ORIGINAL ARTICLE ◄

Neoadjuvant Platinum Containing Regimen for Locally Advanced Triple Negative Breast Cancer

E. Ibrahim, MD[1]; M. Rahal, MD[1]; H. Halawani, MD[1]; A. Al Faraj, MD[1]; H. Ramadan, MD[1]; A. Arini, MD[2]; H. Mosleh, MD[3], N. AlNaimy, MD[4]

(1) Oncology, King Fahad Specialist Hospital, Dammam, Saudi Arabia.
(2) Surgery, King Fahad Specialist Hospital, Dammam, Saudi Arabia.
(3) Pathology, King Fahad Specialist Hospital, Dammam, Saudi Arabia.
(4) Radiology, King Fahad Specialist Hospital, Dammam, Saudi Arabia.

✉ *Corresponding Author: Dr. Ehab Ibrahim, MD*
E-mail: ehabhas@hotmail.com

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Background: Primary systemic chemotherapy is a standard approach to treating women with locally advanced breast cancers, with higher survival rates reported among patients who attain a pathological complete response. Triple negative breast cancer is a special biological entity that remains major challenge to oncologist. Around 12%-20% of breast cancers are triple negative. The current single arm phase II trial was conducted to evaluate the pathological complete response (pCR), efficacy and safety of anthracycline-taxane-cisplatinum containing regimen as neoadjuvant chemotherapy in locally advanced triple negative breast cancer.

Methods: This study is a single arm phase II trial was conducted on eighteen women with stage III triple negative breast cancer who were recruited between July 2007 and February 2010 at King Fahad Specialist Hospital-Dammam, Saudi Arabia. Neoadjuvant chemotherapy consisting of 4 cycles of AC or FEC 100, followed by 4 cycles consisted of docetaxel-cisplatin (75mg/m2 each) every 3 weeks. Primary end point was pathological complete response.

Results: This is a preliminary report on the first eighteen patients included. Median age: 49 y (24-70); premenopausal: 16 ; 25% were below 35 years of age; Median tumor size : 9 cm (3.5-19); Grade III: 15 ; Stage IIIA: 3, IIIB:14, IIIC:1; all but 2 had positive nodes at diagnosis (89%) . All patients completed the anthracycline part with 2 episodes of febrile neutropenia (F.N). Only 10 patients completed all 4 cycles of the second sequence with Docetaxel-Cisplatin; 4 completed 3 cycles. Toxicity related to Docetaxel - Cisplatin: febrile neutropenia: 4; renal impairment: 2; Hypersensitivity reaction: 1. No grade 5 toxicity. Clinical evaluation of response by RECIST criteria pre surgery: Overall response: 16/18 (88.9%), Complete response: 9 (50%); Partial response: 7 (38.9%).The second sequence with Docetaxel-Cisplatin doubled the rate of clinical CR obtained with AC /FEC. Two patients were not operated due to disease progression. Pathological assessment, revealed that 8 (47%) patients had no residual invasive carcinoma in the breast; 3 (18%) had residual occasional scattered tumor cells less than 5 mm (pT1a); 10 (59 %) had negative nodes; 8 achieved CpR and 2 nCpR. Baseline Ki 67 levels for patients with residual invasive component is under evaluation.

Conclusion: This anthracycline-taxane-cisplatin based neoadjuvant chemotherapy regimen was well tolerated and achieved a high rate of pCR/ npCR.

The authors have declared no conflicts of interest.

Introduction

Breast cancer is increasingly recognized as a heterogeneous disease exhibiting substantial differences with regard to biological behavior and requiring distinct therapeutic interventions (1). Steroid hormone receptors, such as estrogen receptor (ER) and progesterone receptor (PR), and the oncogene ErbB-2/ human epidermal growth factor receptor 2 (HER-2) are important factors in distinguishing breast cancer subtypes. In recent years, the term triple negative breast cancer has emerged to describe those cancers which do not express estrogen receptors(ER), progesterone receptors (PR) or over express human epidermal growth factor receptor 2 (Her2) (2). Triple negative breast cancer remains major challenge to Oncologists, and a source of great interest to laboratory investigators. Around 12%-20% of breast cancers are triple negative. Treatment options for triple negative breast cancers are limited because of lack of targeted treatment. Primary systemic chemotherapy is a standard approach to treating women with locally advanced breast cancers, with higher survival rates reported among patients who attain a pathological complete response. Pathological complete response (pCR) provides a surrogate for disease-free and overall survival (3).

BRCA1 plays a central role in repair of double-stranded DNA breaks; a lack of BRCA1 therefore results in genomic instability thereby predisposing to the development of malignant disease. Triple negative breast cancer phenotype is particularly associated with BRCA1 mutations (4). Similarly, about three-quarters of BRCA1- related Breast cancers exhibit a basal phenotype by gene expression microarray (5) or immunohistochemistry (6), particularly among younger patients and patients with a family history of breast cancer who very often also present with p53 mutations. The association of TNBC with BRCA1 mutations and dysfunctional DNA repair may indicate an increased sensitivity toward DNA-damaging agents, i.e. platinum agents. A recent preclinical study demonstrated that over expression of p63 (a p53-related transcription factor) and p73 (p53 associated as well) is common among TN cases and associated with sensitivity to cisplatin (7). Clinical data regarding the use of platinum agents in TNBC are still limited.

The current phase II study was conducted to evaluate the pathological complete response (pCR), efficacy and safety of an anthracycline-taxane-cisplatinum containing regimen as neoadjuvant chemotherapy in locally advanced triple negative breast cancer. All patients provided written consent.

Patients and methods

This single arm phase II study was conducted on eighteen women with stage III triple negative breast cancer who were recruited between July 2007 and February 2010 at King Fahad Specialist Hospital-Dammam, Saudi Arabia. Neoadjuvant chemotherapy consisting of 4 cycles of AC or FEC 100, followed by 4 cycles consisted of docetaxel-cisplatin (75mg/m2 each) every 3 weeks. Primary end point was pathological complete response.

Eligibility criteria:

Patients with clinical stage III (A,B,C) locally advanced triple negative breast cancer histologically confirmed by surgical biopsy or core needle biopsy were included. Patients with age >18, Eastern Cooperation Oncology Group (ECOG) performance status ≤ 2, life expectancy > 12 months, with adequate bone marrow reserve, adequate liver and renal function were eligible.

Exclusion criteria included prior chemotherapy or radiotherapy, clinically significant cardiac disease; severe renal or liver function impairments and pregnancy.

Initial evaluation, assessment of clinical and pathological response

Before entry, all patients underwent the followings: medical history, physical examination, tumor evaluation measurement and staging. Electrocardiogram (ECG), left ventricular ejection fraction (LVEF) evaluation by ECHO, complete blood cell count, serum chemistries, liver and renal function tests, bilateral mammography, Computed tomographic scan of chest, abdomen and pelvis. Complete blood cell count and serum electrolytes were measured before the administration of each treatment cycle.

Clinical objective responses were evaluated according to Response Evaluation Criteria in Solid Tumor (RECIST) (8). Complete response (CR) was defined as the disappearance of all known disease with no evidence of progressive disease; partial response (PR) was defined as a > 30% decrease in the sum of longest diameters of all target lesions with no appearance of new lesions. Progressive disease (PD) was defined as at least 20% increase in the sum of the longest diameters of all target lesions or the appearance of new lesions. Stable disease was defined neither as PR nor as PD.

Pathological assessment:

Tumor samples were collected by needle core biopsy or surgical biopsy prior to systemic chemotherapy. ER, PR, HER-2/neu, and Ki67 were determined by standard immunohistochemical methods. Immunohistochemical (IHC) analysis was performed using rabbit monoclonal antibody clones SPI and IE2 for ER and PR, respectively and (MIB-1) for ki67. Tumors with less than 1% stained cells were considered to have Negative receptor status. HER-2/neu status was assessed by IHC using rabbit monoclonal antibody clone 4B5 only if the results were 0 or 1+ staining and by fluorescence in situ hyperdization (FISH) confirmation if 2+ immunohistochemistry staining was present. In our study, pathological response was considered complete (pCR) if no histological evidence of residual tumor or in situ tumor in all resected specimens of the breast and the axillary lymph nodes could be detected. Near pathological response (npCR) was considered if only occasionally scattered invasive tumor cells with a size of 5 mm or less in aggregates removed from the breast tissue at the time of definitive surgery.

Treatment plan and follow up:

Neoadjuvant chemotherapy consisted of 4 cycles of AC (60mg/m2,600mg/m2) or FEC (500mg/m2,100mg/m2,500mg/m2) followed by 4 cycles consisting of docetaxel-cisplatin (75mg/m2 each) every 3 weeks. Clinical response, complete blood count and chemistry were assessed with every cycle. Surgery was performed on day 28 after completion of preoperative chemotherapy. Adjuvant radiotherapy was administered after surgery. After completion of the treatment plan, follow up was every three months. Toxicity was assessed using the Common Toxicity Criteria Version 2.

Results

Eighteen women with stage III (A,B,C), triple negative breast cancer were recruited between July 2007 and February 2010. Patient's clinical data are shown in table (1). Median age was 49 years with a range of (24-70). Premenopausal were 16 patients; 25% of them below 35 years old, median tumor size: 9cm (3.5-19cm); 15 patients were grade III and all patients except two had positive lymph nodes. Tumor stage, histology, grade and ECOG performance status are shown in table 1. Clinical response rate was 88.9% (16/18), of which clinical complete response rate after anthracycline evaluation was 22.2%, and reached up to 50% after docetaxel-cisplatin evaluation. Progressive disease was detected in 11.1% of cases (two patients). All patients completed the anthracycline part with two episodes of febrile neutropenia. Only 10 patients completed all 4 cycles of Docetaxel-Cisplatin; 4 patients completed 3 cycles. Toxicity related to Docetaxel-Cisplatin was 4 cases with febrile neutropenia; two cases of reversible renal impairment and one case suffered from hypersensitivity reaction. Fifteen patients underwent modified radical mastectomy and one underwent breast conserving surgery. Two patients were not operated due to disease progression. Pathological assessment revealed that 6 (37.5%) patients had pathological complete response (no residual tumor cell in the breast or the axillary lymph nodes); 3 (18%) had residual scattered tumor cells less than 5 mm (near pathological complete response); 8/16 (50%) had negative lymph nodes. Baseline Ki 67 levels for patients with residual invasive component is under evaluation.

Discussion

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer that lacks a therapeutic target, making chemotherapy the primary systemic modality used in the treatment of this disease. The use of neoadjuvant chemotherapy for this sub-group of patients has risen in recent years, likely as a result of recent studies demonstrating that triple negative breast cancer is more chemosensitive than other subtypes of breast cancer (9). Further, the response of the tumor to neoadjuvant chemotherapy provides important prognostic information, whereby patients with a pCR in both the breast and axillary lymph nodes fare better than those with residual disease (10). TNBC is a high risk breast cancer in view of younger age, poorly differentiated tumors and shortened survival. A study by Bauer et al study showed that patients with triple negative phenotype were significantly more likely to be under age 40, had more advanced stage at diagnosis, were more likely to have a poorly differentiated histology and regardless of stage at diagnosis, women with triple negative breast cancer had poorer survival than those with other breast cancers (11). In our study, 25% were below 35 years of age; 83% were grade 3; median tumor size was 9 cm and 77% had stage IIIB disease. Given the importance of chemotherapy in this disease, investigators have focused on optimizing drug selection of existing chemotherapeutic agents. From a biological standpoint, DNA damaging agents such as platinum compounds are of high priority based upon the BRCA1 pathway and DNA repair dysfunction in this subtype as described above, which may enhance sensitivity to DNA- damaging agents (12). It has been suggested

that younger women receive greater benefits from treatment with neoadjuvant therapy than older women (13). The NSABP protocol B-18 demonstrated a trend in favor of preoperative chemotherapy for DFS and OS in women less than 50 years old (14). It is clear from previous studies that TNBCS display higher rates of pCR following neoadjuvant chemotherapy, a major determinant of clinical outcome, than non-TNBCS (15). However, in the setting of residual disease after neoadjuvant treatment, the overall prognosis of this disease is still poor. ***Carey et al*** found that TNBC and HER2+ breast cancers display much higher rates of pCR (27% and 36%, respectively) (16). Additionally, ***Liedtke et al*** performed large study of 1118 patients with early-stage breast cancer and found that patients with TNBC had significantly higher pCR rates (10). The clinical activity of cisplatin and carboplatin against unselected breast cancer was found many years ago to be modest with an overall response rate of 32%-54 % (17). A trial by ***Garber*** using single agent cisplatin in 28 women with triple negative breast cancer demonstrated 22% pCR (18). Another neoadjuvant trial in triple negative disease resulted in 9 of 10 pCRs to single agent cisplatin (19). Taxanes and anthracyclines are active in TNBC and remain important agents. The addition of platinum analogues to other chemotherapeutic agents appears to benefit patients with or without triple negative breast cancer. In our study, the clinical complete response rate after anthracycline was 22% and more than doubled after administration of cisplatinum–taxane combination, reaching close to 50%. Pathological complete response rate was 37.5% and the addition of cases with npCR, the pathological response rate reached 56%. 50% of excised axillary lymph nodes were negative for malignant cells. ***Sirohi et*** **al** reported in his study that overall response rate (CR, PR) was 100% in triple negative tumors and pathological complete response was 17% (20). Our results suggest that there may indeed be some clinical gain with the addition of platinum salts to anthracyclines and taxanes for triple negative tumors. This well tolerated anthracycline-taxane-cisplatin based neoadjuvant chemotherapy regimen achieved a high pCR rate and warrants further large phase III studies.

Table 1: Patient's and tumor's characteristics

Number of patients	18
Menopausal status Pre Post	 16 2
Median age years(range)	49 (24-70)
ECOG Performance status 0-1 2	 17 1
Initial Stage TNM IIIA IIIB IIIC	 3 14 1
Median tumor size (range)	9 cm (3.5-19)
Histology Invasive duct carcinoma	 18
Grade II III	 3 15
Type of surgery Breast conservative surgery Modified radical mastectomy No operation	 1 15 2

Table 2: Clinical and pathologic response after neoadjuvant chemotherapy

Response	No. of Pts (%)
Clinical response after AC, FEC Complete response Partial response	16/18 (88.8%) 4 (22.2%) 12 (66.6%)
Clinical response after cisplatin-docetaxel Complete response Partial response	16/18 (88.8%) 9 (50%) 7 (38.8%)
Progressive disease	2 (11.1%)
Pathological response Complete pathological response(cPR) Near complete pathological response(ncPR) Negative axillary lymph nodes	 6/16 (37.5%) 3/16 (18.7%) 8/16 (50%)

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