Induction of remission in a patient with metastatic breast cancer refractory to trastuzumab and chemotherapy following treatment with gefitinib ('Iressa', ZD1839)

Andreas Schneeweiss[a], Sema Kolay[a], Sebastian Aulmann[b], Gunter von Minckwitz[c], Julie Torode[d], Maria Koehler[e] and Gunther Bastert[a]

Despite new therapies and several treatment options, metastatic breast cancer (MBC) remains incurable. One reason for the low median survival rate may be intense cross-talk between growth factor receptors such as the epidermal growth factor receptor (EGFR/HER1) and the HER2 growth factor receptor. This report describes the case history of a patient with MBC whose disease had progressed despite surgery, radiotherapy and four different chemotherapy regimens, including trastuzumab (a monoclonal antibody that specifically blocks HER2) combined with docetaxel. However, treatment with 500 mg/day gefitinib ('Iressa', ZD1839), an EGFR tyrosine kinase inhibitor, and trastuzumab (2 mg/kg/week) caused a rapid and sustained regression of breast cancer metastases in skin and lymph nodes. Thus, for patients with MBC whose tumors co-express EGFR and HER2, gefitinib in combination with trastuzumab may prevent receptor cross-talk, improving the outcome of MBC. *Anti-Cancer Drugs* 15:235–238 © 2004 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2004, **15:**235–238

Keywords: gefitinib, metastatic breast cancer, trastuzumab

Departments of [a]Gynecology and Obstetrics, [b]Pathology, University of Heidelberg, Heidelberg, Germany, [c]Zentrum fur Frauenheilkunde und Geburtshilfe, Frankfurt, Germany, [d]AstraZeneca, Wedel, Germany and [e]AstraZeneca, Wilmington, DE, USA.

Conflicts of interest: A. S. has previously acted as a consultant and performed contract work for AstraZeneca; G. v. M. has acted as a consultant and received payment from AstraZeneca; J. T. and M. K. are employees of AstraZeneca; S. K., S. A. and G. B. have no conflicts of interest to declare.

Correspondence to: A. Schneeweiss, Department of Gynecology and Obstetrics, University of Heidelberg, Voßstraße 9, 69115 Heidelberg, Germany.
Tel: +49 6221 5635552; fax: +49 6221 567920;
e-mail: andreas_schneeweiss@med.uni-heidelberg.de

Received 10 November 2003 **Accepted** 24 November 2003

Introduction

Unlike early-stage breast cancer, metastatic breast cancer (MBC) is incurable. Despite new therapies and several treatment options (surgery, chemotherapy, hormonal therapy, radiotherapy), only 50–70% of patients respond, with a median survival of 18–24 months [1]. One explanation for the low median survival rate in patients with MBC may be the intense cross-talk between growth-factor-driven signal-transduction pathways [2]. In this situation, blockade of one growth factor receptor may only partially inhibit the signaling pathways involved in the proliferation and survival of breast cancer cells. Two agents that target the epidermal growth factor receptor (EGFR/HER1) and HER2 growth factor receptor in breast cancer have been developed: gefitinib ('Iressa', ZD1839) and trastuzumab. Gefitinib, an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI), has shown antitumor activity against a range of human tumor types *in vitro* and *in vivo* [3], and is currently being examined in phase II and III clinical trials in a range of solid tumors. Trastuzumab is a monoclonal antibody that specifically blocks HER2, and that has been shown to improve response and survival in MBC patients with HER2 overexpression [4]. In preclinical studies, exposure of human breast cancer cells to a combination of gefitinib and trastuzumab resulted in synergistic antitumor effects [2], possibly because HER2 is the preferred heterodimer of the EGFR (Fig. 1) [5]. This indicates that, in a clinical setting, a combination of the two drugs may result in improved outcome. Indeed, this report documents the first clinical evidence of improved outcome in a patient with MBC treated with a combination of gefitinib and trastuzumab.

Case report

In August 2000, a 62-year-old woman was diagnosed with a ductal invasive adenocarcinoma of the left breast (stage pT3 pN2 M0 G3 R0 L1) expressing high levels of HER2 (3+ by immunohistochemistry; Herceptest; Dako, Glostrup, Denmark); hormone (estrogen and progesterone) receptors were undetectable. After modified radical mastectomy of the left breast, the patient received adjuvant chemotherapy with four 3-weekly cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2). This was followed by irradiation of the left thoracic wall with 54 Gy, and of the left axillary and supraclavicular lymph nodes with 50 Gy. During radiotherapy, the patient developed a presternal locoregional relapse; this completely regressed during additional irradiation to the presternal region with 54 Gy followed by four 3-weekly cycles of paclitaxel (175 mg/m^2).

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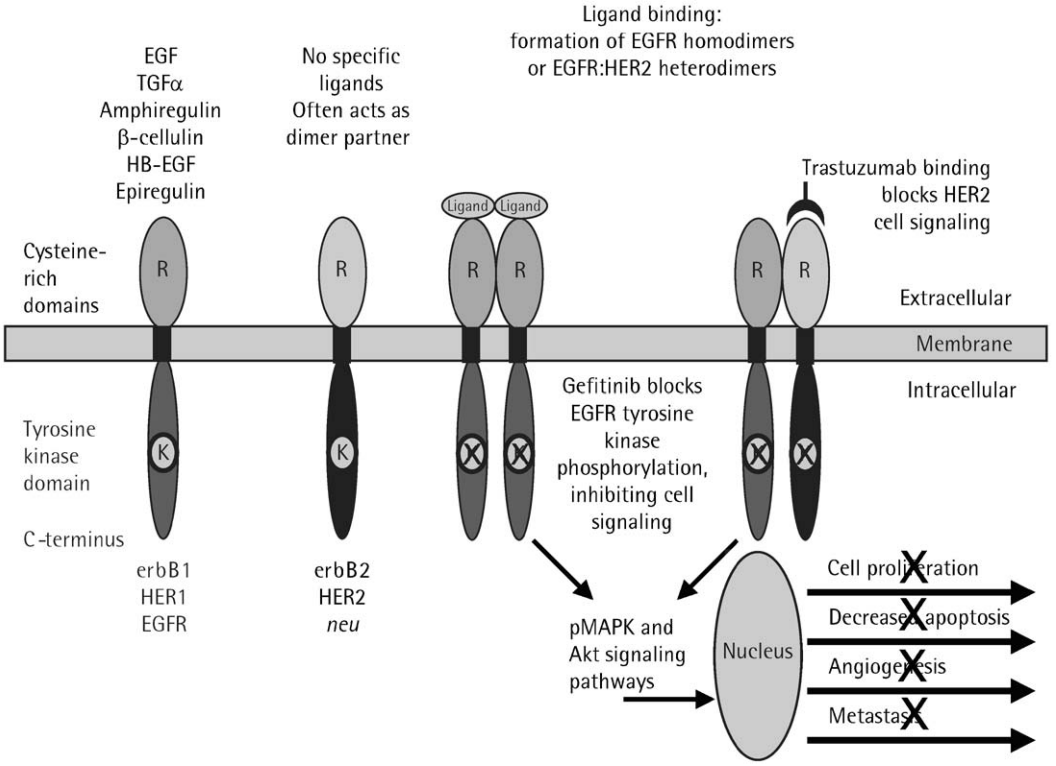
Fig. 1



Dimerization of the EGF and HER2 receptors. HB-EGF=heparin-binding EGF; K=kinase; pMAPK=phosphorylated mitogen-activated protein kinase; R=receptor; TGFα=transforming growth factor-α.

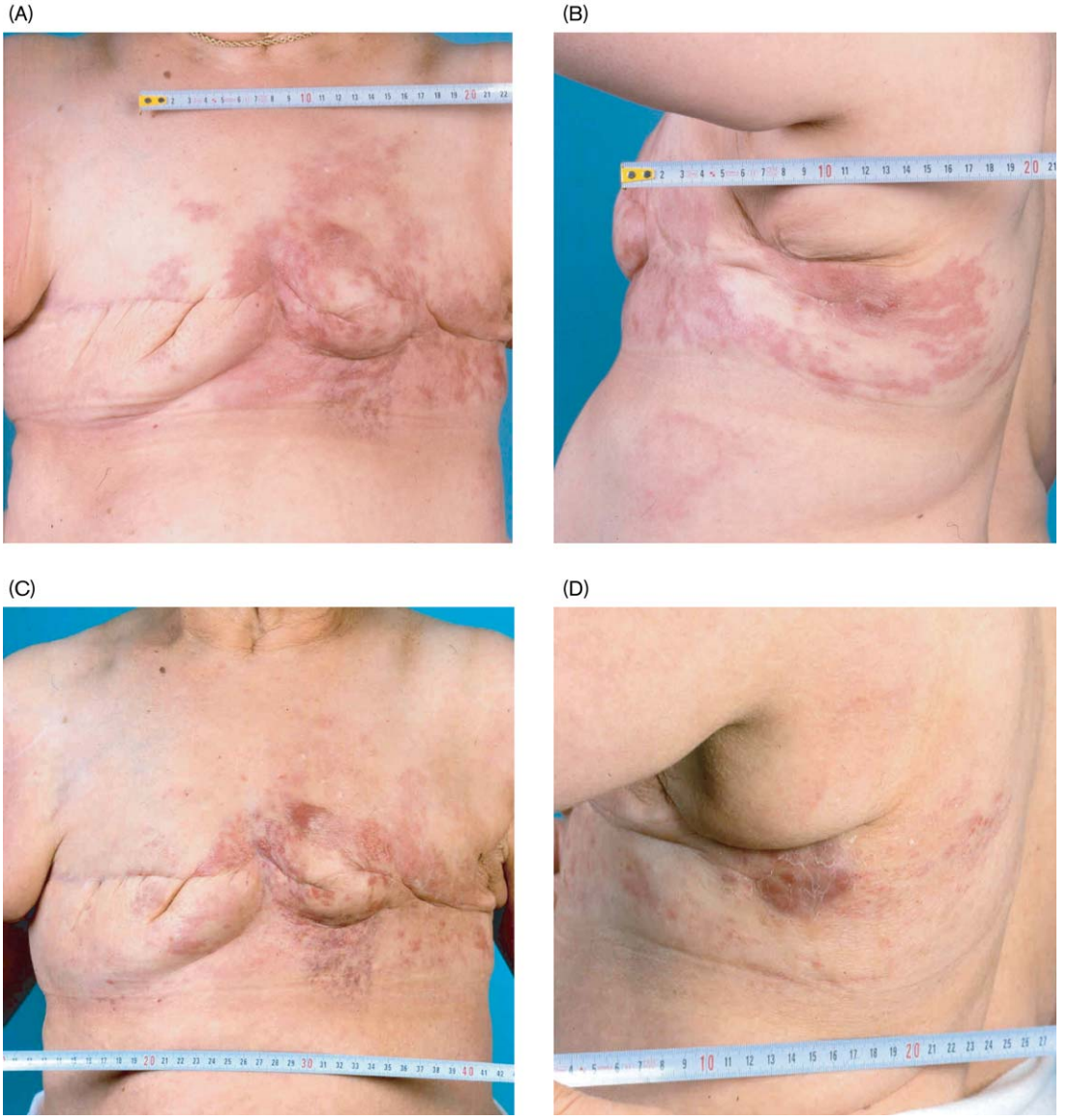
Bone, ipsilateral lymph node and skin metastases of the thoracic wall developed in August 2001. After radiotherapy of painful pelvic and lumbar bone lesions with 38 Gy, combination therapy of monthly pamidronate (90 mg) along with weekly trastuzumab (loading dose 4 mg/kg followed by 2 mg/kg) and vinorelbine (25 mg/m^2) was initiated. In February 2002, while still receiving pamidronate, trastuzumab and vinorelbine, the patient developed a contralateral inflammatory cancer of the right breast (stage pT4d pN2 G3 L1); 100% of cells expressed HER2/neu (3+ by immunohistochemistry) and 20% of cells expressed EGFR (3+ by immunohistochemistry using a commercial test kit; clone G100; Zymed, San Francisco, CA); cells were negative for hormone receptor. Modified radical mastectomy of the right breast was performed, and pamidronate and trastuzumab treatment continued. In addition, a weekly docetaxel regimen (35 mg/m^2) was initiated.

In August 2002, while still receiving pamidronate, trastuzumab and docetaxel, the patient developed supraclavicular lymph node metastases and the left thoracic lesions progressed (Fig. 2A and B, respectively). Docetaxel was stopped and, as the patient was now eligible to enter a gefitinib monotherapy trial (eligible patients must have progressed under taxane and anthracycline therapy, and have had at least one chemotherapy regimen for advanced breast cancer), she began to receive 500 mg/day oral gefitinib. No side-effects other than grade 1 skin rash and diarrhea (both of which resolved) occurred. Unknown to study staff at the time of enrollment into the study, the patient continued to receive weekly trastuzumab as an outpatient. Although this combination was not part of the protocol, AstraZeneca (the trial sponsor) allowed her to continue receiving gefitinib as she was responding to the drug combination. Within 3 months, cervical lymph nodes and skin lesions had substantially regressed (Fig. 2C and D, respectively). However, 1 month later she developed dizziness and brain metastases were detected by computed tomography (CT) scan. Although skin lesions and lymph nodes remained in remission, the patient died within 7 weeks, despite cranial irradiation.

Discussion

We have reported the case history of a patient with MBC whose disease progressed despite surgery, radiotherapy and four different chemotherapy regimens. The combination of trastuzumab with docetaxel was unable to prevent disease progression, which presented as skin and lymph node metastases. However, following entry into

Fig. 2



Development of (A) supraclavicular lymph node metastases and (B) left thoracic skin lesions, and regression of (C) cervical lymph node metastases and (D) left thoracic skin lesions.

a gefitinib trial, a rapid and sustained regression of breast cancer metastases in skin and lymph nodes was achieved by the combination of gefitinib and trastuzumab. Despite continued remission of breast cancer metastases, the patient died from brain metastases shortly afterwards.

Clinical trials have shown both trastuzumab and gefitinib to be effective against breast cancer; trastuzumab increased median survival significantly in patients with MBC, both alone and in combination with paclitaxel [4,6], and gefitinib has shown antitumor activity in 12 of 22 patients with breast cancer [7], with further gefitinib studies being conducted in patients with MBC [8]. For our patient, it is possible that remission was due to gefitinib, as she had received trastuzumab for over 1 year without disease control, and yet within 3 months of gefitinib treatment lymph node and skin lesions had substantially regressed. It is likely, therefore, that the combination of gefitinib and trastuzumab aided regression, although this cannot be shown conclusively.

The mechanism of action of the interaction between gefitinib and trastuzumab remains unclear. Co-expression of different EGF-like peptides and/or EGFR in human breast cancer cells indicates that a network consisting of multiple ligands and receptor molecules may be able to

sustain the autonomous proliferation and survival of human breast carcinoma cells [9–11]. If so, simultaneous blockade of different growth-factor-driven signal-transduction pathways may result in a more significant antitumor effect. Although HER2-overexpressing tumor cells are susceptible to gefitinib [12], in those breast cancers that express EGFR and HER2 receptor heterodimers, signaling could occur in the presence of either gefitinib or trastuzumab alone (Fig. 1). Therefore, by combining gefitinib and trastuzumab, the problem of EGFR/HER2 dimerization may be avoided, potentially increasing the clinical benefit in MBC patients.

Disease progression to the brain and central nervous system is not uncommon in patients with MBC and, while trastuzumab is unable to cross the blood–brain barrier, there is little clinical evidence regarding the efficacy of gefitinib against intracerebral tumors. Two phase II trials in patients with malignant gliomas have now seen disease control using gefitinib [13,14], supporting the preclinical animal studies that observed antitumor activity against intracerebral tumors using gefitinib [15]. In addition, two cases have reported activity against brain metastases using gefitinib, and both received gefitinib as part of a compassionate-use program [16,17]. A male patient with carcinomatous meningitis (which has a very poor prognosis) who had been diagnosed 18 months previously with non-small-cell lung cancer and brain metastases, had chest CT scans and magnetic resonance imaging of the brain that showed tumor shrinkage of lung and brain lesions within 5 months of gefitinib therapy, although he died 6 months later [16]. Regression of brain metastases was seen after 5 months of gefitinib therapy in a female patient who was hospitalized, bedridden and disabled due to metastatic brain lesions from a lung adenocarcinoma primary; she is now active and continues to have stable disease [17]. Therefore, while the combination of trastuzumab and gefitinib was able to control lymph node and skin metastases in our patient, it was unable to control brain metastases, perhaps due to the inability of trastuzumab to cross the blood–brain barrier.

In conclusion, the case report presented here has provided a strong rationale for combination therapy using gefitinib and trastuzumab in patients with MBC whose tumors co-express EGFR and HER2. Further evaluation within the context of a clinical trial is required.

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