Combined paclitaxel and cetuximab achieved a major response on the skin metastases of a patient with epidermal growth factor receptor-positive, estrogen receptor-negative, progesterone receptor-negative and human epidermal growth factor receptor-2-negative (triple-negative) breast cancer

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The epidermal growth factor receptor, a transmembrane receptor tyrosine kinase of the erbB family, is expressed in 15–30% of all breast cancers. Anti-epidermal growth factor receptor agent cetuximab is an IgG1 chimeric monoclonal antibody with a potent antitumor activity. Cetuximab competes with ligand binding to the epidermal growth factor receptor ectodomain, resulting in an efficient blockade of tumor-promoting downstream signaling pathways. Large clinical studies recently demonstrated cetuximab synergy with radiotherapy and chemotherapy agent irinotecan. Studies in human breast cancer xenografts showed cetuximab synergy with paclitaxel, a potent mitosis spindle-cell stabilizer. In this report, combined paclitaxel and cetuximab achieved a major reduction of the skin metastases of a heavily pretreated patient with epidermal growth factor receptor-positive, estrogen receptor-negative, progesterone receptor-negative and human epidermal growth factor receptor-2-negative (triple-negative) invasive ductal breast carcinoma. Treatment was well-tolerated overall and response was not correlated with the appearance of major cetuximab-induced acneiform rash. *Anti-Cancer Drugs* 18:835–837

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Introduction

The identification of specific cell membrane growth factor receptors as well as their various downstream signaling pathways and the recent knowledge of the key role they play, when abnormally activated, in carcinogenesis have led to the development of a new generation of anticancer drugs called anti-epidermal growth factor receptor (anti-EGFR) agents. These novel agents used alone or in combination with standard chemotherapy or radiotherapy have achieved major improvements in the response rates and survival of patients with advanced colorectal, lung, and head and neck carcinomas [1–4].

Studies *in vitro* and in human breast cancer xenografts have shown additive or synergistic activity between cetuximab, a chimeric monoclonal EGFR antibody, and paclitaxel, a potent mitosis spindle-cell stabilizer [5–8].

In this case report, cetuximab was administered in combination with paclitaxel in an EGFR-positive advanced breast cancer patient with refractory skin metastases.

Case report

A 62-year-old woman from Madagascar sought oncologic care because of worsening breast cancer skin metastases. Her invasive ductal carcinoma was diagnosed 3 years before, was staged pT2, pN1a, M0, according to the revised TNM classification [9], and was initially treated with mastectomy followed with adjuvant anthracyclin-based chemotherapy and radiotherapy. The tumor had a histologic grade of III according to Elston–Ellis classification [10] and did not express estrogen (ER) or progesterone (PR) receptors. No amplification of human epidermal growth factor receptor-2 (HER-2) was found on fluorescent in-situ hybridization analysis. A follow-up was installed, and a year later, her neoplasia relapsed to the pectoral and lumbar skin. Immunohistochemical analysis of skin biopsies showed that metastatic breast cancer cells were HER-2-negative, ER-negative

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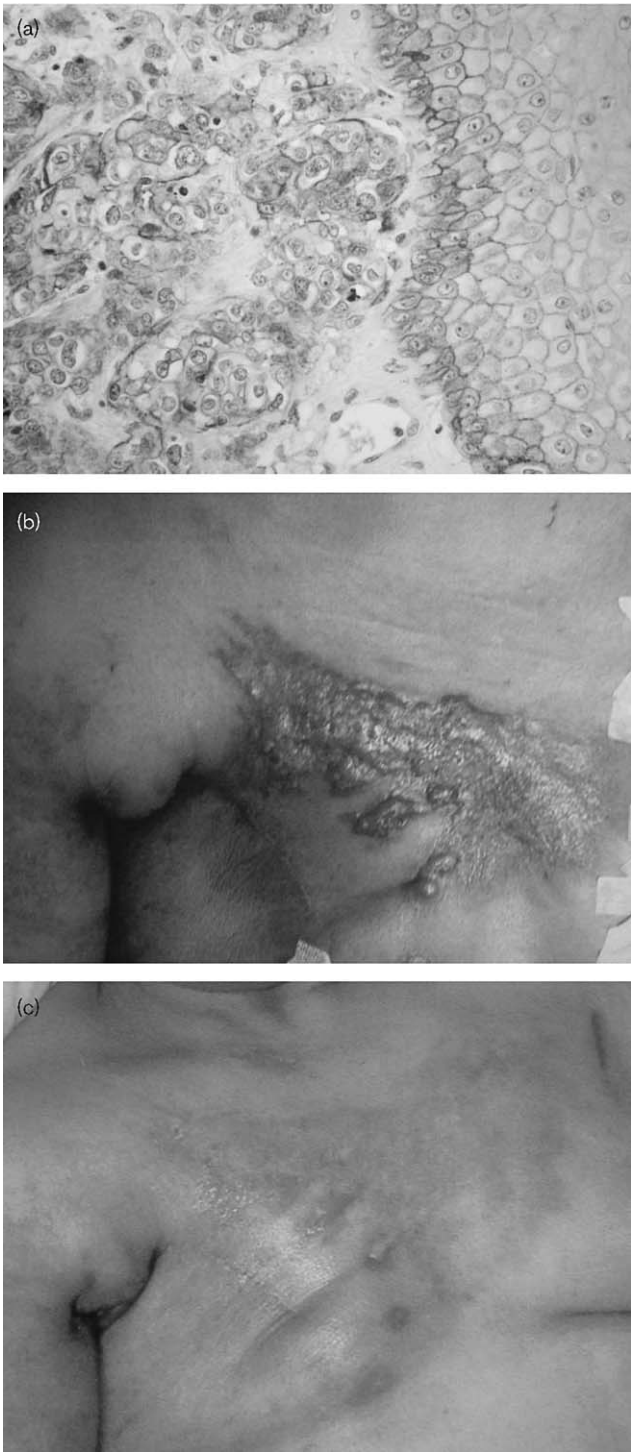
and PR-negative, and EGFR-positive with marked membranous staining (intensity 3+) of cancer cells (Fig. 1a). A thoracic and abdominal computed tomography (CT) scan, and bone scintigraphy ruled out other metastatic sites. Chemotherapy with miltefosine was locally applied, with no clinical response. Three other chemotherapy lines consisting on weekly docetaxel, vinorelbin + fluorouracil administered at 3-week intervals, and weekly paclitaxel and carboplatin were then undertaken, with no response on skin metastases. A fifth chemotherapy line combining weekly paclitaxel at the dose of 80 mg/m^2 and cetuximab at the initial dose of 400 mg/m^2 followed with weekly doses of 250 mg/m^2 was administered. After six courses, there was a major improvement of infiltrating skin metastases (Fig. 1b and c). The only grade 3 or 4 toxicity consisted of a grade 3 nonfebrile neutropenia. A grade 1 facial acneiform rash was noticed. No organ metastases were detected at a subsequent imaging workup after six courses. Treatment was discontinued after a total of 12 courses because of a persistent grade 3 fatigue, with a Karnofsky score of 50%. The patient decided then to return to her native country and was lost to follow-up.

Discussion

The 170-kDa EGFR is one of four members of the erbB family of transmembrane cell receptor tyrosine kinases. EGFR triggers downstream multilayered signaling pathways including the mitogen-activated protein kinase pathway, the phosphatidylinositol-3-kinase/Akt pathway and the Jak/Stat pathway [11]. These pathways, when abnormally activated in malignant cells, result in increased cancer cell proliferation, reduced apoptosis, and enhanced invasion and angiogenesis potentials [6,11]. EGFR is expressed in 15–30% of all breast cancers and in 20–40% of those with HER-2 overexpression [12–14]. EGFR expression is histologically defined as strong membranous staining in more than 10% of tumor cells. Anti-EGFR agent cetuximab is a chimeric IgG1 monoclonal antibody currently approved for the treatment of irinotecan-refractory metastatic colorectal cancer and for that of head and neck squamous-cell carcinoma in association with radiotherapy [1,3]. Cetuximab inhibits ligand-dependent activation of the EGFR, resulting in an aborted dimerization with other erbB receptors, and subsequently, EGFR internalization and inhibition of downstream signaling pathways [11]. Cetuximab can also elicit antitumor activity by antibody-dependant cell cytotoxicity [15]. Paclitaxel prevents cell replication by stabilizing microtubule bundles during mitosis [16]. The most likely hypothesis for the enhanced antitumor activity of combined cetuximab + paclitaxel is an increase in cancer cell apoptosis coupled with a decrease in cell proliferation [7]. Studies on cancer cell cultures and in human tumor xenografts showed that paclitaxel upregulates EGFR and HER-2 receptors, and renders cancer

Fig. 1



(a) Immunohistochemical detection of epidermal growth factor receptor expression on cutaneous breast cancer metastases. Note membranous staining of tumor cells and normal keratinocytes (intensity 3+) with anti-epidermal growth factor receptor antibody (clone 31G7; Zymed Laboratories, San Francisco, California, USA). (b) Cutaneous breast cancer metastases before treatment with weekly paclitaxel and cetuximab (c) Cutaneous breast cancer metastases after six courses of weekly paclitaxel and cetuximab.

cells more susceptible to cetuximab and trastuzumab, respectively [8,17].

Cetuximab has been shown to circumvent tumor resistance to chemotherapy agent irinotecan in some colorectal cancer patients [1]. Mechanisms such as drug efflux abrogation, apoptosis restoration and impairment of DNA-repair activity in cancer cells have been proposed to explain this phenomenon [1,18–20]. In our report, the patient was refractory to paclitaxel + carboplatin, administered as fourth-line chemotherapy. Tumor cell recovery of paclitaxel chemosensitivity when combined with cetuximab is another possible hypothesis for the observed activity, which needs to be verified in further studies.

In breast cancer, although clinical trials demonstrated high activity of the anti-HER-2 agent trastuzumab in HER-2-overexpressing neoplasia [21], targeted therapies against EGFR have to date been quite disappointing [22,23]. The patient presented in our report had an ER-negative, PR-negative and HER-2-negative (triple-negative) invasive ductal carcinoma. Recent studies show that this particular immunophenotype is associated with EGFR expression in more than two-thirds of cases, and exhibits a high histological grade and a high proliferation rate [24]. It corresponds to the basal-like subtype on DNA microarray profiling studies [25]. This specific subgroup that does not qualify for hormonotherapy nor for trastuzumab deserves to be challenged with anti-EGFR agents, as suggested by our results.

In conclusion, this report shows that cetuximab in association with paclitaxel achieved high clinical response on the skin metastases of a heavily pretreated ER-negative, PR-negative and HER-2-negative (triple-negative), EGFR-positive breast cancer patient. Treatment was well-tolerated overall and response was not correlated with the appearance of major cetuximab-induced acneiform rash.

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