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First-line paclitaxel and cisplatin used sequentially or in combination in metastatic breast cancer: A phase II randomized study

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ABSTRACT

Introduction: Breast cancer (BC) is the commonest cancer among females worldwide. Some patients present initially at advanced stages and more than 50% of them will develop metastasis (MBC) at some point. Compared to single agents, combination chemotherapy produces higher response rates (RR), longer progression-free survival (PFS) than single agents. This is associated with remarkably higher toxicities. At the same time, overall survival (OS) is comparable. This study aimed to compare safety and efficacy of combination and sequential chemotherapy.

Patients and Methods: Forty-six MBC patients were randomized to receive 6 cycles of the combination of paclitaxel (175 mg/m^2) and cisplatin (70 mg/m^2) (combination PC) or paclitaxel for 3 cycles followed by cisplatin for 3 cycles (sequential PC). Endpoints were RR, PFS, OS and safety.

Results: Both combination and sequential PC produced similar RR (52% in both arms) and disease control rates (78.3% vs. 73.9%, p = .652). Responses were faster in the combination arm. Median PFS was 8.2 months in the combination compared to 5.0 months in the sequential arm (p = .064). The median OS was 16.5 and 18.8 months in the combination and sequential arms, respectively (p = .866). The combination was more toxic than sequential PC. Grade 3 toxicities were higher with combination PC than to sequential PC (48% vs. 4.3%; p < .001).

Conclusion: Sequential agent chemotherapy may provide similar response rate and overall survival to combination chemotherapy with much lower toxicities. The former can be considered the standard practice in most instances.

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Introduction

Breast cancer [BC] is the most common cancer in women worldwide and in Egypt [1,2]. Also, it is the most common cause of cancer deaths in women [1]. In USA, up to 5% of BCs are metastatic (MBC) at first presentation and additional 30% of early BCs will develop metastases later in the disease course [3]. In Arab countries, up to 25% of BCs are metastatic at presentation and another significant proportion will develop MBC later as they represent with more advanced loco-regional disease [4].

MBC is largely incurable disease and the 5-year overall survival (OS) is still very poor. Treatment intent remains palliative in most of the cases with the goal of improving symptoms, maintaining and improving quality of life (QoL) and prolonging survival [5].

In MBC, cytotoxic chemotherapy is mainly used in patients with life threatening or rapidly progressive visceral metastasis (visceral crisis), resistance to hormonal therapy, HER2 over expression and triple negative disease [6]. Still, there is debate as to whether combination or monotherapy strategies should be pursued. In general, response rates (RRs) tend to be higher and faster with combination regimens when used as first-line therapy, but often at the expense of greater toxicity and short-term deterioration in QoL. Furthermore, most of the clinical trials that assess new combination strategies have not been adequately structured to address whether long-term outcomes (especially OS) are equivalent or superior to using the same agents administered sequentially [7].

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Taxanes were studied extensively in MBC setting and they were the preferred first line in many guidelines including EASO-EASMO ABC3, based on their high RRs ranging from 20% to 60% as single agents [9]. Moreover, a Cochrane meta-analysis documented a statistically significant OS in favor of taxane-containing regimens [10]. Single platinum agents produced less RR ranging from 17% to 36%, and cisplatin RR was 32.6% [11].

Paclitaxel and cisplatin are effective in BC and appear to be synergistic [8]. The aim of this study was to compare safety and efficacy of sequential single agent chemotherapy (paclitaxel followed by cisplatin) to combination chemotherapy (paclitaxel-cisplatin) in MBC in terms of RR, PFS, OS, and toxicity, when used as first line chemotherapy. In the sequential arm, paclitaxel was given prior to cisplatin owing to the reported higher response rates.

Patients and methods

This is a prospective single-center open-label randomized phase II clinical trial. Randomization of patients between treatment arms was done using permuted blocks. The study was conducted in compliance with the rules of Good Clinical Practice (GCP) and it was approved by the institutional review board (IRB) and all patients provided informed consents. The study was conducted at the breast cancer center of the National Cancer Institute, Cairo University, Egypt in the period between August 2014 and March 2017. Recruitment phase lasted for 13 months (August 2014 to September 2015). Follow-up phase lasted for 18 months after recruitment of the last patient (September 2015 to March 2017).

The study involved all eligible MBC patients presenting to the facility during the recruitment period who agreed to participate in the study. During this period 46 patients with MBC agreed to participate in the study. To be eligible, patients had to have histological confirmation of BC, measurable metastatic disease mandating first-line chemotherapy (e.g. visceral crisis, hormone-receptor (HR) negative, HR positive failing tamoxifen and aromatase inhibitors or HER2 positive), no prior chemotherapy for metastatic disease, 12 months or more after taxane-based adjuvant chemotherapy (if used), ECOG performance status 0–2, adequate organ function and age between 18 and 70 years.

Patients were randomized to receive a combination of paclitaxel 175 mg/m^2 and cisplatin 70 mg/m^2 every 3 weeks for 6 cycles (combination PC; 23 patients) or paclitaxel 175 mg/m^2 for 3 cycles followed by cisplatin 75 mg/m^2 for 3 cycles (Sequential PC; 23 patients). Anti-HER2 therapy was not used.

The primary endpoint was PFS. Secondary endpoints were RRs, OS and safety. Response was assessed after each 3 cycles and every 3 months afterwards using Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1. Safety was assessed after each cycle using Common Terminology Criteria for Adverse Events (CTCAE) version 3 [12]. PFS is the time from first day of study treatment to either progression, death or last follow up visit. OS is time from diagnosis of the metastatic disease till death or last follow up visit.

Statistical methods

Statistical analysis was done using IBM© SPSS® version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as median and range. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. Multivariate analysis was done using Cox-proportional hazard regression model with forward stepwise method for the factors with p value up to 0.1 affecting survival on univariate analysis. Hazard ratio (HR) with its 95% confidence interval (CI) was used for risk estimation.

Results

Patients' characteristics

All patients were females with a median age of 48.5 years and range of 28–68 years. Table 1 shows characteristics of the patients in the two groups. Most patients were postmenopausal, with negative family history, without co-morbidities and presented with de novo MBC that was Hormone receptor (HR) positive and HER2 negative. Curative surgery was performed in 34/35 initial M0 patients (MRM in 88% and CBS in 12%). Neoadjuvant or adjuvant chemotherapy was administered to 33/35 patients and anthracyclines were used in 33 patients while taxanes were used in 17 patients. The median taxane-free interval was 19 months. Almost, 55% of patients had ECOG performance status (PS) of 1 and 48% had single metastases. The most common MBC sites were lungs (63%), liver (48%), bone (39%) and soft tissue (lymph nodes and skin; 20%).

Safety

Patients in the combination arm received a total of 106 PC cycles while those in the sequential arm received 126 cycles. Cycles ranged between 1 and 6 with a median of 6 and a mean of mean 4.6 cycles in the combination arm. For sequential arm, it ranged between 2 and 6 with a median of 6 and a mean of 5.5 cycles.

Toxicity was assessed every cycle. Details are provided for 43 out of the 46 patients as three patients in the combination arm received only one cycle due to early death. Almost all patients in both arms experienced at least one episode of nausea and vomiting (Table 2). Other individual toxicities were generally higher in the combination arm. Nevertheless, that was not statistically significant. Of note, grade 3 and non-nausea/non-vomiting toxicities were higher in the combination than the sequential arm (48% vs. 4.3%, p < .001; 78% vs. 52%; p = .063, respectively). One patient in the combination arm withdrew her consent after receiving only two cycles due to toxicities. While none in the sequential arm, 3 patients in the combination arm had dose reduction because of toxicities.

Response rates

Both combination and sequential arms produced similar response rates (52.2%), with slightly higher disease control rates in the combination arm (78.3% vs. 73.9%). However, these were not statistically significant (Table 3). There were two CRs in combination arm and one in sequential arm. Combination chemotherapy produced more early responses than sequential chemotherapy. RR after cycle 3 was 45% for the combination vs. 39% in the sequential arm (p = .691). Disease control rate after cycle 3 was 90% in the combination compared to 65% in the sequential arm (p = .055).

The current study explored the association of response and several factors including patients' and tumor characteristics, type of chemotherapy and toxicity. Only performance status and developing toxicity were significantly associated with the response. Patients with PS II had 38% RR compared to 64% with PS I (p = .022). Patients who developed G3 toxicities had RR of 22% compared to 65% for lower grades (p = .049). The type of chemotherapy (combination vs. sequential) was not associated with response (p = .913). HR positive disease yield 51.4% RR vs. 54.5% RR for HR negative disease, while disease control rate was 80% vs. 63.6% for HR positive and negative disease respectively (p = .35). HER2 positive disease yield 64.3% RR vs. 51.5% RR for HER2 negative disease,

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