

## DOCETAXEL CHEMOTHERAPY IN THE MANAGEMENT OF ADVANCED AND METASTATIC BREAST CANCER IN NIGERIANS A PILOT STUDY

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### ABSTRACT

The aim of this study was to assess whether introduction of Docetaxel into the management will improve palliation of symptoms, quality of life, response rate and probably survival in breast cancer patients.

A total of 19 patients referred from different medical centers in Nigeria were entered into the study. The age range was 25 to 52 years with a median of 34 years. The sex incidence was 18 females, 1 male.

There were 7 patients in stage III and the duration of median response was 30 months.

There were 12 patients in stage IV. Out of these 3 patients with brain metastasis had median response of 4 months.

4 patients with liver metastasis average duration of response was 22 months. 5 patients with pulmonary metastasis average duration of response was 20 months. In all, 16, out of the 19 patients (84%) had median response duration of 20-30 months. Better response rate could have been in patients with cerebral metastasis but for the fact that Docetaxel does not penetrate brain barrier.

Multicentre studies are now needed to reconfirm the superiority of Doxetaxel over existing cytotoxic chemotherapeutic drugs currently in use in the management of advanced and metastatic breast cancer in Nigeria.

### INTRODUCTION

Cancer of the breast was regarded in previous studies as the second commonest cancer among the Nigerian women after carcinoma of the uterine cervix (Abioye 1981)<sup>1</sup>.

However in 1992, data from the National Headquarters of Cancer Registries in Nigeria confirmed that Breast cancer was the commonest female malignancy, followed by cervical carcinoma.

Campbell et al<sup>2</sup> in review of 5000 cancer cases at the Radiotherapy Oncology Centre Ibadan 1988-1992 revealed that 23%

were breast cancer cases and it was the commonest of all malignancies seen at the Ibadan Radiotherapy Centre during the period. Not only was there an increase in the incidence of breast cancer during the period 1980-1990s in Nigeria but a large proportion of these patients presented at first visit to the orthodox doctor with advanced metastatic stages III and IV. Infact, study by Ketiku<sup>3</sup> revealed that 66% of breast cancer patients presented at the Hospital in stages III and IV disease, when palliative radiotherapy and chemotherapy are the mainstay of the treatment. Usage of cytotoxic drugs such as Cyclophosphamide, Methotrexate and 5 Fluorouracil CMF and Cyclophosphamide, Adriamycin and 5 Fluorouracil CAF, yielded 50% and 60% median response of 3-9 months and 10 to 18 months respectively in patients with advanced breast cancer in Radiotherapy and Oncology Centre, Ibadan, as at 1998. This yield was not satisfactory. The use of Docetaxel was explored. Docetaxel, is a semisynthetic antineoplastic drug that is produced from a non-toxic precursor found in the needles of the European yew tree (*Taxus baccata*)<sup>4,5</sup>.

The aim of our study was to assess whether introduction of Docetaxel into the management will improve palliation of symptoms, quality of life, response rate and probably survival in breast cancer patients.

### PATIENTS AND METHODS

A total of 19 patients referred from different medical centers in Nigeria were entered into the study. The age range was 25 to 52 years with a median of 34 years. The sex incidence was 18 females, 1 male.

#### Criteria for inclusion into the study

The blood profile must be normal viz; Full Blood Count, Serum Urea and Electrolytes, Liver function tests, Serum Creatinine.

Radiological profile viz; chest-x-ray, Abdomino-pelvic USS, Skeletal survey should

be carried out.

**Stages:** only patients with stages III and IV were entered into the study.

There must be histological confirmation of breast cancer.

There must be surgical report on the type of breast surgery carried out.

History of previous reactions to any drug must be documented.

Karnofsky performance must be over 70% for each patient.

- Height, weight must be recorded and the surface area documented.

#### **ADMINISTRATION**

The 19 patients satisfied all the inclusion criteria. As this was our first experience with Docetaxel chemotherapy, the patients were admitted to the ward for the treatment in order to monitor very closely toxicities due to doxetaxel. On days 1 & 2, 8mg Dexamethazone was administered orally b.d. (to avert fluid retention) and hypersensitive reactions side effects of Docetaxel). On day 3, 8mg Dexamethazone is first given, then 75mg/m<sup>2</sup> of Docetaxel in 250mgs of 5% Dextrose in H<sup>2</sup>O is administered for 1 hour (antiemetics and sedatives are given pre and post chemotherapy). On Days 4 and 5, 8mg Dexamethazone is given orally b.d. Day 6 patient is discharged home. The cycle of chemotherapy is repeated once in 3 weeks and 6 cycles are administered.

#### **Assessment**

##### **(a) Assessment to therapy**

The Assessment of response to therapy is carried out by;

- (i) clinical assessment
- (ii) radiological assessment
- (iii) laboratory assessment

##### **(b) Assessment of side effects of Docetaxel**

The assessment of side effect of Docetaxel is carried out for

- (i) Neutropenia
- (ii) Fluid retention characterized by
  - (a) peripheral oedema
  - (b) weight gain (pleural effusion ascites).
- (iii) Hypersensitivity reactions
- (iv) Cutaneous changes (rash, eruptions, usually accompanied by pruritus).
- (v) Periperal neuropathy
- (vi) Alopecia
- (vii) Asthenia
- (viii) Nausea and diarrhoea

#### **RESULTS**

There were 7 patients in stage III and the duration of median response was 30 months.

There were 12 patients in stage IV. Out of these 3 patients with brain metastasis had median response of 4 months.

4 patients with liver metastasis average duration of response was 22 months. 5 patients with pulmonary metastasis average duration of response was 20 months. In all, 16, out of the 19 patients (84%) had median response duration of 20-30 months. Better response rate could have been in patients with cerebral metastasis but for the fact that Docetaxel does not penetrate brain barrier.

#### **DISCUSSION**

Breast cancer is no longer the exclusive preserve of the prosperous Western World. While 1 in 12 women in United Kingdom will develop breast cancer, during their life time, studies have confirmed that 1 in 14 Nigerian women will succumb to breast malignancy. Despite the advancement in breast cancer therapy, 50% of patients diagnosed progressed to advanced (Stage III) and metastatic stage (Stage IV). Therapy for patients in stages III and IV is usually with palliative intent, the aim being to enhance quality of life and improve survival. The main palliative therapy options are endocrine and cytotoxic chemotherapy for this group of patients. The indications for cytotoxic chemotherapy are (a) Tumour refractory to hormone therapy (b) High risk women usually with visceral metastasis or bulky disease. Findings from our Radiotherapy and Oncology center in Ibadan reveal that monochemotherapy with drugs such as anthracyclines (Doxorubicin, Epirubicin), Cyclophosphamide, Mitoxantrone, 5 Fluorouracil, Mitomycin have yielded 20-60% response rate of 3-9 months, while polychemotherapy CMF and CMFV yielded 20-60% of 3-9 months duration response. CAF yielded response in 50%-60% with median duration of 10-18 months. For CAF regime, cumulative dose of Doxorubicin which may be cardiotoxic limits the use of CAF. In order to improve the response rate obtained in chemotherapy of advanced and metastatic breast cancer, it was decided to carry out a pilot study using Docetaxel for this cohort of patients. The high activity of Docetaxel has been proven in various studies. Docetaxel is an active agent. It is a semisynthetic taxane, a class of anticancer agents that bind to beta tubulin, thereby stabilizing microtubules and inducing cell-cycle arrest and apoptosis (6). Docetaxel was first approved for the treatment

of anthracycline refractory metastatic breast cancer in the mid-1990s. Since then several randomized trials have reported improved time-to-progression overall survival, or both in metastatic breast cancer treated with single-agent docetaxel or docetaxel-based combination regimes. In this study 84% of the patients had duration response of 20-30 months (compared to 20-60% of 3-9 months duration response recorded for CMF and 50%-60% of 10-18 months duration response recorded for CAF (Table 1). Toxicities to Docetaxel (Table II) were well tolerated as demonstrated in this study. Improved response rate in advanced and metastatic breast cancer is enhanced when docetaxel is combined with other antineoplastic drugs. The results have shown that docetaxel exhibits synergistic activity (i.e. antitumoural activity of the combination is superior to that of the best single agent) when it is combined with Cyclophosphamide, Fluorouracil, Vinorelbine, Methotrexate or Etoposide<sup>7,8,9</sup>. In a study with mouse mammary tumours, near-optimal doses of docetaxel (80-100%) could be delivered in combination with Vincristine, Vinblastine or Vinorelbine, while only 60-70% of the optimal dose of docetaxel could be delivered when it was combined with Doxorubicin, Etoposide, Cyclophosphamide, Fluorouracil, or Methotrexate<sup>9</sup>. Patients with metastatic breast cancer (MBC) are frequently exposed to high cumulative doses of anthracyclines and are at risk of resistance and cardiotoxicity. Phase II trial by PARK et al revealed that combination of Doxetaxel and Cisplatin produced 95% complete response, and overall survival of 23 months. This combination was found to be active and safe chemotherapy regime for patients with MBC resistant to anthracyclines<sup>10</sup>.

The Ibadan pilot study is an encouraging index of efficacy of docetaxel in treatment of advanced and metastatic breast cancer. The tolerability of the toxicities associated with Docetaxel was good. In view of the enhanced therapeutic activity when docetaxel is combined with some cytotoxic drugs, it is recommended that these drugs be used in combination with Doxetaxel to improve response rates in these patients. Multicentre studies are now needed to reconfirm the superiority of Doxetaxel over existing cytotoxic chemotherapeutic drugs currently in use in the management of advanced and metastatic breast cancer in Nigeria.

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**TABLE 1: COMPARATIVE ANALYSIS OF RESPONSE TO DOXETAXEL AND OTHER CHEMOTHERAPY REGIMES**

CHEMOTHERAPY REGIME	PERCENTAGE OF PATIENTS WHO RESPONDED	MEDIAN RESPONSE DURATION
CMF	) 20-60%	3-9 MONTHS
CMFV	)	
CAF	50-60%	10-18 MONTHS
DOXETAXEL	84%	20-30 MONTHS

**CMF** - Cyclophosphamide, Methotrexate, 5 Fluorouracil

**CMFV** - Cyclophosphamide, Methotrexate, 5 Fluorouracil and Vincristine

**CAF** - Cyclophosphamide, Adriamycin, and 5 Fluorouracil

**Source of Data:** Department of Radiotherapy, University College Hospital, Ibadan.

## TOLEABILITY

**Table II: Assessment re toxicities of Docetaxel.**

TOXICITIES	NO. OF PATIENTS 19
1. Neutropenia	2
2. Fluid Retention	NIL
3. Hypersnsitivty Reaction	NIL
4. Cutaneous Changes	NIL
5. Peripheral Neuropathy	3
6. Alopecia	5 (GRADE I)
7. Asthenia	(Low grade) 19
8. Nausea	4
9. Diarrhoea	4

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