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Trastuzumab in Primary Inflammatory Breast Cancer (IBC): High Pathological Response Rates and Improved Outcome

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Abstract

Inflammatory breast cancer (IBC) represents a rare but aggressive and lethal form of locally advanced breast cancer (LABC) and frequently with HER-2 neu overexpressed or amplified. We retrospectively identified 16 newly diagnosed HER-2/neu-positive IBC patients who were treated with preoperative trastuzumab. We determined the pathological complete response rate (pCR) when trastuzumab was added to preoperative chemotherapy in patients with HER2/neupositive IBC. Furthermore, we assessed the expression of CXCR4 in metastatic recurrence sites. Ten patients (62.5%) achieved a pCR. Six patients (37.5%) achieved a partial response. Median follow-up of all patients was 24.2 months. Four (25%) patients have experienced a progression, of which three were in the brain. Two-year progression-free survival was 59.4% (95% CI 35–100). High expression of CXCR4 was detected in the brain metastases. We conclude that in spite of high pCR rates among women with HER-2/neu-positive IBC treated with neoadjuvant trastuzumab-based regimens the outcome remains dismal and brain recurrences are frequent. CXCR4 may represent a novel therapeutic target.

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Keywords

CXCR4; inflammatory breast cancer; trastuzumab

Inflammatory breast cancer (IBC) represents a rare but aggressive and lethal form of locally advanced breast cancer (LABC) (1). Despite the introduction of anthracycline-based polychemotherapy regimens, which has significantly improved the survival of women with early stage breast cancer (2), the prognosis of patients diagnosed with IBC remains poor, with 15-year survival rates ranging from 20% to 30% (3,4).

Previous phase II trial (5,6) demonstrated pathological complete response (pCR) rates of 60% when patients with early stage operable, HER-2/neu-positive breast cancer received preoperative chemotherapy. We thus hypothesized that the incorporation of trastuzumab into preoperative treatment regimens of patients with IBC would produce similarly high pCR rates and would change the prognosis of patients with HER-2/neu-positive IBC.

The peculiar distribution of metastases in various cancers was first recognized in 1889 by Paget (7) and called the “seed and soil” hypothesis, essentially indicating that different organs provide growth conditions optimized for specific cancers. CXCR4, is the most common chemokine receptor expressed in human cancer cells and shown to be involved in migration and / or survival of a variety of tumor cells (8–10). As the cohort of our present study was restricted to patients with HER-2/neu positive IBC, and HER-2/neu may play a supportive role for this chemokine receptor we hypothesized that the SDF-1/CXCR4 axis may determine the pattern of metastases in this population.

PATIENTS AND METHODS

Patient Population

After obtaining institutional review board approval, we used a prospectively maintained data base in the Department of Breast Medical Oncology of the MDACC to identify newly diagnosed, HER-2/neu-positive, treatment-naive IBC. A clinical diagnosis of IBC required the presence of diffuse erythema, heat, ridging, or peau d’orange (corresponding to T4d) utilizing 2002 American Joint Committee on Cancer (AJCC) staging guidelines (11). All patients included in the analysis had to have received preoperative chemotherapy and trastuzumab, have undergone breast surgery for subsequent assessment of pathological response. Variables recorded included patient demographics, stage of the disease, hormone receptor status, type of preoperative chemotherapy, pathological response to chemotherapy, time to progression/recurrence and site of failure.

Pathology Review of Pre- and Postoperative Specimens

Pre- and postoperative breast and / or axillary lymph node specimens were reviewed. Histological grade of preoperative tumor specimens was based on the modified Black’s nuclear grading system (12). Hormone receptor status was assessed using immunohistochemical staining (IHC). This was carried out using the modified avidin–biotin complex method in a DAKO autostainer (DAKO, Carpinteria, CA) with primary antibodies

targeted against the estrogen receptor (ER, clone: 6F11; Novocastra, Newcastle upon Tyne, UK, 1:50) and the progesterone receptor (PgR Ab-9, clone: 1A6; Neomarker/Labvision Corporation, Fremont, CA, 1:30). HER-2/neu status was assessed either by IHC or by determination of gene amplification using fluorescence in situ hybridization technique (FISH).

Immunohistochemical Analysis of CXCR4

When possible, metastatic lesions that developed subsequent to primary breast tumor treatment were biopsied and / or excised and assessed for CXCR4. Assessment was performed with IHC avidin–biotin complex method using 4-μm paraffin embedded specimens with primary antibodies targeted against CXCR4 (4417.111, IgG_{2b}; R&D Systems, Minneapolis, MN, 1:150 dilution) (13). Intensity of staining was scored as low, moderate or high (>50% tumor cells) compared to background staining.

Definitions and Statistical Analysis

Patient and disease characteristics were tabulated or described by their median and range. Pathological complete response was defined as the absence of any residual invasive cancer in the breast and axilla. Progression-free survival (PFS) was measured from the start of treatment to the date of disease recurrence or last follow-up. Overall survival (OS) was measured from the start of treatment to the date of death from any cause or to the date of the most recent follow-up.

RESULTS

Patient Characteristics

Between September 2001 and October 2006, 16 patients who were treated with trastuzumab as part of their preoperative chemotherapy regimen were identified. Median age at presentation was 51 years (range 30–63 years). Fourteen (87.5%) patients had ER-negative disease. Three patients (19%) had stage IV disease at presentation. Seven (44%) patients received paclitaxel (80 mg/m^2) administered weekly for 12 weeks followed by FEC_{75} (fluorouracil 500 mg/m^2 i.v, epirubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2) administered every 3 weeks for four cycles with trastuzumab given on a weekly schedule throughout. Five (31%) patients received TCH (Docetaxel 75 mg/m^2, Carboplatin, Trastuzumab) every 3 weeks for six cycles. Two (12.5%) patients received AC (Adriamycin 60 mg/m^2, Cyclophosphomide 600 mg/m^2) every 3 weeks for four cycles followed by paclitaxel (80 mg/m^2), and trastuzumab weekly for 12 weeks. Two (12.5%) patients received other anthracycline combinations of chemotherapy that incorpoated weekly trastuzumab. All patients received trastuzumab on a weekly schedule administered as a loading dose of 4 mg/kg i.v over 90 minutes on the first day and subsequently given weekly at a dose of 2 mg/kg over 30 minutes. An average of 20 weeks of trastuzumab was administered preoperatively. Following chemotherapy, all patients underwent a modified radical mastectomy followed by chest wall radiation therapy and hormonal therapy as directed by tumor hormonal receptor status.

An objective response was observed in all patients (100%) followed by mastectomy, including the three patients with metastatic disease at presentation. Ten patients (62.5%, 95% CI 35.4–84.8) achieved a pCR of whom two had stage IV disease at presentation. Six patients (37.5%, 95% CI 15.2–64.6) achieved a partial response. The three patients who presented with stage IV disease at presentation did not have any radiologic evidence (which had been documented at baseline by CT scanning) of distant metastases at the end of preoperative chemotherapy.

Survival Estimates

Median follow-up of all patients was 24.2 months (range 6.4–61.6 months). Four patients (25%) have experienced disease progression. At the time of this analysis the median PFS has not been attained. Of the four patients who progressed, three had stage III disease (of whom two had achieved a pCR) and one had stage IV disease at presentation (who did not achieve a pCR). Three patients (13%) progressed in the brain with symptomatic disease. Two patients had concomitant evidence of local-regional recurrence. The 2-year PFS was 59.4% (95% CI 35–100). Of the four patients who experienced disease progression, one has died. At the time of this analysis six (38%) patients have completed 1 year of trastuzumab.

CXCR4 – Staining of Metastatic Lesions

Of the four patients with evidence of progression, biopsy specimens of metastatic lesions for CXCR4 assessment were available for three patients. Two patients had biopsy samples from recurrent chest wall lesions that had negative and moderate staining for CXCR4. The third patient had a resected metastatic brain lesion that exhibited strong staining for CXCR4.

DISCUSSION

This represents the first report on the clinical activity and long-term outcome of trastuzumab-based regimens in IBC. The retrospective study confirmed the significant increase in pCR compared to historical controls in the subset of patients with HER-2/neu-amplified disease. Moreover, we demonstrated that this cohort of patients continues to have a risk of recurrence in the chest wall and, relatively early recurrence in the brain in spite of high pCR. These data suggest that IBC patients treated with preoperative, trastuzumab-based regimens may need additional postoperative treatment modalities to significantly modify long-term outcome.

The goal of improving pCR in IBC requires the introduction of HER2 targeted therapies in neoadjuvant setting. Few prospective clinical trials among patients with HER-2/neu-positive disease where trastuzumab was incorporated into preoperative chemotherapy regimens, have reported pCR rates ranging from 12% to 23% (14–16). Hurley *et al.* (14) achieved a pCR rate of 17% in a cohort of 48 patients with HER-2/neu-positive LABC (including four patients with IBC) who received 12 weeks of preoperative treatment with a combination of docetaxel, cisplatin and trastuzumab. The largest experience was reported by Baselga *et al.* (16) with the preliminary data of the NOAH (Neoadjuvant Herceptin) phase III trial evaluating the addition of trastuzumab in the neoadjuvant treatment of LABC, including IBC. They observed a significant improvement of pCR rate (54.8% versus 19.3%, with and

without trastuzumab, respectively, p = 0.002) in 31 HER-2 positive IBC patients treated with three cycles of neoadjuvant doxorubicin-paclitaxel (AT), four cycles of paclitaxel and three cycles of cyclophosphamide/methotrexate/5-fluorouracil (CMF).

Another important preliminary observation, to be confirmed in larger series, is the role of chemokines, particularly how the CXCR4/SDF1 axis can contribute to the homing of breast cancer cells to the brain. It has been recently suggested that expression of CXCR4 could be regulated by HER-2/neu by increasing the expression of CXCR4, which is required for HER-2/neu-mediated invasion in vitro and lung and brain metastases in vivo (17).

In conclusion, trastuzumab-based regimens are extremely active and well tolerated in patients with newly diagnosed IBC. Despite initial response, early recurrence continues to be a reality with biology of disease probably implicated in distant failure involving the brain. The use of combined adjuvant modalities with agents able to affect the metastatic process or the use of novel HER-2 targeted therapies with tyrosine-kinase inhibitors such as lapatinib may represent a rational approach to further improve the prognosis of patients with IBC (18,19).

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