors. Short-term treatment of tumor-bearing rats with Iressa caused decreases in cell proliferation and phosphorylated epidermal growth factor receptor and increases in apoptosis. To examine treatment regimens that might decrease the skin toxicity associated with Iressa, both intermittent treatments and combinations of lower doses of Iressa with other effective agents were evaluated. Treatment with Iressa (10 mg/kg body weight per day) continually or intermittently (either “3 weeks on/3 weeks off” or “4 days on/3 days off”) reduced cancer multiplicity by 91%, 24%, and 68%, respectively. However, all regimens reduced tumor weights >85%. Finally, combining suboptimal doses of Iressa with suboptimal doses of vorozole (an aromatase inhibitor) or targetretin (a retinoid X receptor agonist) yielded greater chemopreventive efficacy than any of these agents given alone. [Mol Cancer Ther 2008;7(4):972 – 9]

Introduction
Inhibition of epidermal growth factor receptor (EGFR) activity with small molecules or antibodies is a new therapeutic modality in the treatment of several forms of cancer (1, 2). The appeal of EGFR as a molecular target is because this receptor is often overexpressed and sometimes mutated in various human cancers, including a high percentage of malignant gliomas, non–small cell lung cancer, breast cancer, and ovarian cancer (1, 2). Furthermore, the related family member EGFR2/HER2/Neu, which routinely forms a heterodimer with EGFR1, is an oncoprotein that is intimately involved in ~25% of human breast cancers (3). In general, the EGFR proteins are known to stimulate cell growth, promote tumor cell proliferation, and decrease apoptosis. A significant number of both estrogen receptor–positive (ER+) and ER− human breast cancers overexpress EGFR (4, 5). Although EGFR inhibitors as monotherapies in metastatic breast cancer exhibit limited efficacy (6, 7), treatment with these inhibitors during earlier periods of carcinogenesis may be more promising. For example, Polychronis et al. (8) found that 30% of ER+ mammary cancers responded to Iressa as a monotherapy in the neoadjuvant setting. Because the EGFR family (EGFR1/2) plays a significant role in many human breast cancers, we determined whether the small molecular inhibitor Iressa might be an effective preventive agent in the methylnitrosourea (MNU)-induced mammary cancer model. Although the EGFR inhibitors seem to have significant therapeutic efficacy, skin rash (their primary toxicity) may be an impediment to their use in a prevention setting (9). Therefore, protocols that may significantly decrease the occurrence or severity of rash are of significance for any proposed chemoprevention studies using this class of agents.

Chemically induced models of mammary carcinogenesis were initially developed by Huggins (10). Subsequently, female Sprague-Dawley rats treated with MNU were shown to develop multiple hormonally responsive mammary cancers starting within 5 weeks after carcinogen administration (11). These cancers seem to be histologically similar to ER+ mammary cancers in humans (12). Gene expression profiling has also revealed significant similarities to well-differentiated ER+ human breast cancer (13). As might be expected, treatments that alter the hormonal axis...
(e.g., selective ER modulators and aromatase inhibitors) are strong chemopreventive agents in this model (14, 15). In addition, the cancers in this model are responsive to various agents, including a variety of retinoid X receptor (RXR) agonists and farnesyltransferase inhibitors, which may not act on the hormonal axis (16, 17).

Most prevention experiments use decreases in cancer incidence and cancer multiplicity as their primary end points. We have recently examined a series of short-term end points that might reflect the long-term efficacy of specific treatments (18). One group of end points is the effects of short-term exposure to agents on proliferation and apoptosis in small palpable mammary cancers. These end points have been used in examining a wide variety of agents, including aromatase inhibitors, selective ER modulators, and farnesyltransferase inhibitors (18), as well as in screening a variety of RXR agonists for chemopreventive activity (19). An excellent correlation was found between decreases in proliferation and increases in apoptosis and long-term chemopreventive and therapeutic efficacies. A second method for evaluating potential efficacy is to look at end points directly related to the mechanism of action of the agent; in the present study, the end points included phosphorylation of EGFR or certain of its downstream effector molecules (6).

In this series of studies, we used the MNU-induced model of mammary carcinogenesis to determine (a) the preventive and therapeutic effects of continual treatment with the EGFR inhibitor Iressa; (b) the preventive efficacy of intermittent treatment with Iressa; (c) the effects of Iressa treatment on biomarkers, including proliferation, apoptosis, and phosphorylation of EGFR; and (d) the chemopreventive effects of combining lower doses of Iressa with suboptimal doses of the aromatase inhibitor vorozole or the RXR agonist taretgin.

**Materials and Methods**

**Chemicals and Animals**

MNU was obtained from the National Cancer Institute Chemical Carcinogen Repository. The carcinogen was dissolved in sterile acidified saline (pH 5.0) and injected i.v. (75 mg/kg body weight) via the jugular vein when the animals were 50 d of age. Teklad mash diet (4%) and Sprague-Dawley rats were obtained from Harlan Sprague Dawley, Inc. Rats were obtained at 28 d of age and housed in polycarbonate cages (five per cage) in a room lighted 12 h per day and maintained at 22°C ± 2°C. The preventive/therapeutic agents were obtained as follows: Iressa and taretgin were made by custom synthesis and confirmed by verified analytic techniques and vorozole was supplied gratis by Johnson & Johnson Pharmaceuticals. Taretgin was incorporated into the diet by mixing with Teklad (4%) mash diet using a liquid-solid blender (Patterson-Kelly Co.). Iressa and vorozole were given by gavage, seven times per week, in a volume of 0.5 mL/gavage. The vehicle for the agents was ethanol/polyethylene glycol 400 (10:90, v/v).

**Data Collection and Analyses**

In all studies, rats were palpated for mammary tumors twice each week and weighed once per week. Body weights of the rats did not differ >5% in either the prevention, intermittent, therapeutic, or combination studies. Mammary tumors were excised at necropsy, weighed, and processed either for histologic classification or for immunohistochemistry. Statistical analyses of cancer incidence and latency were determined using log-rank analysis, and differences in cancer multiplicity were determined by the Armitage test as previously described (20).

**Iressa Prevention Study—Various Doses**

Prevention studies were done as previously described (17, 21). Briefly, treatment of rats with Iressa was initiated 5 d after MNU administration (or at 55 d of age). The number of rats per group was 15. Rats were palpated for mammary tumors twice per week. At the end of the study (120 d after MNU administration), the animals were sacrificed. In an initial study, Iressa was given at 20 mg/kg body weight per day. The dose was toxic and the experiment was terminated after 4 wk of treatment. In the present study, Iressa was given continuously throughout the duration of the study at dose levels of 10, 3, and 1 mg/kg body weight per day.

**Iressa Therapeutic Study**

Rats received MNU at 50 d of age and were observed for the development of mammary cancers. When an animal developed a tumor of approximately 100 to 200 mm², the rat received Iressa (10 mg/kg body weight per day) for 6 wk. Tumor size was determined with calipers before initiation of treatment and twice each week during the course of treatment. The largest diameter of the cancer was measured and this value was multiplied by the perpendicular diameter (size expressed in mm²). The Iressa-treated and control groups each had 10 to 12 rats with mammary cancers that were evaluated.

**Biomarkers**

Animals bearing small palpable MNU-induced mammary cancers (approximately 200–300 mm³), as described under the therapeutic study section, were treated with vehicle or Iressa (10 mg/kg body weight per day) for a period of 7 d. Rats were injected i.p. with bromodeoxyuridine (BrdUrd), 100 mg/kg body weight in saline, 2 h before the time of sacrifice. After sacrifice of the animals by CO₂ asphyxiation, cancers were removed and fixed overnight in 10% formalin for assessment of histopathology, BrdUrd labeling, and apoptosis. Differences in proliferation index and apoptotic index were evaluated using Wilcoxon rank sum analysis (17, 18).
Apoptosis

Apoptotic cells were identified by the terminal deoxy-nucleotidyl transferase–mediated dUTP nick end labeling method as previously described (17–19) using methods recommended by the ApopTag in situ hybridization detection kit (Oncor Co.). The top sections of each slide, which were incubated without digoxigenin-dUTP, were used as a negative control. Rat mammary glands taken 6 d after ovariectomy (when the number of apoptotic cells was high) were used as positive controls. Tissue sections were counterstained by methyl green for visualization of tumor morphology. From each tumor, >1,500 cells were evaluated for the presence of apoptotic cells (apoptotic index).

Immunohistochemical Detection of EGFR Phosphorylation

Mammary tumors were excised and drop fixed in Zamboni’s fixative [0.03% picric acid (w/v) and 2% paraformaldehyde (w/v)] for 48 h at 4°C and then transferred to a 20% sucrose solution with 0.05% sodium azide in PBS for storage. Processing and staining of tumors were carried out according to a published procedure (22). Whole tumors were cryosectioned into 80-μm sections. Floating sections were incubated first with 1:200 anti-phosphorylated EGFR (Tyr1173) raised in goat (Santa Cruz Biotechnology), washed, and then incubated in 1:1,000 anti-goat IgG, conjugated to Cy2 (Jackson ImmunoResearch), raised in donkey. Washed samples were mounted in agar, dehydrated in ethanol, cleared with methyl salicylate, and mounted in DEPEX (Electron Microscopy Science). Optical sections were captured by laser scanning confocal microscopy.

Intermittent Dosing Study

Rats received MNU at 50 d of age and were given Iressa (10 mg/kg body weight per day) beginning 5 d later (15 rats per group). Rats were given Iressa continuously or two different intermittent regimens were used: (a) rats were given Iressa by gavage for 3 wk followed by 3 wk of vehicle or (b) rats were given Iressa for 4 d followed by 3 d of vehicle. These intermittent schedules were continued throughout the duration of the study. The study was terminated 135 d after MNU treatment. All mammary tumors were removed and histologically classified.

Combination Studies

Iressa was given either alone or in combination with suboptimal doses of vorozole or targretin beginning 5 d after the administration of MNU when the rats were 50 d of age (15 rats per group). In the first study, Iressa was given at a dose of 2 mg/kg body weight per day and vorozole at 0.12 mg/kg body weight per day. In the second study, Iressa was given at 6 or 2 mg/kg body weight per day either alone or in combination with targretin at a dose of 40 mg/kg diet. For both studies, the rats were sacrificed at 126 d after MNU. All mammary tumors were removed and histologically classified.

Results

In the initial study to evaluate various doses of Iressa in the prevention of MNU-induced mammary cancers, the agent was given continuously at dose levels of 10, 3, or 1 mg/kg body weight per day. These doses caused no toxicity or significant decrease in body weights of the rats. At the end of the study (126 days after MNU), the carcinogen-treated only group had a mammary cancer multiplicity of 4.0. The high, middle, and low doses of Iressa reduced the number of mammary cancers by 93%, 43%, and 20%, respectively (Fig. 1). The mammary cancer weights in rats receiving Iressa at 10 and 3 mg/kg body weight per day were reduced by >85%, showing that both doses strongly inhibited tumor growth.

To evaluate the effectiveness of Iressa as a therapeutic agent, rats with established mammary tumors were treated with the compound for 5 weeks. In this model, cancers in nontreated animals exhibit variable growth rates but routinely show increases in size during the observation period (Fig. 2A). Iressa at the 10 mg/kg body weight per day dose caused complete regression of 67% of the mammary cancers to a size that could not be measured and caused significant regression of an additional 25% of the tumors (Fig. 2B). We similarly treated rats bearing small palpable lesions for only 7 days and measured cell proliferation as determined by BrdUrd labeling. As indicated in Fig. 3A, treatment of rats bearing mammary cancers with Iressa at 10, 3, or 1 mg/kg body weight per day for 7 days resulted in a dose-related decrease in the proliferation index of the cancers. Significant decreases in proliferation were observed at all three doses. In contrast, a significant increase in the apoptotic index of the mammary cancers was only observed in rats that received the high dose of Iressa (Fig. 3B).

When EGF binds to the extracellular domain of the EGFR, the receptor undergoes dimerization and becomes

Figure 1. Chemopreventive effects of various doses of Iressa in female Sprague-Dawley rats that received MNU. The groups were the following: ○, Iressa (1.0 mg/kg body weight per day); □, Iressa (3.0 mg/kg body weight per day); Δ, Iressa (10 mg/kg body weight per day); ●, none. Data analyses for all prevention studies (Figs. 1, 5, and 6) were done using the Armitage test and log-rank analysis.
phosphorylated on several tyrosine residues within the cytoplasmic domain. This results in EGFR activation and increased tyrosine kinase activity toward a variety of intracellular substrates (23). Autophosphorylation of Tyr$^{1173}$ is critical to EGFR signaling (24). To determine the effect of Iressa on EGFR phosphorylation at Tyr$^{1173}$, we used immunohistochemistry to examine mammary tumors excised from rats treated or not treated with Iressa (10 mg/kg body weight per day for 7 days). Results indicated a marked decrease in phosphorylated EGFR in treated rats (Fig. 4).

To examine whether the toxicity (skin rash) associated with Iressa treatment could be reduced, two approaches were examined: (a) intermittent dosing or (b) combination with other agents at lower doses. Iressa was given by three different treatment regimens: either "3 weeks on/3 weeks off," "4 days on/3 days off," or continuously. As shown above in the initial study of Iressa, continual treatment with Iressa at 10 mg/kg body weight per day was highly effective (91% decrease in mammary cancer multiplicity). The 4 days on/3 days off regimen was also effective, causing a 68% decrease of tumor multiplicity (Fig. 5). In contrast, treatment with the 3 weeks on/3 weeks off regimen was not as effective because only a 24% decrease in tumor multiplicity occurred. However, as shown in Fig. 5, only a few cancers appeared during the time Iressa was given. With regard to tumor weights, it should be noted that both intermittent schedules decreased the tumor weights >85%, indicating that those tumors that did grow out in the presence of Iressa were smaller than those that occurred in control rats.

In an attempt to determine whether lower doses of Iressa could be used if combined with other effective agents, Iressa (2 mg/kg body weight per day) was given concomitantly with a suboptimal dose of vorozole (0.12 mg/kg body weight per day). At the end of the study, the MNU-treated control group had a 100% incidence of mammary cancers with a cancer multiplicity of 5.1. Suboptimal doses of Iressa or vorozole alone caused 51% and 43% decreases, respectively, in tumor multiplicity.
whereas the combination resulted in a 76% decrease. Furthermore, the incidence of cancers in the rats receiving the Iressa and vorozole together was only 47% at the end of the study, and the time of appearance of the cancers was greatly delayed (Fig. 6A). A final study was done to evaluate the efficacy of Iressa in combination with the RXR antagonist targetein. In this experiment, Iressa was given at either 6 or 3 mg/kg body weight per day and targetin at 40 mg/kg diet. When given alone, Iressa at the high and low doses caused 71% and 34% decreases, respectively, in tumor multiplicity, whereas targetin alone caused a 29% decrease. Iressa at the high dose in combination with targetin reduced the cancer multiplicity by 82%, whereas the combination of the low dose of Iressa with targetin resulted in a 68% decrease (Fig. 6B).

Discussion
The EGFRs are a series of receptors that transfer signals from the extracellular environment and generally stimulate cell proliferation. These receptors are involved in carcinogenesis in a wide variety of organs (1, 2). Strong overexpression and amplification of HER2/Neu is associated with 25% of human breast cancers (3, 4). Strong overexpression of EGFR seems to be associated with some breast cancers, although it is more commonly expressed in cancers of the head and neck, lung, and colon (1, 2). The various EGFRs tend to form heterodimers with one another. Thus, even a cancer with obvious alterations in HER2/Neu may respond to inhibitors of EGFR. Iressa (a small molecule) is a competitive inhibitor for EGFR1 kinase activity (25). It has a $K_i$ in the low nanomolar range when used against purified EGFR1. In contrast, it has limited activity against Neu (EGFR2) or most of the better-characterized protein kinases. In the present experiments, the effect of Iressa as both a preventive and therapeutic agent was examined in a chemically induced model of ER$^+$ mammary cancer in rats. The effects of this agent on proliferation, apoptosis, and phosphorylation of the target molecule EGFR1 were also determined in small (<200 mg) palpable mammary tumors treated short-term with Iressa.

In the initial study, Iressa was tested at multiple doses. These doses were well within the human dose range when one considers the normal equivalency factor for rats, which is roughly six times the human dose on a mg/kg body weight basis. Thus, to achieve a human equivalent dose in rats would require dosing in the range of 20 to 40 mg/kg body weight per day. In the present study, Iressa was tested in a standard prevention protocol at multiple doses (10, 3, and 1 mg/kg body weight per day) and caused a 93%, 43%, and 20% decrease in tumor multiplicity, respectively. The middle dose, which was moderately effective, was considerably less than the comparable
human dose and raises the possibility that a significant preventive efficacy might be achieved with less than that required for therapy.

To evaluate the therapeutic activity of Iressa, rats received MNU and were treated with the agent when they developed the first palpable cancer. Iressa (10 mg/kg body weight per day) was highly effective, causing complete regressions of 7 of 10 treated tumors over the 5-week observation period. This finding agrees with our prior studies showing that agents (aromatase inhibitors, RXR agonists, and farnesyltransferase inhibitors) that are profoundly effective as preventive agents tend to be therapeutic as well in this model (18).

Using palpable MNU-induced mammary cancers, the effects of short-term exposure to Iressa (10, 3, or 1 mg/kg body weight per day) on tumor cell proliferation and apoptosis were examined. As can be seen in Fig. 3A and B, a dose-dependent effect was observed. The decrease in proliferation index was significant ($P < 0.05$) at all three doses of Iressa. At the highest dose, the effects on proliferation were relatively homogeneous (all proliferation indices were <1.5%), whereas at the lower doses responses were more variable. In contrast to the effects on proliferation, the two lower doses of Iressa did not significantly affect apoptosis. The highest dose of Iressa caused a significant increase in the apoptotic index of 3% ($P < 0.05$). We used proliferation and apoptotic indices as our initial end points because they are likely to be used in human trials and because they are relevant to a wide variety of agents. Our laboratories have previously shown with a series of RXR agonists (19), as well as with a much more diverse series of agents (18), that compounds that strongly decreased proliferation and increased apoptosis were highly significant preventive agents and tended to be therapeutic in this mammary cancer model. In fact, in a neoadjuvant setting examining stage I/II tumors that were ER$^+$ and EGFR$^+$, Polychronis et al. (8) showed that Iressa significantly decreased proliferation and caused >50% partial or complete responses during a 12-week treatment as a monotherapy. This clinical study had three important implications: (a) the use of these nonspecific biomarkers may be useful in identifying agents that are effective in early-stage cancer therapy and/or prevention; (b) the percentage of partial and complete responses in this subset of patients was much higher than one would have expected based on results in patients with advanced cancers, where <5% responded to Iressa; and (c) it was anticipated that Iressa would be considerably less effective than an aromatase inhibitor, given the profound efficacy of aromatase inhibitor, plus the chemotherapeutic drug paclitaxel showed greater efficacy in ER$^+$ tumors. This result was even more surprising because greater efficacy in ER$^-$ cancers was expected. Thus, the ER$^-$ Neu group may depend in part on forming heterodimers between Neu and the other EGFR receptors, whereas ER$^-$ cancers of the basal phenotype (ER$^-$/PR$^-$, and Neu$^-$) tend to overexpress EGFR (4). Furthermore, there was significant preventive activity with Iressa in a Neu-driven ER$^+$ model of breast cancer in mice (26). However, a recent study in advanced tumors with Iressa plus anastrozole (an aromatase inhibitor) in this subset of ER$^+$ tumors. This result was even more surprising because greater efficacy in ER$^-$ cancers was expected. Thus, the ER$^-$ Neu group may depend in part on forming heterodimers between Neu and the other EGFR receptors, whereas ER$^-$ cancers of the basal phenotype (ER$^-$/PR$^-$, and Neu$^-$) tend to overexpress EGFR (4). Furthermore, there was significant preventive activity with Iressa in a Neu-driven ER$^+$ model of breast cancer in mice (26). However, a recent study in advanced tumors with Iressa plus anastrozole (an aromatase inhibitor) in this subset of ER$^+$ tumors showed greater activity in ER$^+$ tumors (27). Thus, our strong efficacy in this ER$^+$ cancer model is not as surprising as might have been initially anticipated.
Another short-term variable that is indicative of efficacy is a decrease in expression of phosphorylated EGFR. This alteration confirms that the agent had reached its target molecule and achieved its primary function. Figure 4 shows that cancers treated with the high dose of Iressa exhibited lower levels of EGFR phosphorylation than control tumors. Although the efficacy of Iressa, or any EGFR inhibitor, is likely to be associated with inhibition of EGFR phosphorylation, such a decrease in phosphorylation seems to be insufficient to cause efficacy against all lesions (6).

Treatment with EGFR inhibitors is frequently associated with specific toxicities (primarily skin rash), which might limit their acceptability in a prevention setting (9). In an attempt to attenuate cumulative toxicity, we evaluated two regimens that limited total Iressa exposure. First, the use of intermittent dosing with Iressa was evaluated. Either a short-term intermittent (4 days on/3 days off) schedule or long-term intermittent (3 weeks on/3 weeks off) schedule was used (both of which could be used clinically). The intermittent schedules were not as effective as continuous treatment in decreasing tumor multiplicity (continual, 91%; short term, 68%; and long term, 24%). However, all three regimens decreased tumor weights >85%, which is indicative of a strong effect on tumor growth.

As an alternative strategy to potentially reduce toxicity, the effects of suboptimal doses of Iressa, together with a suboptimal dose of the RXR agonist targretin (16) or the aromatase inhibitor vorozole (15), were determined. Similar combination studies have been done previously (28). Combinations of Iressa with vorozole or targretin were more effective than either vorozole or targretin alone. Thus, these combinations of lower suboptimal doses seem promising. However, in an ER\(^+\) cancer, which is unlikely to respond to an aromatase inhibitor, the only effective agent would be Iressa.

For agents (e.g., aromatase inhibitors) in which effective doses are known in women, it may be difficult to use lower doses from an ethical standpoint. In a recent neoadjuvant study, the effects of anastrozole alone versus anastrozole plus Iressa were evaluated in all ER\(^+\) tumors (29). However, unlike the Polychronis et al. trial (8), tumors were not selected for EGFR expression at baseline. These studies showed similar efficacy of anastrozole alone and anastrozole plus Iressa, roughly 50% to 65% regressions during a 16-week interval. However, both anastrozole and Iressa were used at their standard full doses and the effects of anastrozole alone were quite striking. Thus, under these circumstances, it may not be possible to observe increased efficacy in this population.

In summary, these studies evaluated the effects of Iressa in the prevention and treatment of experimentally induced mammary cancers using several strategies to decrease total drug exposure. The experiments showed (a) a dose-dependent inhibition of mammary cancer formation; (b) that doses that were highly effective in prevention were also effective in a therapeutic setting; (c) that the effects of these agents on proliferation and apoptosis paralleled their effects on prevention and therapy; (d) that higher doses of Iressa were effective in targeting and decreasing phosphorylation of EGFR (Tyr\(^{1173}\)); (e) that the use of intermittent dosing (which may decrease the toxic effects of inhibitors) was effective in preventing cancers, although less so than continual treatment; and (f) that combining lower, less toxic, doses of Iressa with suboptimal doses of an aromatase inhibitor (vorozole) or a RXR agonist (targretin) was more effective than either agent alone.

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References


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