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Original Article

Docetaxel (Taxotere®) Combined Regimens in Early Stage Breast Cancer (Adjuvant and Neoadjuvant), Glimpses from the "Real World" Practice in Egypt

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ABSTRACT

Background: The use of docetaxel has emerged as a treatment of choice for patients with breast cancer. The purpose of this study is to investigate patient characteristics and safety data from Egyptian patients with early breast cancer receiving docetaxel based regimens.

Subjects and Methods: A total of 82 newly-diagnosed-patients with breast cancer and prescribed to docetaxel (as neoadjuvant or adjuvant treatment in operable breast cancer patients with high risk of recurrence) were observed for 6 months and assessed for medical, histopathological and safety profiles.

Results: The mean age of patients was 49.7±10.8 years and their BMI was 32.3 ± 5.3 kg/m². The majority of patients (93.9%) underwent previous breast surgeries and 46.3% were subjected to radiotherapy. The median of follow up period was 3.25 months with (range 2.7 to 6 months). Most patients (84.1%) were diagnosed with moderately differentiated tumor cells (G2). More than half of patients (56.1%) were administered to a sequential 3 cycles regimen of (5-fluorouracil–epirubicin–cyclophosphamide) followed by 3 Cycles of docetaxel , and almost 60% of patients were prescribed to docetaxel 75 mg/m². Throughout the period of follow-up, no serious adverse events have been reported.

Conclusion: Docetaxel is mainly used as adjuvant chemotherapy in the management of patients with early breast cancer in Egypt. No serious adverse events and no breast cancer relapses were reported during the follow-up period and the adverse events were consistent with the known safety profile of docetaxel

Keywords

Docetaxel,
Safety,
Efficacy,
Breast cancer

INTRODUCTION

One out of every seven women in Egypt is estimated to have breast cancer throughout her life, which puts cancer breast on the top of female malignancy list in Egypt.[1] Data emerging from other countries in the Middle East show as high rates as the national ones, making breast cancer a challenging epidemic[1–3].

While breast conservative surgery remains the treatment of choice for breast cancer, systemic induction therapy has been advocated for lumps larger than 2 cm prior to surgery[4,5]. Adjuvant therapy is also recommended for micro-metastases, since it improves patients' disease-free survival and overall survival[6].

Recently, taxanes, in particular docetaxel, have emerged as an effective agent in adjuvant and neoadjuvant setting of early breast cancer patients, with favourable activity over anthracyclines and safe combination with doxorubicin[7].In the BCIRG 001 trial a combination of docetaxel plus doxorubicin and cyclophosphamide was compared to 5-FU plus doxorubicin and cyclophosphamide in operable node -positive patients, and docetaxel arm showed superiority in overall survival[8]. More studies have proven the efficacy of docetaxel in improving survival rates, mitigating the side effects, and minimizing the chances of relapse[9–11].

Despite the previous literature that enhance the use of docetaxel in breast cancer, and highlight its effectiveness and preferred combinations, there is a lack of data about the "in practice" approach to docetaxel in women with breast cancer in Egypt. The aim of this study is to investigate the medical and histopathological characteristics of the Egyptian patients prescribed to docetaxel for their breast cancer, detect the regimens, and dosing administrated, and explore the safety profile of docetaxel in those patients.

SUBJECTS AND METHODS

Study design and population

The present observational study was conducted in five sites in Alexandria between April 2013 and October 2015. Patients were included if they met the following criteria: 1)Female patients > 21 years who were newly diagnosed breast cancer under docetaxel combined regimen as neoadjuvant or adjuvant in operable breast cancer patients with high risk of recurrence after surgery, 2)No prior therapy (other than surgery) and 3) agreed to sign data release consent.

In this concern, high risk of recurrence included node positive and node negative breast cancer with other high risk factors for recurrence such as tumor size, pathologic grade, receptor status and age. Determination of being high risk or not was judged by the investigator.

Patients with bilirubin >upper limit of normal (ULN), ALAT >1.5 x ULN, ASAT >1.5 x ULN concomitant with Alkaline phosphatase >2.5 x ULN, neutrophil counts of < 1500 cells/mm3, history of hypersensitivity reactions to docetaxel or other drugs containing polysorbate 80, or pregnant or lactating females were excluded.

TREATMENT

In order to reflect the "in practice" approach to the treatment of patients with early breast cancer in Egypt, the regimen used with docetaxel was left to the routine practice of the participating investigators**.**

All patients received treatment for an average of 6 months, during which docetaxel was administered by IV infusion. The physi-cians were guided by the prescribing information outlined in the summary of product characteristics/product information. Dexamethasone premedication and proper antiemetic, antihistaminic prophylaxis and other chemotherapy-related adverse events were managed by investigators according to their regular practice strategy.

Parameters and outcomes

For the participating patients, the following were assessed; demographic characteristics, medical history, pathological staging and histopathological grading according to American Joint Committee on Cancer (AJCC) staging.[15] Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) performance status was assessed.[16]

Safety outcomes were measured throughout the course of treatment. All adverse events, whether related to the chemotherapy or not, were recorded from the first day of chemotherapeutic administration. Seriousness of the adverse events, actions taken in this regard, and corrective medications given were also monitored during the six months of follow-up.

Data collection and statistical analyses:

Data entry, verification, and validation were carried out us -ing standard computer software. A double-entry method was used to ensure that the data were transferred accurately from the case report forms to the database. Data were analyzed using the software, Statistical Package for Social Science (SPSS Inc. Released 2009, PASW Statistics for Windows, version 18.0: SPSS Inc., Chicago, Illinois, USA), then processed and tabulated. Frequency distribution with its percentage and descriptive statistics with mean and standard deviation were calculated. Chi-square, t-test, correlations were done whenever needed. P values of less than 0.05 were considered significant. Regarding sample size calculation, it was reported that the age-adjusted incidence of breast cancer in less developed countries including Egypt is 23.8 per 100,000 population, while the a total population of 20,000,000 females in the age group 15 - 60 years is recorded. Thus, around 4800 new breast cancer cases are introduced in Egypt per year **.** A sample size of 100 patients represents 2% of the newly diagnosed cases and allows for a confidence level of 95% and a confident interval of ±9.7.

Ethical considerations

The study was conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki, and data for each patient were collected only

after obtaining that patient's signed written data release forms.

This is an observational study and the Competent Authorities (CA) approval was missed to be obtained prior to the study start

RESULTS

A total of 82 newly-diagnosed-patients with breast cancer and treated by docetaxel-based regimen (as neoadjuvant or adjuvant treatment in operable breast cancer patients with high risk of recurrence) were enrolled. The mean age of the 82 participating patients was 49.7±10.8 (28-74) years, and their mean weight and height stood at 82.1± 14.5 kg and 159.8 ± 5.9 cm, respectively, making the mean BMI 32.3 ± 5.3 kg/m². Out of the 82 patients, 70 (85.4%) patients recorded 0 in performance status and 12 (14.6%) patients recorded 1 (with 0 indicating that the patient is fully active and able to carry on all pre-disease activities without restriction and 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature) (Table 1).

Only 16 (19.5%) of study subjects had positive history of at least one disease other than cancer. Hypertension, diabetes and hypothyroidism were the most likely diseases to be reported 9 (11%), 5 (6.1%) and 2 (2.4%), respectively. In addition, 19 (23.2%) patients were prescribed to other medications by the time of the study for their medical conditions, 38 (46.3%) patients reported a history of radiotherapy for their breast cancer, and 77 (93.9%) underwent surgeries related to their conditions; modified radical mastectomy and breast conservative surgery & lumpecto-

Table 1: Demographic and medical characteristics of the participating patients

Characteristics		Frequency, n=82 (%)
Age (Mean with range) years		49.7 (28 -74)
BMI (Mean with range) kg/m²		32.3 (20.5 – 47)
Performance status	0	70 (85.4)
	1	12 (14.6)
Medical history		**16 (19.5)**
	Hypertension	9 (11.0)
	Diabetes Mellitus	5 (6.1)
	Hypothyroidism	2 (2.4)
	Gastritis	1 (1.2)
	Bronchial Asthma	1 (1.2)
	Hysterectomy	1 (1.2)
	Uterine Fibroid	1 (1.2)
Concomitant medications		19 (23.2)
Radiotherapy		38 (46.3)
Surgery		**77 (93.9)**
	Modified radical mastectomy	54 (65.9)
	Breast conservative surgery& Lumpectomy	20 (24.3)
	Skin sparing mastectomy and axillary clearance	2 (2.4)
	Lumpectomy without axillary clearance	1 (1.2)

Table 2: Histopathological Grade classification of the participating patients

Classification	Frequency, n=82 (%)
GX : Differentiation cannot be assessed	3 (3.7)
G1 : Well differentiated	5 (6.1)
G2 : Moderately differentiated	69 (84.1)
G3 : Poorly differentiated	5 (6.1)

Table 3: TNM staging of the participating patients

Staging	Frequency, n=82 (%)
1A : T1 N0 M0	2 (2.4)
2A : T1 N1 M0, or T2 N0 M0	17 (20.7)
2B : T2 N1 M0, or T3 N0 M0	14 (17.1)
3A : T1 N2 M0, or T2 N2 M0, or T3 N1 M0, or T3 N2 M0	31 (37.8)
3B : T4 N0 M0, or T4 N1 M0, or T4 N2 M0	10 (12.2)
3C : Any T N3 M0	8 (9.8)

my were the most common reported surgeries (Table 1).
Regarding the histopathological grade classification, the majority of patients (84.1%) were diagnosed with moderately differentiated tumor cells (G2). This was followed by well differentiated (G1) and poorly differentiated (G3), 6.1% each (Table 2). For TNM classification, 37.8% of the patients were 3A (T1 N2 M0, or T2 N2 M0, or T3 N1 M0, or T3 N2 M0), followed by 2A (T1 N1 M0, or T2 N0 M0) in 20.7% of patients (Table 3).
Of the enrolled 82 patients, only 4 (4.9%) patients were administered to a combined regimen of 6 cycles of (docetaxel–adriamycin–cyclophosphamide), while the majority of patients 78 (95.1%) were prescribed to sequential regimens as follows: 46 (56.1%) patients to 3 cycles of (5-FU – epirubicin – cyclophosphamide) followed by 3 cycles of docetaxel, 17 (20.7%) patients to 4 cycles of (adriamycin – cyclophosphamide) followed by 4 cycles of docetaxel, 5 (6.1%) patients to 4 cycles of (5-FU – epirubicin – cyclophosphamide) followed by 4 cycles of docetaxel, 4 (4.9%) patients to 3 cycles of (5-FU–adriamycin–cyclophosphamide) followed by 3 cycles of docetaxel, 2 (2.4%) patients to 4 cycles of (adriamycin–cyclophosphamide) followed by 3 cycles of docetaxel, 2 (2.4%) patients to 4 cycles of (epirubicin – cyclophosphamide) followed by 4 cycles of docetaxel, 1 (1.2%) patient to 4 cycles of (5-FU – adriamycin – cyclophosphamide) followed by 3 cycles of docetaxel and another patient to 6 cycles of docetaxel (Table 4).
The mean docetaxel prescribed dose was 83.1±24.1 mg/m^2. Almost 60% of patients were prescribed to docetaxel 75 mg/m^2, 16% to docetaxel 70 mg/m^2, 12% to docetaxel 80 mg/m^2, 7.5 % to docetaxel 160 mg/m^2, 2.5% to docetaxel 100 mg/m^2, and the rest of patients to docetaxel 130 and 140 mg/m^2 (Figure 1). Regrading the prescribed regimens, the majority of patients (95.1%) were prescribed sequential regimen including: 46% received 3 Cycles of FEC (5 FU – Epirubicin – Cyclophosphamide) followed by 3 Cycles of docetaxel ; while 17% received 4 Cycles of AC (Doxorubicin – Cyclophosphamide) followed by 4 Cycles of docetaxel. Five percent of the patients were prescribed 4 Cycles of FEC (5 FU – Epirubicin – Cyclophosphamide) followed by 4 Cycles of docetaxel, 4% were prescribed 3 Cycles of FAC (5FU – Doxorubicin – Cyclophosphamide) followed by 3 Cycles of docetaxel, and 2% of patients were prescribed 4 Cycles of AC (Doxorubicin – Cyclophosphamide) followed by 3 Cycles of docetaxel and4 Cycles of EC (Epirubicin – Cyclophosphamide) followed by 4 Cycles of docetaxel. One patient received 4 Cycles of FAC (5 FU – Doxorubicin – Cyclophosphamide) followed by 3 Cycles of docetaxel and 6 Cycles of docetaxel.
Throughout the period of the study, 42 (51.2%) patients experienced 114 non-serious adverse events; of them 70 adverse reactions were considered to be associated with the study medication(s) and were experienced by 35 (42.7%) patients. The most frequently reported non-serious events were oral candidiasis (34.1%), followed by vomiting (32.9%), diarrhea (31.7%), neutropenia (14.6%), anemia (3.7%), leuckocytopenia (3.7%), hypersensitivity reaction (2.4%) and rash (2.4%). Regarding severity of the reported non-serious events, five patients (6.1%) had mild AEs, 37 patients (45.1%) had moderate AEs, four patients (4.9%) had severe AEs but none of these was serious .No action was taken with chemotherapy in 39 patients (47.6%); while chemotherapy was permanently discontinued in 3 patients (3.7%) as a result of adverse events. (Table 5).

Table 4: Prescribed regimen to the participating patients

Prescribed regimen	Frequency, n=82 (%)
Non-sequential regimen	4 (4.9)
6 cycles of (docetaxel– adriamycin – cyclophosphamide)	4 (4.9)
Sequential regimen	78 (95.1)
3 cycles of (5-FU – epirubicin – cyclophosphamide) followed by 3 cycles of docetaxel	46 (56.1)
4 cycles of (adriamycin – cyclophosphamide) followed by 4 cycles of docetaxel	17 (20.7)
4 cycles of (5-FU – epirubicin – cyclophosphamide) followed by 4 cycles of docetaxel	5 (6.1)
3 cycles of (5-FU – adriamycin – cyclophosphamide) followed by 3 cycles of docetaxel	4 (4.9)
4 cycles of (adriamycin – cyclophosphamide) followed by 3 cycles of docetaxel	2 (2.4)
4 cycles of (epirubicin – cyclophosphamide) followed by 4 cycles of docetaxel	2 (2.4)
4 cycles of (5-FU – adriamycin – cyclophosphamide) followed by 3 cycles of docetaxel	1 (1.2)
6 cycles of docetaxel	1 (1.2)

Table 5: Incidence of adverse events amongst the participating patients treated with docetaxel

Adverse events	Frequency, n=82 (%)
Oral candidiasis	28 (34.1)
Vomiting	27 (32.9)
Diarrhea	26 (31.7)
Neutropenia	12 (14.6)
Anemia	3 (3.7)
Leukopenia	3 (3.7)
Hypersensitivity	2 (2.4)
Rash No	2 (2.4)
Constipation	1 (1.2)
Deep vein thrombosis	1 (1.2)
Fatigue	1 (1.2)
Skin exfoliation	1 (1.2)
Hyperglycemia	1 (1.2)
Musculoskeletal pain	1 (1.2)
Peripheral neuropathy	1 (1.2)

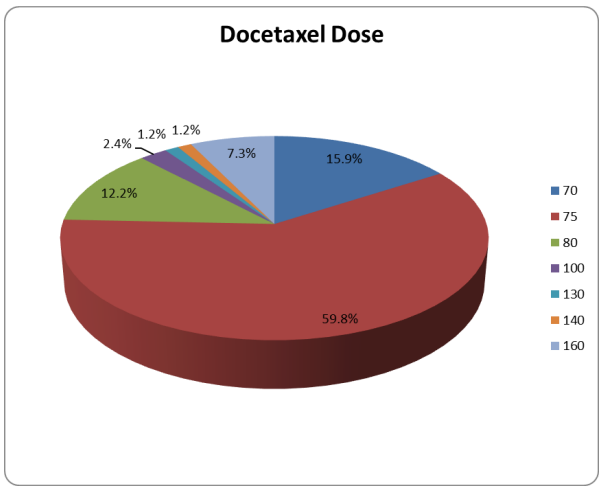

Figure 1: Docetaxel dosing

DISCUSSION

This observational study was conducted on 82 female patients with newly diagnosed operable breast cancer in Alexandria, Egypt. All the patients were at high risk of recurrence after surgery and their physicians decided to prescribe docetaxel containing regimen as neoadjuvant or adjuvant for an average 6 months as a part of physicians' practice.

The mean age of the patients in the study was 49.7±10.8 years which consist with previous reports from Nigeria[11], Pakistan[12], and Turkey[13], and almost five years lower a study from Spain.[19] However, unlike these reports, our study included only newly diagnosed patients.

According to data obtained from the current study, most of patients (84.1%) were diagnosed with moderately differentiated tumor cells (G2) and 37.8% of the patients were stage 3A (T1 N2 M0, or T2 N2 M0, or T3 N1 M0, or T3 N2 M0). Additionally, the vast majority of the patients (93.9%) underwent surgeries for their breast cancer. The histopathological classification and the medical profile of our patients help in understanding the reasons why physicians prescribed docetaxel as an adjuvant therapy, since administrating patients to docetaxel as adjuvant chemotherapy has been proven to improve disease-free survival and overall survival as reported by previous literatures[8,10,11,14], in addition to the convenient , intermittent and brief infusion of the chemotherapy with manageable adverse effects[8].

This progress in the use of docetaxel as an adjuvant chemotherapy has been made possible through the use of new combinations, tailored personalized dose-intensity, and better selection of patients who would benefit from adjuvant chemotherapy[8] . Such factors have made docetaxel to be the most widely prescribed chemotherapy for breast cancer in the United States[15].

Further, our study showed that physicians' regular clinical practice was to prescribe docetaxel as a sequential regimen commonly following 3 cycles of a combination of 5-FU, epirubicin and cyclophosphamide, while the second commonly prescribed regimen was 4 cycles of adriamycin and cyclophosphamide followed by 4 cycles of docetaxel.

In the PACS 01 trial, a combination of 5-FU, epirubicin and cyclophosphamide were followed by 3 cycles of docetaxel and the investigators noticed a significant improvement in disease-free survival and overall survival with less cardiac events and neutropenia[16]. Other trials examined different combinations with docetaxel, and in all these studies docetaxel showed an added benefit[9,10].

Additionally, it was noted that docetaxel average prescribed number of cycles in our study was 3 with a mean dosage of 83.1 mg/m^2, and more than half of patients were receiving docetaxel 75 mg/m^2. This dosing was comparable to the recommended regimen by Chilcott and colleagues[15]. In their exploratory analysis, Bono and colleagues found no significant difference between docetaxel 80 mg/m2 and docetaxel 100 mg/m2 in terms of overall survival and progression-free survival of patients with early breast cancer; moreover, the 80mg/m2 dose showed less side effects and better adherence[17]. Such findings led to the recommendation of 75 mg/m^2 dose for operable node-positive patients and 100 mg/m2 for locally advanced or metastatic patients[18].

Moreover, our results indicated the occurrence of 114 adverse events with an incidence rate of 51.2%. The commonly reported adverse events were oral candidiasis, vomiting and diarrhea. Almost 77% of the reported non-serious events were associated with the chemotherapy regimen. Gastrointestinal disturbances were also reported in the

study by Kim et al[19]. The latter study[19] and Martin et al[8] referred to neutropenia as a common adverse event, however the use of prophylactic medications for neutropenia in our study masked this event. Nevertheless, docetaxel was associated with manageable safety profile in the present study

In contrast to another study by Kim et al[20] which reported docetaxel related death in 1.6% and breast cancer relapse in 3% of the patients, the current study did not indicate any cases of death or breast cancer relapses during the treatment period, however the investigators in that study followed the patients for 18 months compared to only 6 months in our registry.

In conclusion, docetaxel is commonly prescribed as adjuvant chemotherapy in the management of patients newly diagnosed with breast cancer in Egypt. No serious adverse events or cancer relapse were reported during the follow-up period and the adverse events were consistent with the known safety profile of docetaxel.

Conflict of Interest

None.

Acknowledgement

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