EVALUATION OF CHEMOTHERAPEUTIC OUTCOME OF BREAST CANCER AT AHMADU BELLO UNIVERSITY TEACHING HOSPITAL, ZARIA

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NIGERIA

DECEMBER, 2015

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BY

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DECEMBER, 2015

DECLARATION

I declare that the work in this thesis titled 'Evaluation of Chemotherapeutic Outcome of Breast Cancer at Ahmadu Bello University Teaching Hospital, Zaria' are from original research work performed by me in the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria.

The information and all citation derived from the literature has been adequately acknowledged in the text and a list of references provided. No part of this thesis has been previously presented for another higher degree or diploma at any other institution.

Ebele Joan AJAGUN	----------	----------
Name of Student	Signature	Date

CERTIFICATION

This thesis titled 'Evaluation of Chemotherapeutic Outcome of Breast Cancer at Ahmadu Bello University Teaching Hospital, Zaria' by Ebele Joan AJAGUN meets the regulations governing the award of Master degree in Pharmacology in the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria and is approved for its contribution to scientific knowledge and literary presentation.

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DEDICATION

This research is dedicated to every member of my family – Dr. and Dr. (Mrs.) A. Ajagun, Makafan, Imu, Ebinbin and Onini and sons Nathan and Maurice Iguda. I can't thank God enough for giving such a loving and understanding family like you all. Thank you.

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ABSTRACT

Cancers are abnormal cells growing uncontrollably at the same time to invade other body cells. Breast cancer is a malignant proliferation of the epithelia tissues / cells of the milk duct and lobules occurring in both men and women with high global deaths.

The main aim of this study was to evaluate the outcomes of the chemotherapeutic management of breast cancer patients who attended the Oncology and Radiotherapy clinic of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria over a five-year study period (January 2005 to December 2009) retrospectively.

The disease index cards, registers and folders of patients from the National Cancer Registry of the Oncology and Radiotherapy Department of this study centre was retrieved and the total number of the various cancer types diagnosed in the five year study period including the number of breast cancer cases diagnosed in each of the 5 year study period together with relevant information for each patient as stipulated in a detailed data capturing form was extracted. Data obtained was then analyzed to examine the prevalence, incidence, associated risk factors, response pattern to chemotherapeutic regimens used as well as outcomes of treatment amongst others.

The results revealed breast cancer as the most common documented type of cancer with a steady / progressive increase in incidence over the five year study period and a male to female ratio of 1:27 with a peak incidence of occurrence at 36-45 years. Of the two hundred and eight women in this study, 43.3% reported their age at menarche within 13-16 years, 56.7% had pre-menopausal status and 40.4% responded negatively to the use of oral contraceptives. Non-preventable risk factor (age at menarche, contraceptive use and menopausal status) was demonstrated for the

increase in incidence of breast cancer amongst the female patients. 12.0% had a positive first degree familial history for breast cancer. Late presentation was the norm with obvious evidence of metastasis to the body's vital organs irrespective of age at presentation and educational level of the patient. Drug regimen preferences were Cyclophosphamide, Adriamycin (Doxorubicin) and 5-Flourouracil (CAF) and Cyclophosphamide, Methotrexate and 5-Flourouracil (CMF) prior to presentation at ABUTH, Zaria. Other popular drugs regimens encountered include Paclitaxel monotherapy and 5-Flourouracil, Epirubicin and Cyclophosphamide (FEC) regimens after presentation. No added advantage was observed in overall survival of breast cancer patients placed on the newer / more costly regimens (Paclitaxel 4.6%) as against FEC (12.5%). Only 31 patients (14.4%) of the study population had a disease free interval of $\geq$ 5 years with a mean time to progression of 18months (±6months). Calculated percentage death and loss to follow-up was 36.5% and 49.1% respectively.

It may not be possible to ascertain the pathological complete remission (pCR) of the patients that maintained disease free interval (DFI) at the end of the 5 year study. However, the complete response (disease remission) obtained at stage I and early stage II as well as the progression free survival (PFS) of 2-5 years in late presentation from these commonly prescribed chemotherapeutic regimens may suffice for good therapeutic outcomes.

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ABBREVIATIONS

ACS	American Cancer Society
AJCC	American Joint Committee of Cancer
ASCO	American Society of Clinical Oncology
BCFF	Breast Cancer Facts and Figures
CFF	Cancer Facts and Figures
DNA	Deoxyribonucleic Acid
ER	Estrogen Receptor
GLOBOCAN	Global Burden of Disease (Cancer)
HER2/neu	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ICD-O-3	International Classification of Disease (Oncology). Third Edition
NBCF	National Breast Cancer Foundation
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall Survive
PFS	Pathogen Free Survival
PR	Progesterone Receptor
QoL	Quality of Life
RNA	Ribonucleic Acid
RR	Response Rate
SEER	Surveillance, Epidemiology and End Result
TNM	Tumour, Node and Metastasis
TTP	Time to Progression
WHO	World Health Organization
-ve	Negative
+ve	Positive

REGIMENS

AC	Doxorubicin-Cyclophosphamide,
CAF	Cyclophosphamide-Doxorubicin-5-Flourouracil,
CAF-M	Cyclophosphamide-Doxorubicin-5-Flourouracil-Methotrexate,
CAM	Cyclophosphamide-Doxorubicin-Methotrexate,
CA-P	Cyclophosphamide-Doxorubicin-Paclitaxel,
CMF	Cyclophosphamide-Methotrexate-5-Flourouracil,
CMF-A	Cyclophosphamide-Methotrexate-5-Flourouracil-Doxorubicin,
CMF-E	Cyclophosphamide-Methotrexate-5-Flourouracil-Epirubicin,
EC	Epirubicin-Cyclophosphamide,
EC-P	Epirubicin-Cyclophosphamide-Paclitaxel,
E-P	Epirubicin-Paclitaxel,
FEC	5-Flourouracil-Epirubicin-Cyclophosphamide,
VAC	Vincristine-Doxorubicin-Cyclophosphamide,
VAC-P	Vincristine-Doxorubicin-Cyclophosphamide-Paclitaxel,
VAC-Pr	Vincristine-Doxorubicin-Cyclophosphamide-Prednisolone,

TREATMENT MODALITIES

C	chemotherapy
CH	chemotherapy+ hormonal therapy
CR	chemotherapy+ radiotherapy
CRH	chemotherapy +radiotherapy+ hormonal therapy
CRHT	chemotherapy+ radiotherapy+ hormonal therapy+ targeted therapy
CRT	chemotherapy+ radiotherapy+ targeted therapy
H	hormonal therapy
NON	no treatment prior to presentation
SCH	surgery +chemotherapy +hormonal therapy
SCHT	surgery +chemotherapy +hormonal therapy+ targeted therapy
SCRH	surgery +chemotherapy +radiotherapy+ hormonal therapy
SCRHT	surgery +chemotherapy+radiotherapy+hormonal therapy+targeted therapy
SCR	surgery +chemotherapy+ radiotherapy
SC	surgery +chemotherapy
SH	surgery +hormonal therapy
S	surgery

CHAPTER ONE

1.0 INTRODUCTION

1.1 Adjunctive Use of Chemotherapy with Surgery and Radiation in Breast Cancer Management

The inability of old or damaged cells to detach or undergo apoptosis often disrupts the normal growth of new replacing cells resulting in uncontrolled and unregulated division or growth of many abnormal cells (tumour or cancerous cells) at same time. These cancer cells usually divide uncontrollably to invade other body cells (NCI, 2012; ACS, 2013). The continuum cell cycle (mitosis, cytokinesis and interphase phases) consists of cell division (duplication), proliferation and differentiation giving rise to two progeny or daughter cells. The mitotic division of the cellular content of a cell leads to its cytokinetic splitting into two progeny cells that maintain separate cellular functions for some time (Go) called the resting period. The interphase is a growth phase that occurs in three stages of Gap1 (G1), synthesis (S) and Gap2 (G2), corresponding to a doubling in size at steady state growth, cellular DNA synthetic duplication and a protein synthesizing growth phase that precedes mitosis (M-phase). Cancer or tumour cells often begins from the alteration or deregulation of some regulatory factors that control the rate of cellular proliferation from Go to G1 and/or G1 to S stages of cell growth.

Cancers are classified based on the cells / tissues or organs of origin; for instance, lung cancer from within the bronchi or from epithelial tissues as carcinomas (Curado *et al*., 2010). The histological nomenclatural standard of cancer classification provided by the International

Classification of Diseases for Oncology (ICD-O-3) (Percy *et al*., 2000) grouped the different hundred types of cancers into six major categories- carcinomas, sarcomas, myelomas, leukemia, lymphomas and mixed types (NCI, 2014; SEER, 2014). This histological type of classification categorized breast cancers as carcinomas.

Breast cancer is the malignant proliferation of the epithelia cells and tissues of the milk duct and / or lobules of the breast. It occurs in both men and women, although the incidence in males is rare (ACS, 2006; ACS, 2012C). It is the most common of all cancers in women (Parkin *et al*., 2010; Ferlay *et al*., 2013), ranking second to lungs in cancer-related deaths globally (ACS, 2007; Parkin *et al.*, 2010).

The American Joint Committee on Cancer (AJCC) staging system provides a strategy for the grouping of patients with breast cancer with respect to prognosis. This is known as the TNM classification and based on their classification the different stages of breast cancers include:

i.) Stage 1A breast cancer- T1N0M0 (tumour size < or = 2cm, no regional lymph node metastasis and no distant metastasis)

ii.) Stage 1B breast cancer- T1N1M0 (tumour size < or = 2cm, metastasis to movable ipsilateral auxiliary lymph nodes and no distant metastasis) (Appendix II).

Other common types of breast cancers based on histological nomenclature include:

i.) Ductal cancer: - which accounts for over 75% of all breast cancer types and can be either in-situ or invasive to the epithelia cells of the breasts ducts.

ii.) Lobular cancer: - affects breast lobes and also can be either in-situ or invasive in nature. The in-situ types of lobular carcinomas (LCIS) are usually often regarded as risk factors to breast cancer development.

However, less common types of breast cancers also occur, some of which are the inflammatory breast cancer (often misdiagnosed for an infection) and some regarded as benign such as metaplastic, papillary, or paget cancer that originates from nipple ducts (Bursein *et al*., 2008).

Although the histological type of classification is still currently used, other newer classifications also now used are based on patterns of gene expression or molecular features of the cancer cells; and of which breast cancer is of three groups including:

i. luminal (A&B)
ii. HER2-neu
iii. basal type

Previous management strategies of cancers in the 1960s regarded as local methods of treatment were majorly based on surgery and radiotherapy. However, due to rampant occurrence of micro-metastases, chemotherapy was introduced to be used concurrently especially for metastatic cancers. Thus, drugs or chemotherapy are now applied in conjunction with surgery and / or radiation treatments to manage issues of micro-metastases especially in cases of advanced breast cancers (DeVita and Edward, 2008).

Cancer chemotherapy is the use of chemical agents / drugs (anti-neoplastic or cytotoxic agents) to inhibit the spread or cellular division and / or cause the death of cancerous cells. They are

systemic and are used either alone or in combination with other treatment methods prior to or after surgery and / or radiation therapy. The use of chemotherapy as a form of cancer therapy is dated as far back as the twentieth century when transplantable tumours in rodents were used to screen various available chemicals for cytotoxic activities (Law *et al.*, 1949; DeVita and Edward, 2008). Cancer chemotherapy to-date has become highly valued especially in the development of new treatment options.

1.2 Statement of the Research Problem

Breast cancer is one of the high morbidity and mortality cancer types and the most common of all cancers in women that ranks second to lung cancer in cancer-related deaths globally (ACS, 2007; Parkin *et al.*, 2010; Ferlay *et al*., 2013). Thus, breast cancer is a major health care problem in both developed and developing countries. World Health Organization (WHO) in 2004 noted cancer generally, as a disease of global burden and reported in 2005 that a vast majority - more than 70% of the 7.6 million documented global cancer-related deaths occurred in developing countries including Africa in which Nigeria is situated.

The high death rate from breast cancer (40% in middle income countries and 60% in low incomes countries) often linked to inadequate diagnostic programmes for early detection and / or poor health care systems has persisted despite series of awareness campaigns on frequent self breast examinations for early detection and / or improvement in treatment options of chemotherapeutic regimens (Parkin *et al*., 2003; Carrick *et al*., 2005).

1.3 Justification of Study

The increasing prevalence and incidence of breast cancer in developing countries has made it necessary to re-evaluate the chemotherapeutic management schedule to ascertain the causes of the high mortality rate associated with breast cancer. There is also the need to assess the end of treatment outcome of each chemotherapeutic regimen, with regards to associated frequency of relapses (reoccurrences and refractoriness) and / or toxic effects, disease free intervals and the overall response patterns.

There is need to evaluate the management protocols related to the prevalent choice of chemotherapeutic regimens in the light of WHO and the international agency for cancer research guidelines; as to access the outcomes of such choices in complete remission for survival, in the various presenting stages of breast cancer to enable optimum drug selection.

Although the overall poor clinical response rate to neoadjuvant chemotherapy in advanced breast cancers is primarily due to late presentation, poor attitude of patients to therapy and follow-up, and the fact that metastatic breast cancers remain essentially incurable (O'Shaughnessy, 2005; Arowolo *et al.,* 2010); there is need to ascertain regimens of highest degree of activity for palliative care of patients at the terminal stages of cancer.

The study centre, Ahmadu Bello University Teaching Hospital, Zaria, in Kaduna state of northern Nigeria, is a centre for excellence in cancer research and treatments. It treats referrals from other centres all over Nigeria as well as patients within the state; and thus, is a good heterogeneous care centre for cancer patients for a study of this sort, which to the best of the researcher's knowledge had not yet been conducted.

1.4 Aim and Objectives of the Study

1.4.1 Aim

The main aim of this study is to evaluate the outcomes of the chemotherapeutic management of breast cancer patients at Ahmadu Bello University Teaching Hospital (ABUTH), Zaria retrospectively.

1.4.2 Specific Objectives

The specific objectives of the study include:

1. To assess the frequency of occurrence of breast cancer at Ahmadu Bello University Teaching Hospital (ABUTH), Zaria within the 5 years study period.
2. To evaluate the documented predisposing risk factors and to ascertain the expression patterns of presented cases of breast cancer at ABUTH, Zaria within the study period.
3. To assess the overall chemotherapy response outcome of breast cancer patients at ABUTH, Zaria.

1.5 Research Questions

1. Are there any differences in the prevalence of breast cancer amongst male and female patients at ABUTH, Zaria?

2. What predisposing risk factors have been documented for breast cancer in the Nigerian woman at ABUTH, Zaria?

3. Do the newer chemotherapeutic agents confer any additional benefit on the cancer patients when used in terms of overall survival?

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Incidence and Prevalence

Breast cancer is highly invasive and had been rated the second most frequent cancer type in both men and women (Boyd, 2001; Ferlay *et al*., 2013). It is a global disease occurring most in developed countries, but majority of all breast cancer-related deaths occur in developing countries (WHO, 2004; Ahmedin *et al.*, 2011). It accounts for 22.9% of all invasive cancers and women are highly susceptible to it. Out of the 16% women deaths from all cancer types, 13% was due to breast cancer (Ahmedin *et al.*, 2011). The low survival rate from breast cancer in developing countries as reported by Coleman *et al.* (2008) has been attributed to various factors including:

- lack of early detection programs and / or late presentation to clinics: this is because cancer is preventable and also responds well to treatment at its early phase of development during which complete remission is possible. Late presentation at the advanced stage of the cancer is associated with an attendant poor prognosis (Ekanem and Aligbe, 2006).
- lack of adequate diagnostic measures and primary health care management and / or treatment facilities which is commonly observed in developing countries.

The incidence of breast cancer in sub-Saharan African and in Nigeria particularly is steeply rising with a male to female ratio of 1:67 (Anyanwu, 2000; Steward and Kleiheves, 2003; Curado *et al.*, 2007). The number of women at risk of breast cancer in Nigeria increased steeply

from 24.5 million in 1990 to approximately 40 million in 2010 and had been projected to rise to 50 million in 2020 (Ankarolol-Anthony *et al.*, 2010). Majority of the female breast cancer cases in Nigeria had been shown to occur at the peak age of the fifth decade with the most common of these breast cancers being the invasive ductal carcinoma (Ekanem and Aligbe, 2006; Abdulkareem, 2009). However, a study conducted in the eastern part of Nigeria sometime ago, showed that 45% of the women with breast cancer were at age 40 and below (Njeze, 2001). The estimated prevalence of male breast cancer in Nigeria is 3.7-8.6% (of all breast cancers cases), which is higher than the 1% recorded from other parts of the world (Ekanem and Aligbe, 2006; Abdulkareem, 2009).

2.2 **Aetiological Risk Factors**

The aetiology of breast cancer in humans remains largely unknown and it has also not been possible to detect the specific risk factors involved in breast cancer (Broeders and Verbeek, 1997; Kahlenborn *et al.*, 2006; Lacery, 2009). However, three main factors involved include:

i. Family history (genetic predisposition)
ii. Hormonal and reproductive factors
iii. Environmental factors

Positive first degree familial history and /or presence of some germ-line gene abnormalities such as breast cancer – 1 (BRCA-1) gene mutation has been implicated. The genetic predisposition of cancer risks is usually for specific types of cancer initiated in gene within families and which being inheritable cannot be controlled.

The effect of hormonal and reproductive risk factors is also well documented. Although the overproduction of some proliferative and multiplicative hormones such as the growth factor

hormones also tend to cause cancer formation, women are also compulsorily exposed to some other endogenous reproductive hormones at the onset of menarche for maintenance of the reproductive cycle. Most of the replacement therapies and / or contraceptives in use are also of hormonal formulations. Thus, both the endogenous and exogenous estrogen exposure contributes to an increase in the risk of development of breast cancer in women (Kumle *et al.*, 2002A, B).

Epidemiologic analysis in 2005 attributed 73% of breast cancers to environmental factors (Tuncer, 2005). Environmental causes could be from:

- Physical carcinogenic agents (x-ray irradiation, tobacco smoking, stress etc)
- Chemical carcinogens (benzopyrene, polycyclic aromatic hydrocarbons etc)
- Biological carcinogens (viral toxins: aflatoxins, human papilloma virus, mycotoxins; and bacterial toxins)
- There is also the implication of urbanization and / or adoption of western lifestyle / diets as critical predisposing risk factor as well as occupational exposures (ACS, 2012B). Mesothelioma - a rapidly fatal tumour that spreads over the pleural covering of the lung had been associated with exposure from asbestos industry.

Although some risk factors are largely preventable, such as postmenopausal obesity, physical inactivity, use of exogenous oestrogen and progesterone in hormonal replacement therapy and / or contraceptives use, some other risk factors as it relates to sex, age and familial history are not.

The incidence of breast cancer increases with age and although 81% of the cases occur at 50 years and above, Nigerian women were noted to have peak incidence of breast cancer as from 40 years (Adebomowa and Ajayi, 2000). According to the American Cancer Society (ACS, 2009),

95% of new cases and 97% of deaths from breast cancer occur in women 40 years and above. Breast cancer in younger women although less common, when they do occur they tend to be more aggressive with lower survival rates (Ogundiran and Ezeoma, 2008). It had been estimated that 1 in 8 women have a life time risk of breast cancer (Adebomowo and Adekunle, 1999; ACS, 2012A; Youlden *et al.*, 2012).

2.3 Signs and Symptoms

At the earliest phase, most breast cancers are asymptomatic except for an unexplained lump in one or both breasts. However, not all lumps are cancerous and thus, such needs confirmatory evaluations. Breast cancer symptoms are usually later detected long after the appearance of the cancer and include:

i. nipple abnormalities as: nipple erosion or tenderness, milky or bloody discharge swelling on a part or entire breast with or without lump
ii. reddish colour or texture changes of the overlying skin of the breast
iii. pain may or may not be present, but is mostly absent except in advanced cases

The late stage symptoms include: pain and discomfort including bone pain, skin ulcers, swelling of arm next to the affected breast, lymph nodes enlargement and unexplained weight loss (ACS, 2012A).

2.4 Diagnosis

The diagnosis of breast cancer consists of:

i. Physical or clinical breast examination comprising of visual examination for visible changes in colour, texture, nipple inversion as well as auxiliary lymph nodes inspection.

ii. Mammography
iii. Ultrasound
iv. Magnetic resonance imaging (MRI) and Positron emission tomography (PET) Scans
v. Definitive biopsy (NCI, 2014)

Self awareness has been shown to be more effective in detecting breast cancers than structured breast examination (Semiglazov *et al.,* 1999; Smith *et al*., 2011).

Mammography is a low dose x-ray procedure that screens the internal structures of the breast. It is mostly effective for early detection of breast cancer prior to the appearance of symptoms and it tends to differentiate between benign and cancerous tumours (Smith *et al.*, 2011). However, it does not easily detect lobular carcinoma which could be missed out when used alone.

Breast ultrasound uses sound waves to examine the breast lumps detected from routine mammography and differentiates solid tumours from cysts (fluid filled cell mass).

Magnetic resonance imaging (MRI) is a diagnostic test that utilizes powerful magnets and radio waves to create visual images of the part of the body being examined. It is often used to confirm the presence or absence of breast cancers. It can also be used to detect whether the tumour has metastasized (Sashon *et al*., 2007). MRIs are used to supplement and not to replace mammography.

Positron emission tomography (PET) scan is a technique that uses radioactive tracer substances to detect lumps and / or cancerous masses within the breast.

Breast biopsy is the surgical removal and examination of tissue samples of the breast for the presence / absences of cancerous cells. The different types of biopsies used in breast cancers detections include open / surgical, fine needle aspiration (FNA), core and sentinel lymph node biopsies.

Following diagnosis, immunohistology and compatibility testing are then carried out on cancerous cells to detect the presence or absence of hormone receptors. The principle is based on the fact that tumour cell surfaces contain receptors that are capable of binding to either oestrogen or progesterone denoted as ER / PR (estrogen or progesterone receptors). Usually, the more the number of receptors on the tumour cell surface as ascertained by the ER / PR test post histology, the more responsive it would be to hormonal therapy (Abdulkareen, 2009). Other tests are also used to measure the levels of the human epidermal growth-factor receptor 2 gene (HERs 2-neu) on tumour surfaces. Thus, a tumour cell might be of ER positive, PR positive, HERs 2-neu positive or of their negatives. These characterizations could also occur in varied combinations and often serve as aid in the selection of treatment options.

2.5 Classification of Breast Cancer

1. Breast cancer has been classified based on the tumour size, lymph node involvement and metastasis (TNM) stages. This type of classification reflects the extent and spread of the cancer cell as it relates to size, lymph node involvement and evidence of metastasis. This classification by TNM stage system of the American Joint Committee on Cancer (AJCC, 2002) provides a strategy for grouping of breast cancer with respect to prognosis as to enable therapeutic decisions. This method of classification uses both the anatomical and pathological features of the breast cancer to group them as either stages 0, IA, IB, IIA, IIB, IIIA, IIIB and IV (Appendix II).

2. Breast cancer had also been classified based on the molecular features / gene expression patterns and the various types include:

i. Luminal types (A&B):- these are of oestrogen receptor positive (ER+) of varied growth rate and prognosis. Luminal A is of low grade, slow growth and good prognosis, while luminal B is of high grade, rapid growth and poor prognosis.

ii. HER2 types: - these are of human epidermal growth factor receptor 2 gene-proteins' over expression. It is of high grade with rapid growth and poor prognosis.

iii. Basal or triple-negative type: - these are of normal growth factor receptor 2 genes, but also lack oestrogen or progesterone receptors. It is of high grade, rapid growth with poor prognosis. It is usually from genetic predisposition of germ-line abnormality of breast cancer-1 (BRCA-1) gene mutation **(**Edge *et al.*, 2010; Adisa *et al*., 2012).

The prognostic status including tumour size, lymph node status, metastasis, oestrogen-progesterone-receptor levels and presence of human epidermal growth factor receptor status are usually the primary determinants of treatment decisions. The selection of various treatment options is influenced by these clinical and pathological features thereby reducing the cumbersomeness of regimens selection (NCI, 2000).

2.6 Breast Cancer Management

The major goal of breast cancer management is curative, which is to completely rid the body of cancerous cells and possibly prevent reoccurrence. However, this is often not possible in cases of advanced / metastatic breast cancers, for which the treatment aim becomes palliative to control symptoms as to improve patients' quality of life (QoL) and / or prolong survival time (Karamouzis *et al*., 2007; NCCN, 2013; WHO, 2013).

The choice of treatment option in breast cancer management is determined by several factors, including i.) the clinical and pathological features of the cancer, and ii.) cost and availability of health-care facilities (chemotherapeutic agents, surgical and radiotherapy). Treatment options for breast cancer may be broadly divided into local and systemic types. The local treatments are surgery and radiotherapy, while the systemic treatment refers to the use of hormonal, targeted and chemo- therapies (ACS, 2015).

2.6.1 Local treatments (surgery and radiotherapy)

2.6.1.1 Surgery

Surgery is often used to detect, repair or remove a diseased part of the body. In breast cancer management, it is used to remove the cancerous cell / tissues of the breast. The various types of surgeries used in breast cancer management include:

1. Breast conserving surgery

2. Mastectomy (simple / total mastectomy, modified radical mastectomy, radical / halsted mastectomy, partial mastectomy and subcutaneous (nipple-sparing) mastectomy) (NCI, 2014).

2.6.1.2 Radiotherapy

Radiation or radio- therapy utilizes high energy rays (x- or gamma rays) to destroy cancerous cells. It is a targeted treatment directed to the cancer cells to destroy them as to prevent their further growth. Radiation-induced damaged cells are often not able to undergo repair. It is used as an adjunct therapy to breast conservative surgery (BCS) or mastectomy. The two types of radiation therapy are brachytherapy (internal beam radiation therapy) and teritherapy (external

beam radiation therapy - EBRT), the choice of which is to be used depends on the type, stage and location of the tumour. The associated side effects include sunburn-like reddening and peeling of breast skin, Loss of underarm hair, pin-needle sensation in the treatment area and fatigue.

2.6.2 Systemic treatments (targeted, hormonal and chemo- therapies)

2.6.2.1 Targeted therapy

There are also targeted drug formulations designed to selectively identify and attack specific cancer cells without damaging normal cells. The cancer cell growth promoting protein (HER2-neu) which has been found to be overproduced in about 15-30% of all breast cancer cases is an example of the many sites of targeted therapies (ACS, 2012A; Shu Guang and Li, 2013). HERs-2-neu is often associated with breast cancers of rapid growth and high reoccurrence rate (Crown *et al*., 2002). Some targeted drug therapies used in breast cancer management include the monoclonal antibodies (Trastuzumab, Rituximab) and tyrosine kinase inhibitors (Imatinib, Gefitinib).

2.6.2.2 Hormonal therapy

Hormonal therapy is usually indicated in the treatment of hormone receptor positive (ER_+&PR_+) breast cancer cases. This type of drugs used to manipulate the endocrine system includes anti-estrogens, aromatase inhibitors and luteinizing hormone-releasing hormone (LHRH) inhibitors and their analogues.

2.6.2.3 Chemotherapy

The chemotherapeutic agents used in the treatment of cancers are cytotoxic (antineoplastic) agents and are used for maximum damage to the cancer cells, but which most times also cause

some damage to healthy cells (ACS, 2014). Chemotherapy can be used as either the primary or secondary treatment options and may either be for palliative or curative treatment. Chemotherapy acts to prevent micro-metastases of the cancer cells to other tissues / organs by inhibiting rapidly dividing cancer cells via interference with the cancer cell divisions and / or their other metabolic processes. The benefit to be derived from breast cancer chemotherapy often depends on a number of factors such as:

- tumour size
- Number of involved lymph nodes
- Presence / absence of estrogen and progesterone receptors
- Amount of HERs-2neu protein available for the cancer cells

Specific chemotherapeutic treatment schedules or cycles are usually maintained during treatments and most of which are completed within 3 to 6 months (ACS, 2013). Chemotherapy is most effective when the full dose and cycle is completed in a timely manner. Although some single drug therapies such as cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin, paclitaxel and docetaxel had been used in the treatment of HERs-2neu negative breast cancer types, combination therapies had been found to be more effective than single therapies in most breast cancer cases (NCCN, 2014).

2.7 Indications for Chemotherapy in Breast Cancer

The three basic indications for the use of chemotherapy in breast cancer include:

2.7.1 Primary systemic chemotherapy (Neoadjuvant)

Neoadjuvant chemotherapy is used for the treatment of cases of locally advanced breast cancer where surgery is inappropriate. This type of chemotherapy slows down the rate of growth of

tumour cells and thus, is often used prior to surgery to cause shrinkage of large tumours and making them operate-able.

2.7.2 Palliative chemotherapy

Palliative chemotherapy is used for advanced cases of breast cancer involving metastases to various vital organs. It slows down the rate of growth of secondary cancers and improves the patient's quality of life.

2.7.3 Adjuvant chemotherapy

This is often used after surgery (either breast-conservative or mastectomy) and also prior to radiotherapy. Adjuvant chemotherapy prevents the possibility of reoccurrence and its use is usually initiated 4 weeks after surgery (EBCTCG, 2005).

2.8 Chemotherapeutic Drugs for Breast Cancer Management

Cytotoxic agents are generally classified based on their chemical structure, biological source or mechanisms of action (cell cycle specific and cell cycle non-specific agents). The most used classification of chemotherapeutic agents is that based on the mechanism of action and of which the types of drugs for breast cancer include:

i. **Alkylating Agents**

- Nitrogen mustards (cyclophosphamide)
- Platinum complexes (cisplatin)
- Non-classic alkylators (temozolomide -in cases of brain metastasis)

ii. **Antimetabolites**

- Folate analogs (methotrexate)
- Pyrimidine analogs (capecitabine, gemcitabine)

iii. **Natural Products**

- Antitumor antibiotics (doxorubicin, epirubicin)
- Microtubule agents (docetaxel, paclitaxel, vinblastine, vinorelbine - in cases of brain metastasis)

iv. **Targeted Agents**

- Monoclonal antibodies (bevacizumab, trastuzumab)

v. **Others**

- Bisphosphonates (in cases of bone metastasis) (Takinoto, 2008).

2.8.1 Alkylating agents

The alkylating agents act by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups of biologically important molecules to impair their cellular functions. The most important molecular sites of alkylation are the DNA, RNA and essential proteins. They include nitrogen mustards (cyclophosphamide), nitrosoureas, and platinum complexes (cisplastin) (DeVita and Edward, 2008). Major side effects of all alkylating agents include: - Hematopoietic (low counts), gastrointestinal (nausea and vomiting), gonadal, pulmonary, immunological, dermatological effects; cyclophosphamide and ifosfamide are associated with alopecia (Chabner *et al*., 2008).

2.8.2 Antimetabolites

Antimetabolites are structural analogs of natural substrates in the DNA and RNA synthesis that resembles the normal metabolites (purine or pyrimidine) required for cellular functions and replication. Antimetabolites interact directly with specific metabolic enzymes and either inhibits the production of the enzymes or produce nonfunctional end products (Takimoto et al., 2008). They can also exert their cytotoxic activity by either competing for the catalytic or regulatory sites of the enzyme with normal metabolites or substituting for a metabolite that is normally incorporated into DNA and RNA. They are most active when cells are in the S-phase of a high growth fraction and have little effect on cells in the G_0 phase. The antimetabolites used in breast cancer chemotherapy include folic acid antagonist (e.g. methotrexate), pyrimidine antagonist (e.g. gemcitabine, fluorouracil) and purine antagonist (e.g. 6-mercaptopurine - 6-MP).

2.8.3 Natural products

A wide variety of semi-synthetic and synthetic compounds of antitumor activity manufactured from isolates of natural substances such as plants, fungi, and bacteria has also over the years been used. These natural antitumor products are majorly antibiotics of cell cycle specific effects that act by inhibiting the nucleic acids' (DNA & RNA) synthesis or functions (Demain and Preetiv, 2011). The antitumor antibiotics used in breast cancer chemotherapy include: anthracyclines (e.g. doxorubicin also called adriamycin, epirubicin), anthracenidiones (e.g. mitoxantrone), chromomycins (e.g. dactinomycins), miscellaneous (e.g. mitomycin, bleomycin).

2.8.3.1 Doxorubicin

Anthracycline antibiotic is obtained from the fungus (*Streptomyces percetus var caesius)*. The basic anthracycline structure contains a glycoside that is bound to an amino sugar –

daunosamine, but they are of differing modes of action that includes their ability to inhibit topoisomerase II enzyme, ability to insert in-between DNA base pairs and also ability to produce oxygen radicals for interfering with mitochondrial function. Doxorubicin is maximally cytotoxic during the S-phase and its major side effects include myelosuppression, mucositis, stomatitis, cardio- and hepato- toxicities.

2.8.3.2 Vinca alkaloid

The cytoskeletal tubulin is a dimeric protein that tends to polymerize into microtubules. Vinca alkaloids derived from the periwinkle plant (*Vinca rosea)* are often highly affiliated to this cytoskeletal tubulin and tend to bind rapidly to it, thus disrupting its normal polymerization into intracellular microtubular system. This binding occurs mostly at the S-phase, but often results in impaired mitotic (M-phase) spindle formation and / or inadequate cellular division and replication (mitosis). The vinca alkaloids used in breast cancer chemotherapy are vinblastine, vincristine and vinorelbine.

2.8.3.3 Microtubule agents (Paclitaxel)

Paclitaxel (Taxol) is a complex diterpin taxane obtained from the bark of Western yew tree. It is a new cytotoxic agent of a novel mechanism of action, often called a mitotic inhibitor. It acts by targeting and sticking on to rapidly growing or dividing cancer cells to prevent and / or inhibit the division process such that progeny cells are not formed or produced vis a vis preventing metastases (Horwitz, 1994). Major adverse effects of paclitaxel include: myelosuppression, chest pain, arthralgia, myolgia, edema and mucositis.

2.9 Combination Therapy Regimens Used for Breast Cancer Management

Drugs can be used singly or in fixed dosage combinations. Combination therapy is a method of overcoming the global challenge of drug resistance. It is the simultaneous use of two or more drugs co-formulated or co-administered which have independent modes of action and different biochemical targets for synergistic effects. Several combination therapies are available for different ailments. The use of combination therapy (polytherapy) in most breast cancer cases has been found to be more effective than single drug therapy especially in metastatic breast cancers (Carrick *et al.*, 2005). Although, the impact of such combined breast cancer regimens on the overall survival is not well documented (Pronzato and Rondini, 2006), those of efficacious and safety profile are being used for palliative therapy, while monotherapy is still currently encouraged. The commonly used combination chemotherapeutic regimens that had been found to be effective include:

- **CAF** **(**Cyclophosphamide, Adriamycin, 5-Fluorouracil)
- **FEC** (5-Flourouracil, Epirubicin, Cyclophosphamide)
- **AC** **(**Doxorubicin (Adriamycin), Cyclophosphamide)
- **CMF** (Cyclophosphamide, Methotreaxate, 5-flourouracil)
- **E-CMF** (Epirubicin-Cyclophosphamide, Methotrexatre, 5-Flourouracil)
- **FEC-T** **(**5-Flourouracil, Epirubicin, Cyclophosphamide-Taxanes)

These regimens for adjuvant chemotherapy use have their respective recommended durations of administration (therapeutic schedules or cycles) ranging from 3-6 months with intermediate periods of recovery or effectiveness assessment prior to another dose-course of the drug (ACS, 2009; NCI, 2014; NCCN, 2014).

2.10 Factors that Influence Choice of Chemotherapeutic Regimens

The choice / selection of the chemotherapeutic regimens for use depend on various factors such as: age, comorbidity, hormone receptor status, site and number of metastases and performance status or outcome of previous therapy (Grag *et al.*, 2008; Dear *et al.*, 2009).

2.10.1 Age and comorbidities

The incidence of breast cancer increases with age and although 81% of the cases occur at 50 years and above, Nigerian women were noted to have peak incidence of breast cancer as from 40 years (Adebomowa and Ajayi, 2000). Comorbidity increases with increasing age and majorly affects treatment selection. Research has shown that multidrug therapy is not only of synergistic benefits, but may also be of synergistic side effects especially in impaired vital organs functions such as renal inadequacy that often occurs in advancing age with increased risk of drug toxicities (Floyd and Nguyen, 2005; Burdette-Radoux and Muss, 2006).

2.10.2 Hormone-receptor status

Apart from the tumour size and lymph node status, the oestrogen - progesterone-receptor levels as well as presence of human epidermal growth factor receptor status over expression are also the primary determinants of treatment decisions. These clinical and pathological features of tumour cells if determined often help to reduce the cumbersomeness of regimens selection. Usually, the more the number of hormone receptors on the tumour cell surface (positives) as ascertained by the ER/PR post histology test, the more responsive the tumour would be to hormonal therapy. Thus, Hormone receptor positives benefit less from adjuvant systemic chemotherapy and this may not serve an optimal treatment choice in such cases if used alone (Vanc der Hage *et al.*, 2007). Breast cancers of ER/PR negatives and/or HERs 2-neu positive are

often regarded as aggressive and thus, requires prompt chemotherapeutic management. When a tumour cell expresses hormone receptor negatives, such tumor may not be effectively managed by hormonal and targeted therapies and may rather require chemotherapy of various combinations and vice versa. Researchers have established that triple-negative breast cancers have poor prognosis as they lack common therapeutic targets that thereby make the clinical management particularly difficult as against the triple positive types that are usually more responsive to hormonal and targeted therapies (Verma *et al.*, 2011).

2.10.3 Site and number of metastases

Visceral metastases are generally more aggressive cases and hence would require prompt and aggressive therapy, while confined cancers (either to the bones or soft tissues) are milder. In all however, metastatic breast cancers remain essentially incurable, but indicates the use of regimens of highest degree of activity for palliation (O'Shaughnessy, 2005).

2.10.4 Performance status or outcome of previous therapy

The status of the disease as well as tolerability to previously used drugs also determines regimen selection. Patients could present with recurrent breast cancer in form of relapses and thus may require a change to a regimen of a long relapse-free interval. Relapses that occur before 12 months are most often assumed to be due to the ineffectiveness of the regimen. The efficacy and safety profile of the available chemotherapeutic regimens also varies among the types of breast cancer cases and patients. Patients that present serious side effects to particular regimens also need to be reevaluated in terms of dose adjustments or regimen changes (Pronzato and Rondini, 2006). Thus, in addition to efficacy, the convenience of dosing (for example once daily against

three or four times daily) and the potential of fewer side effects also influence the choice of an initial medication.

2.11 Outcome of Chemotherapy in Breast Cancer

The growing number of available chemotherapeutic agents, combination regimens and sequences of administration arose due to the significant achievements demonstrated in the systemic treatment of advanced cases of breast cancer. However this has made the clinical development of novel therapies progressively more complex. Many randomized trials in both early-stage and metastatic breast cancer have studied various clinical end-points of chemotherapy such as: progression free survival (PFS), overall survival (OS), pathologic complete remission (pCR), time to progression (TTP), hazard ratio (HR) and response rate (RR). These outcomes are grouped as either primary or secondary end-points depending on the nature and duration of the study.

The outcomes / response to the different chemotherapeutic regimens are assessed either physically, radiographyically, histologically and/ or sonographically. Most randomized studies on solid tumor oncology have used RR, TTP and PFS as primary endpoints of chemotherapy. Very few phase III randomized trials have compared two different chemotherapy regimens. However for the few conducted the usual outcome apart from the safety profile of the regimen, were those relating to RR and TTP. Very few reported any data on the survival rate of the medications.

Although anthracyclin-cyclophosphamide (AC) is a commonly used first-line chemotherapy regimen, recent data from phase III trials show RR as low as 37-57% with a mean TTP of 6-

9months for FAC-type regimen (Biganzoli *et al*., 2002). The addition of paclitaxel (PXT) to AC provided a significant increase in the duration of disease-free survival than when AC was used alone. However, no significant change was observed in the overall survival of both groups (Mamounas *et al.*, 2005).

A single-center descriptive study on the impact of neoadjuvant chemotherapy on advanced breast cancer produced a poor overall clinical response rate which can be attributed to late presentation of cases and poor attitude of patients to therapy and follow-up (Arowolo *et al*., 2010). However a similar study conducted in the eastern part of this country, showed the efficacy of using an A-based regimen as neoadjuvant chemotherapy of breast cancer in advanced premenopausal breast cancer (Anyawu *et al*., 2010).

2.12 Side Effects of Chemotherapy

The toxic effects associated with cancer chemotherapy are as a result of the inability of chemotherapeutic agents to distinguish between healthy cells and cancer cells. Hence, most of the noted adverse effects are as a result of the toxic effects of the drugs on normal healthy cells and are peculiar to the drug types, the dose administered and the duration of therapy. However, most of the side effects are short-term and reversible, some of which include alopecia, mucositis, anorexia, increased appetite, nausea and vomiting, bone marrow suppression (which may result in fatigue, an increased susceptibility to infections and / or risk of hemorrhage). Some side effects specific to breast cancer drugs include:

- Neuropathy: Taxanes (docetaxel & paclitaxel), and Platinum agents (cisplatin)

  Vinorelbine

- Cardiomyopathy: Doxorubicin, Epirubicin
- Hand-foot syndrome: Capecitabine and liposomal doxorubicin. Early symptoms include numbness, tingling, and redness, progressing to swollen and painful hands and feet.

These side effects are usually considered during drug selection and patients must be instructed about the symptoms or signs that would require the health care provider's attention for a close follow-up and/or prompt reversal (Lowenstein, 2008).

CHAPTER THREE

3.0 MATERIALS AND METHOD

3.1 Study Design

This retrospective study was conducted using the hospital medical records (folders) of patients from the National Cancer Registry of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Kaduna State. Ethical approval (Appendix I) for the study was obtained from the Ethical Committee of the Teaching Hospital prior to commencement of the study. Folders of patients diagnosed with breast cancer at the Oncology and Radiotherapy Department of ABUTH, Zaria within the study period of January 2005 to December 2009 was retrieved.

3.2 Study Area

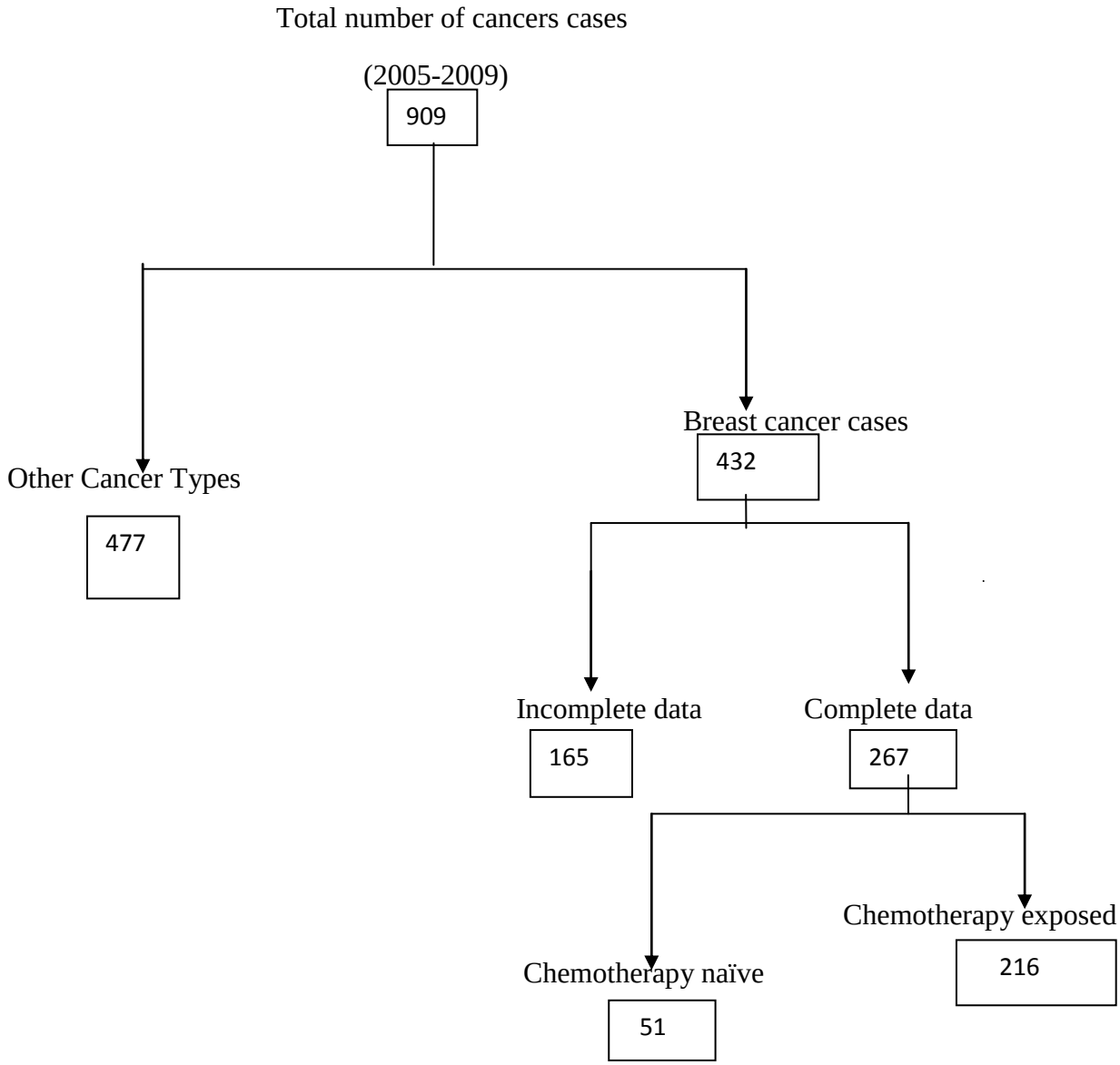
Zaria is one of the major cities in Kaduna state located in the northern Nigeria which is ranked the third most populous state in Nigeria (NPC, 2006). It has an adjusted population of over 420,000, with a good representation of all tribes of the country. It also houses the centre for excellence in cancer research and treatment in ABUTH, Zaria. The centre provides care and treatment to patients all over Nigeria. It also serves as a referral centre. Hence this provides a heterogeneous study population.

3.3 Inclusion and Exclusion Criteria

Inclusion: All cases of breast cancer diagnosed and managed in the Oncology and Radiotherapy unit / clinic of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria within the study period irrespective of the sex of patient, age, menopausal status, presence or absence of cofactors, stage at presentation at the clinic and whether or not, the patient has had any form of treatment prior to presentation.

Exclusion: All patients diagnosed with any other type of cancer during the selected period of study and those having not been on any form of chemotherapeutic regimen (chemotherapy naïve) were excluded.

3.4 Sampling



In all, 216 folders of patients diagnosed with breast cancer that were in attendance to the clinic within the study period fulfilled the criteria for this study.

3.5 Data Collection

The folders, registers and disease index cards of patients from the National Cancer Registry section of the Oncology and Radiotherapy Department of this study centre were retrieved and the

totality of the various cancer types diagnosed in the five year study period including the number of breast cancer cases diagnosed in each of the 5 year study period together with relevant information for each patient as stipulated in a detailed data capturing or extraction form designed for data collection (Appendix III).

3.6 Data Analysis

Statistical Package for Social Science (SPSS) software program version 18 was used for data analysis. Descriptive statistics was used to analyze the patients' socio-demographic data, predisposing risk factors, expression pattern, organs of metastases, age and level of education of patients, treatment modalities and as well as disease free interval. Results are presented as charts or tables where appropriate.

CHAPTER FOUR

4.0 RESULTS

4.1 Prevalence of Various Types of Cancer in ABUTH within 2005-2009

From the recorded data of the disease index cards of ABUTH, Zaria; breast cancer had the highest frequency of occurrence within the study period (47.5%), followed by cancer of the cervix (35.9%) (Table 4.1).

Table 4.1: Recorded Types of Cancers from the Index Cards of ABUTH, Zaria within 2005 to 2009

Type	**Frequency**	**Percentage (%)**
Breast	432	47.5
Cervix	326	35.9
Skin Melanoma	65	7.2
Naso- pharynx	32	3.5
Prostrate	18	2.0
Kaposi Sarcoma	11	1.2
Rectum	10	1.1
Bone	8	0.9
Non-Hodgkin's	4	0.4
Hodgkin's	3	0.3
TOTAL	**909**	**100**

4.2 Incidence of Breast Cancer within the Study Period of 2005-2009

Generally, there was a progressive increase in the number of breast cancer cases from 2005 to 2008. However, a decline in the number was noted in 2009 (Fig. 4.1).

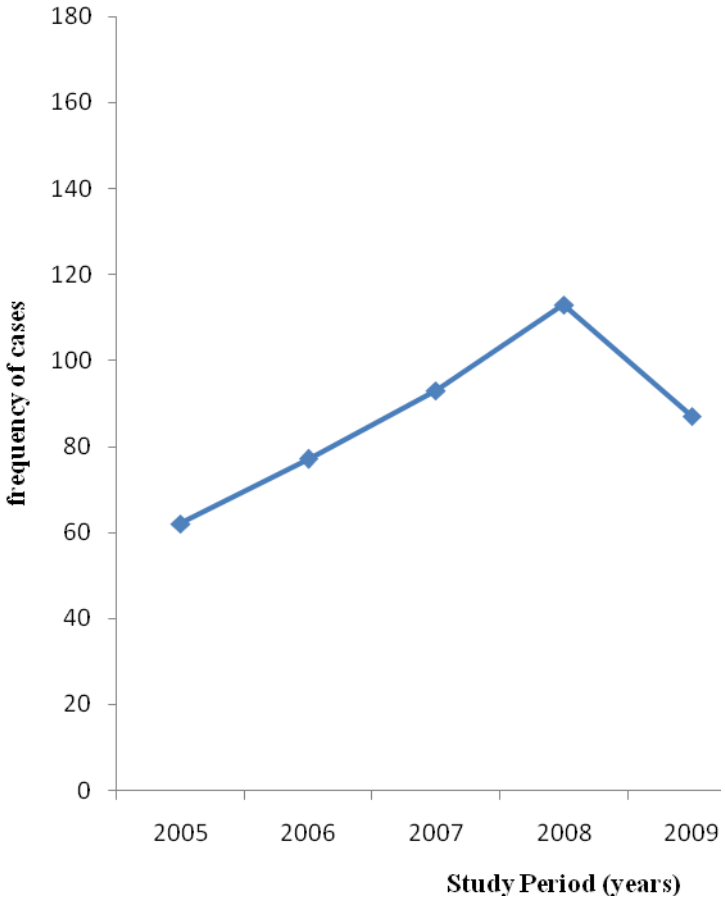


Fig 4.1: Breast Cancer Cases Presented at ABUTH, Zaria, in each of the 5 years Study Period

4.3 Socio-Demographic Characteristics of Breast Cancer Patients Seen in ABUTH, Zaria within the Study Period

Table 4.2 showed that out of the total of 216 cases of breast cancer, majority (74) of the patients were within the age range of 36-45 yrs, followed by 46-55 yrs. Females had the highest (208) numbers of the cases, majority (105) were civil servants, had tertiary education (115), and were married (193).

Table 4.2: Documented Bio-data of Patients with Breast Cancer at ABUTH, Zaria

Bio-characteristics	Observations	No. of cases	Percentage (%)
Age (yrs) at Diagnosis	≤35	45	20.8
	36 – 45	74	34.3
	46 -55	53	24.5
	56 - 65	28	12.9
	≥66	16	7.4
Gender	Female	208	96.3
	Male	8	3.7
Occupation	House wife	89	41.2
	Civil servant	105	48.6
	Trader	17	7.9
	Tailor	3	1.4
	Farmer	2	0.9
Level of Education	Illiterate	4	1.9
	Primary School	19	8.8
	Secondary School	44	20.4
	Tertiary Education	115	53.2
	Islamic Education	34	15.7
Marital Status	Single	6	2.8
	Married	193	89.4
	Divorced	6	2.8
	Widowed	11	5.1

4.4 Predisposing Risk Factors of Breast Cancer Cases Presented at ABUTH, Zaria within the Study Period

Table 4.3 showed that 16 patients had their age at menarche to be within 9-12 years, 35 patients were within 16-20 yrs age range at their first full term birth, majority (118) of the patients were of premenopausal status. For the contraceptive use, 75 patients were found to have used contraceptives, 26 patients have a positive family history of breast cancer, while 7 patients reported other cancer types within their family.

Table 4.3: Recorded Predisposing Risk Factors of Breast Cancer Patients in ABUTH, Zaria from 2005 - 2009

Risk Factors	Observations	No. of cases	Percentage (%)
*Age at menarche (years)	9-12	16	7.7
	13-16	90	43.3
	17-20	15	7.2
	NA	87	41.8
*Age at first full term birth (years)	11-15	7	3.4
	16-20	35	16.8
	21-25	25	12.0
	26-30	16	7.7
	31-35	6	2.9
	NA	119	57.2
*Menopausal status	Pre	118	56.7
	Post	77	37.5
	NA	13	6.3
*Parity	0	57	27.4
	1-5	83	39.9
	6-10	29	13.9
	11-15	5	2.4
	NA	34	16.3
*Contraceptive Use	No	84	40.4
	Yes	75	36.1
	NA	49	23.5
Family History	Breasts:		
	No	143	66.2
	Yes	26	12.0
	NA	47	21.8
	Other Cancers:		
	No	141	95.3
	Cervical	2	28.6
	Prostate	1	14.3
	Hodgkin's	2	28.6
	Oesophagus	1	14.3
	Colon Cancer	1	14.3

* Indicators apply to only female patients NA- not available

4.5 Age and Educational Status of Patients at the Stages of Presentation within the Study Period

Patients with stage IV disease presented in all the age groups, and many of the patients at this stage were within 36-45 years (Fig 4.2a). Patients with tertiary level of education were majorly diagnosed in all the stages. Patients with primary education and illiterates were the least diagnosed at the various stages (Fig 4.2b).

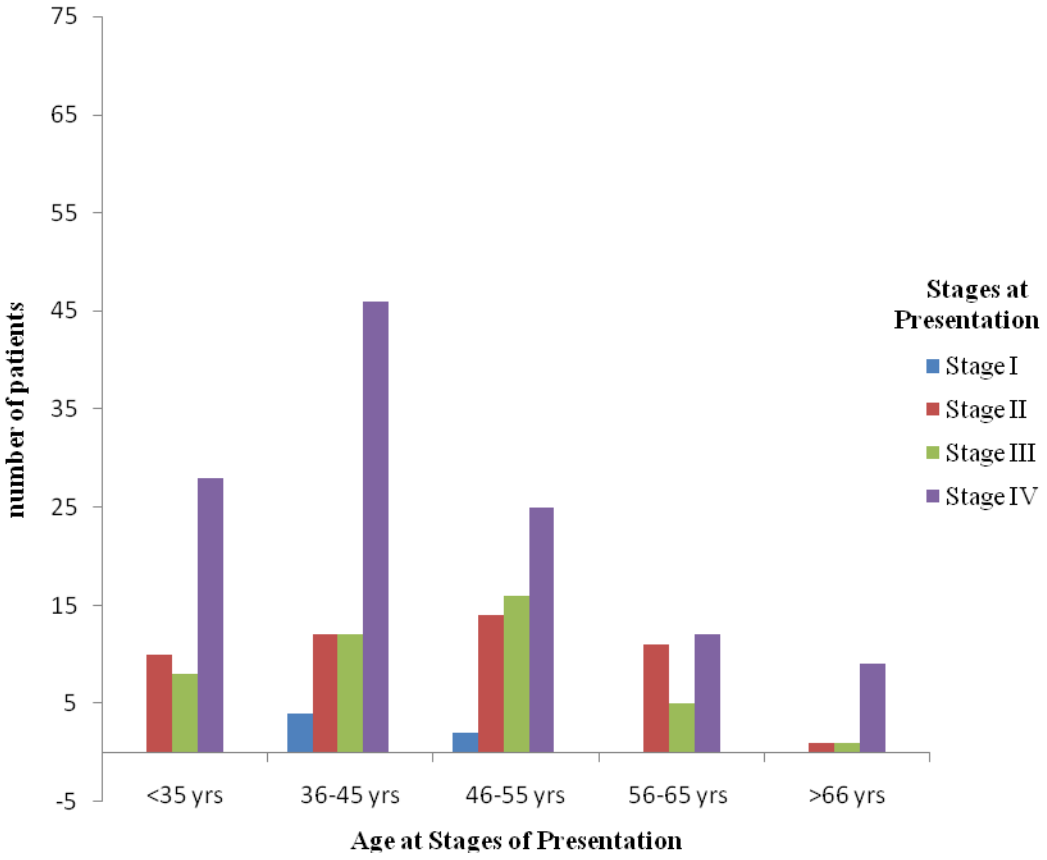


Fig 4.2a: Age at the Stages of Presentation within the Study Period

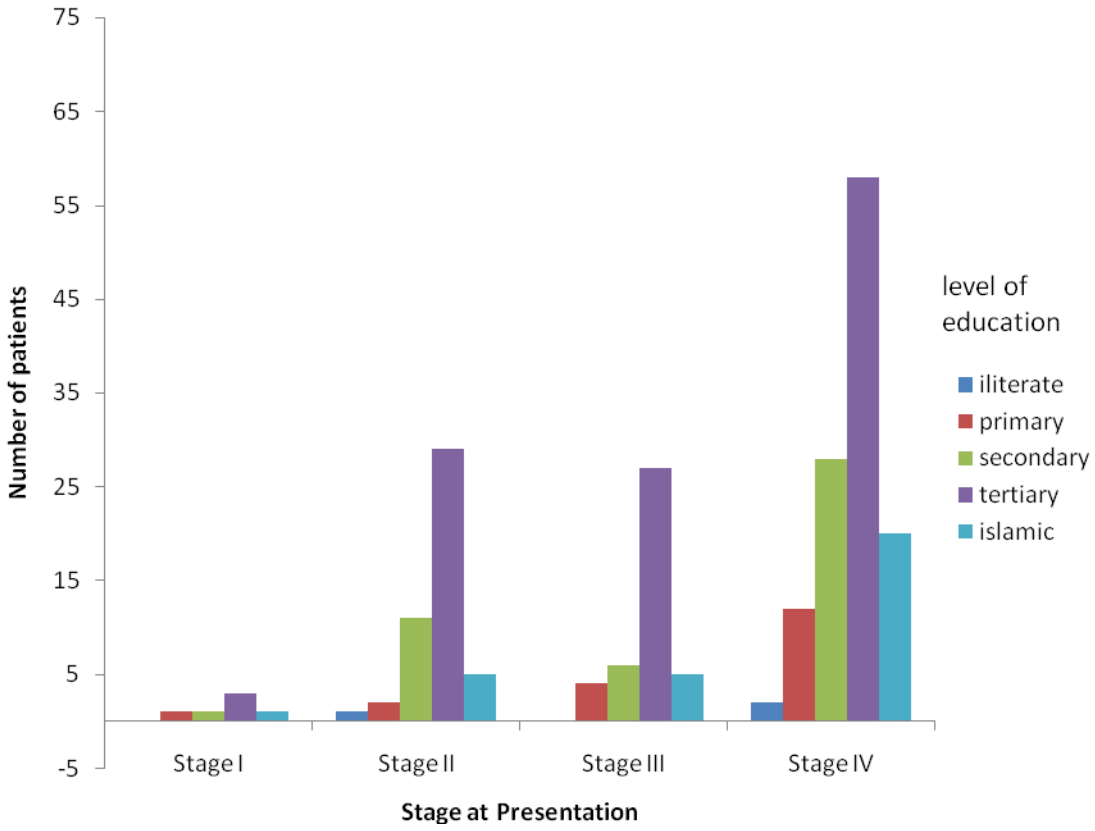


Fig 4.2b: Educational Status at the Stages of Presentation within the Study Period

4.6 The Various Expression Patterns of Breast Cancer Cases Seen at ABUTH, Zaria

Four types of breast cancers based on the histological nomenclature were seen within 2005 to 2009. One hundred and seventy-nine patients had invasive ductal type of breast cancer; seven patients had triple negative ($HER2_{-VE}$, PR_{-VE}, ER_{-VE}) and only five patients had bilateral breast cancer (Table 4.4).

Table 4.4: Expression Patterns of Breast Cancer Cases at ABUTH, Zaria

Expression pattern	Histological findings	No of cases	Percentage (%)
Types	Invasive ductal	179	82.9
	Medullary	15	6.9
	Invasive ductal and lobular	2	0.9
	Invasive lobular	20	9.3
Receptor	$HER2_{+ve}$ ER_{-ve} PR_{-ve}	1	9.1
	$HER2_{-ve}$ ER_{-ve} PR_{-ve}	7	63.3
	$HER2_{+ve}$ ER_{+ve} PR_{-ve}	1	9.1
	$HER2_{+ve}$ $ER_{+ve}PR_{+ve}$	2	18.2
Involved Side	Left	101	46.8
	Right	110	50.9
	Both	5	2.3

HER-2= Human Epidermal growth factor rexptor-2, ER= Estrogen receptor, PR= Progesterone receptor, -ve= Negative, +ve= Positive

4.7 Organs Involved in Metastasis at Various Diagnostic Stages at Presentation

Metastasis was documented for stages III and IV involving organs such as the contra-lateral breast, bone, liver, lung and brain, but the lung seemed more prone to the spread than the other organs as seen in stage IV of diagnosis (Fig 4.3).

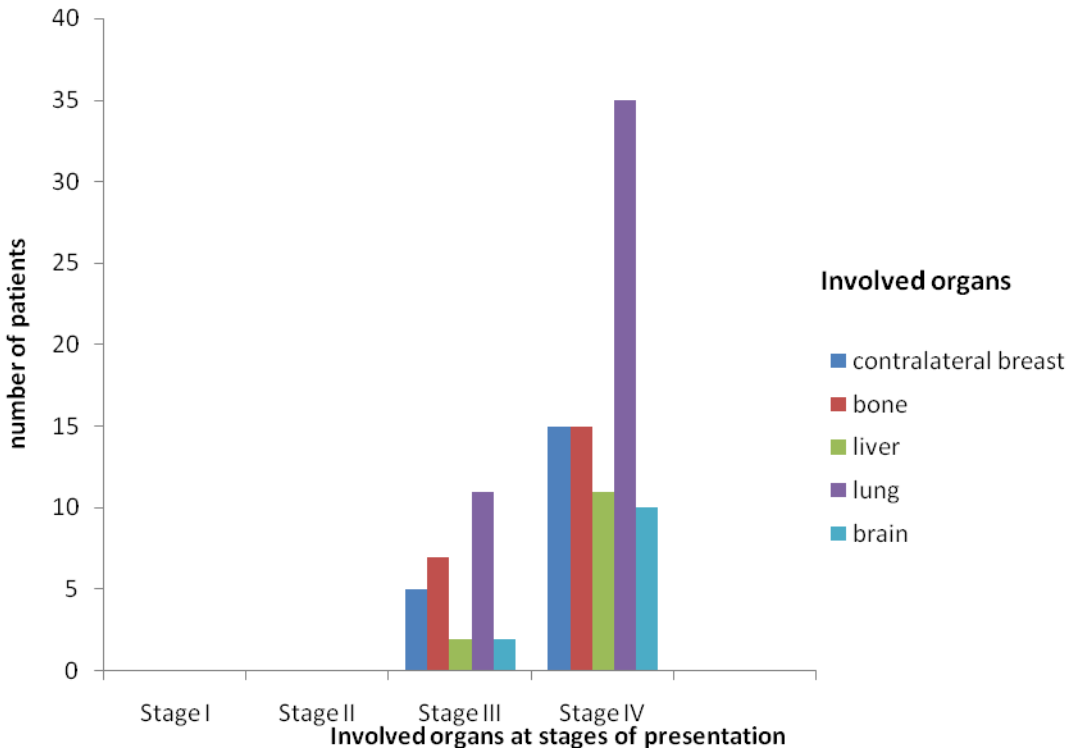


Fig 4.3: Organs Affected in Breast Cancer Metastasis at Each Stage of Diagnosis

4.8 Management Procedures Used For Breast Cancer Cases Prior to and After Presentation to ABUTH, Zaria within the Study Period

Prior to presentation, majority of the patients were found to have undergone surgery and had completed chemotherapy (62). One patient was found to have had targeted therapy prior to presentation. After presentation to ABUTH, chemotherapy, radiotherapy and hormonal treatment combination (79) was highly used (Table 4.5).

Table 4.5: Management Strategies Employed for Breast Cancer Treatments Prior To and After Presentation at ABUTH, Zaria

	Presentation	
Treatment modalities	Prior to	After
CH	1	18
S	58	0
SC	62	3
SH	33	0
SCR	3	14
H	1	0
SCH	31	4
C	5	22
NONE	19	0
SCRH	2	14
SCHT	1	0
CR	0	47
CRH	0	79
CRHT	0	8
CRT	0	5
SCRHT	0	2

C-chemotherapy; **CH**-chemotherapy, hormonal therapy; **CR**-chemotherapy, radiotherapy; **CRH**-chemotherapy, radiotherapy, hormonal therapy; **CRHT**-chemotherapy, radiotherapy, hormonal therapy, targeted therapy; **CRT**-chemotherapy, radiotherapy, targeted therapy; H-hormonal therapy; **NONE** -no treatment; **SCH** -surgery, chemotherapy, hormonal therapy; **SCHT**-surgery, chemotherapy, hormonal therapy, targeted therapy; **SCRH**-surgery, chemotherapy, radiotherapy, hormonal therapy; **SCRHT**-surgery, chemotherapy, radiotherapy, hormonal therapy, targeted therapy; **SCR**-surgery, chemotherapy, radiotherapy; **SC**-surgery, chemotherapy; **SH**-surgery, hormonal therapy; **S**-surgery

4.9 Regimens Used Prior to and After Presentation at ABUTH, Zaria within The 5 year Study Period

Before presentation at ABUTH, Zaria, majority (28 patients) of the patients used CMF, followed by CAF (27patients). After presentation, CAF was found to be the highest prescribed regimen (78 patients), followed by FEC (48 patients) and paclitaxel (37 patients). CMF was used to an extent of 8.4% (18 patients) (Table 4.6).

Table 4.6: Prescribed Chemotherapeutic Regimens Prior to and After Presentation at ABUTH, Zaria

	Presentation	
Regimens	Prior to	After
CMF	37	18
CAF	27	78
AC	9	4
VAC-Pr	7	0
VAC	7	0
FEC	5	48
CAF-M	5	0
EC	2	0
CAM	2	1
CMF-A	3	0
Cisplastin	1	2
Paclitaxel	0	37
Capecitabine	0	7
AC-P	0	9
Gemicitabine	0	5
VAC-P	0	4
E-P	0	2
Docetaxel	0	1
Total	**105**	**216**

CMF= Cyclophosphamide-Methotrexate-5-Flourouracil; **CAF**= Cyclophosphamide-Doxorubicin-5-Flourouracil; **AC=** Doxorubicin-Cyclophosphamide; **CAF-M=** Cyclophosphamide-Doxorubicin-5-Flourouracil-Methotrexate; **CAM=** Cyclophosphamide-Doxorubicin-Methotrexate; **AC-P=** Doxorubicin-Cyclophosphamide-Paclitaxel; **CMF-A=** Cyclophosphamide-Methotrexate-5-Flourouracil-Doxorubicin; **EC=** Epirubicin-Cyclophosphamide; **E-P=** Epirubicin-Paclitaxel; **FEC=** 5-Flourouracil-Epirubicin-Cyclophosphamide; **VAC=** Vincristine-Doxorubicin-Cyclophosphamide; **VAC-P=** Vincristine-Doxorubicin-Cyclophosphamide-Paclitaxel; **VAC-Pr**= Vincristine-Doxorubicin-Cyclophosphamide-Prednisolone;

4.10 Prescribed Chemotherapeutic Regimens for the Various Stages of Breast Cancer at ABUTH, Zaria

CAF was found to be the highest prescribed regimen, followed by FEC. Both were mainly used in stages I, II and III of the disease while CAF and paclitaxel were the chemotherapeutic regimens mainly prescribed in stage IV of the disease (Fig 4.4).

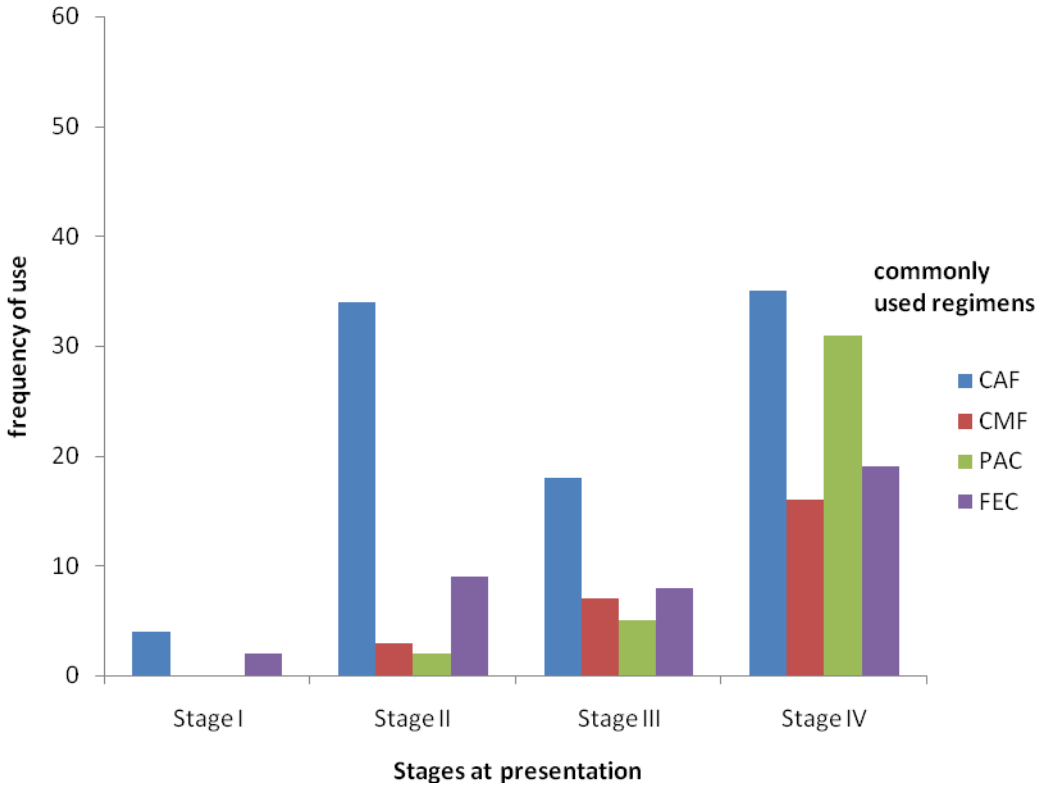


Fig 4.4: Drug Regimens at each Stage of Presentation

CAF - Cyclophoshamide, Doxorubicin (Adramycin), 5-Flurouracil
CMF- Cylophosphamide, Methotrexate, 5-Flurouracil,
PAC- Paclitaxel
FEC- 5-Flurouracil, Epirubicin, Cyclophosphamide,

4.11 Response Pattern to Chemotherapy at Each Stage of Presentation at ABUTH, Zaria

All the patients diagnosed at stage I and majority of the patients at early stage II of the disease showed a complete response to chemotherapy with no reoccurrences. Patients at stage III showed no response and the disease progressed. However, many patients at stage IV showed partial response and disease progression in which the regimens did not produce any clinical response (Fig. 4.5)

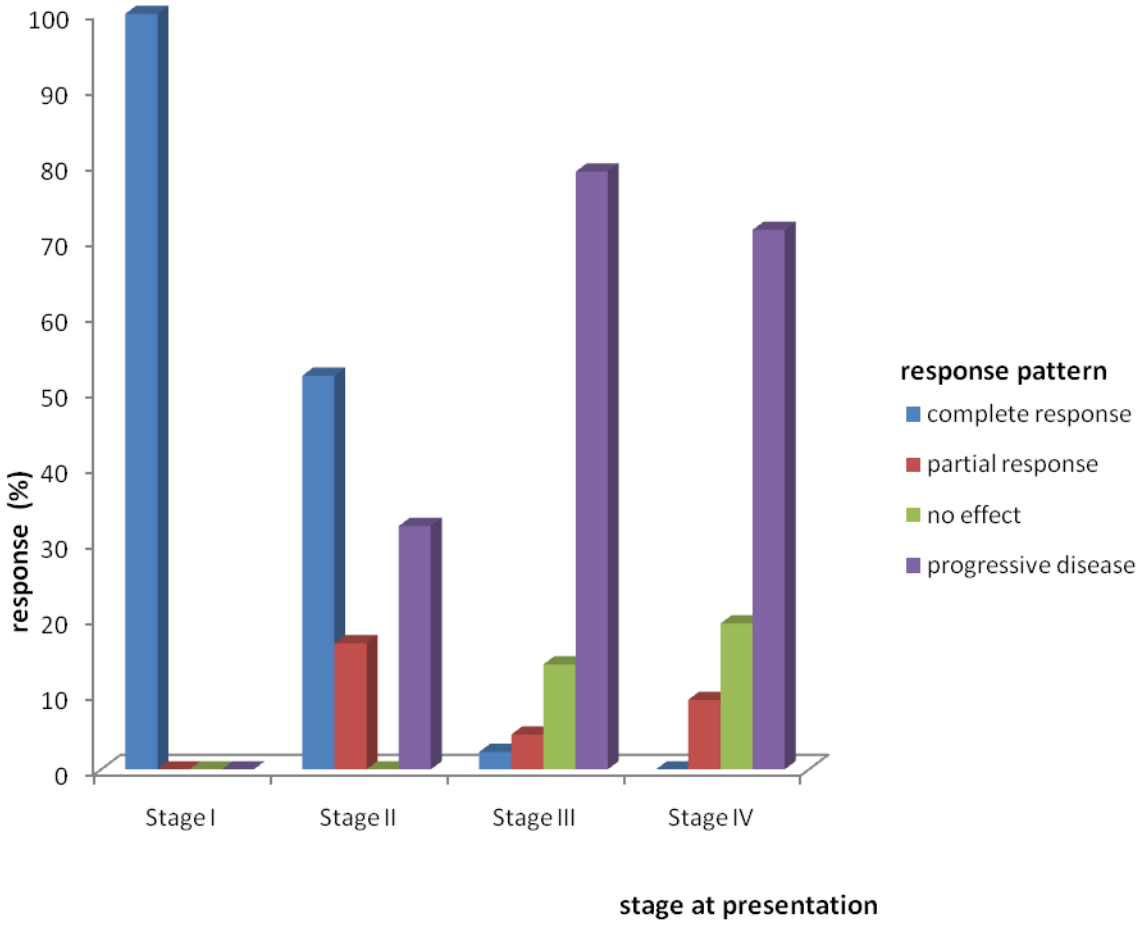


Fig 4.5: Response Pattern to Chemotherapy at the Clinical Stages of Presentation

4.12 Toxicity Profiles of the Various Regimens Used for Breast Cancer Management at ABUTH, Zaria

The documented side effects of the drug regimens were of the gastrointestinal tract (nausea, vomiting and diarrhea) and blood (anaemia and neutropenia) seen for almost all the regimen. Other side effects including those specific to components of regimens occurred in 1 or 2 patients. (Table 4.7).

Table 4.7: Documented Toxicities to the Various Chemotherapeutic Regimens Used at ABUTH, Zaria

Toxicity	CAF (n= 18) %	CMF (n= 5) %	FEC (n=8) %	Taxen-based (n= 13) %	Capecitabine (n= 3) %
Nausea	83.3	40	25	61.5	0
Vomiting	83.3	40	25	61.5	0
Jaundice	5.6	0	0	0	0
Headache	16.7	0	12.5	0	0
Alopecia	5.6	20	12.5	15.4	0
Pruritis	5.6	0	0	0	0
Diarrhoea	27.8	60	25	7.7	0
Fever	5.6	40	0	15.4	0
Blurred vision	5.6	0	0	0	0
Abdominal pain	5.6	40	37.5	0	0
Hypoglycemia	5.6	0	0	0	0
Anorexia	5.6	0	0	0	0
Chills	0	20	0	15.4	0
Hand /foot syndrome	0	0	0	15.4	66.7
Edema	0	0	0	15.4	0
CHF	0	0	0	0	33.3
Dyspnea	0	0	0	0	33.3
Anaemia	11.1	20	25	23.1	0
Neutropenia	27.8	80	62.5	61.5	0
Thrombocytopenia	5.6	20	0	0	0

4.13 Disease Free Intervals for the Prescribed Chemotherapeutic Regimens at ABUTH, Zaria within the Study Period

A progressive reduction was observed in number of patients that maintained disease free intervals following completed chemotherapeutic regimens. FEC had the most survivals after the 5 year period constituting 12.5% of its population as against the newer regimens such as Paclitaxel (4.6%) as shown by Fig 4.6.

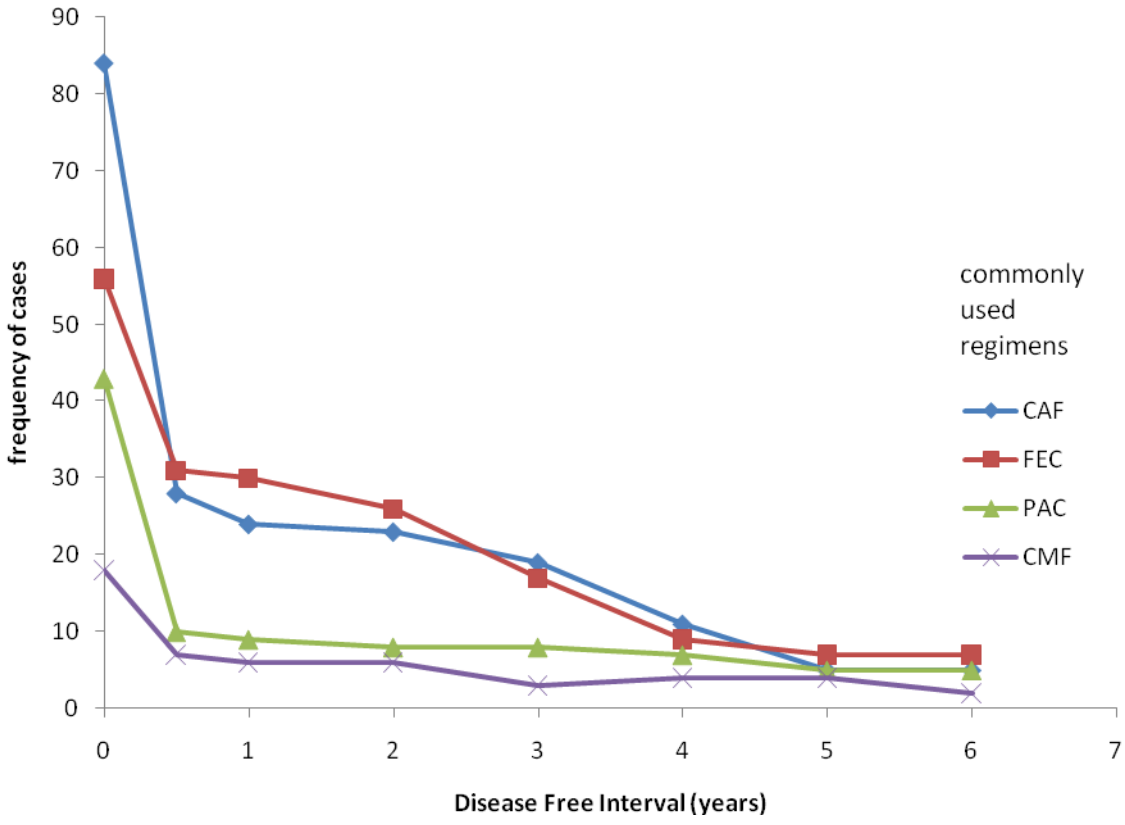


Fig. 4.6: Disease Free Intervals of Cancer Patients in the 5 years Study Period

CAF- Cyclophoshamide, Adramycin, 5-Flurouracil
CMF- Cylophosphamide, Methrotexate, 5-Flurouracil,
PAC- Paclitaxel
FEC- 5-Flurouracil, Epirubicin, Cyclophosphamide,

4.14 Changes in Chemotherapeutic Regimens and Reasons

Forty-eight patients previously on paclitaxel later had course to change to CAF (39.5%) and FEC (19.7%) based on the cost. Other patients changed from CAF to paclitaxel because of disease progression and side effects.

Table 4.8: Change of Chemotherapeutic Regimens

Reason	**Previous regimens**	**Present regimens**	**Percentage of cases (%)**
Cost	Paclitaxel	CAF	39.5
		FEC	19.7
Disease progression	CAF	Paclitaxel	34.6
Side effects	CAF	Paclitaxel	6.2

4.15 Outcome in Survival, Lost to Follow-up, Death and Reoccurrence Time of Patients

At the end of the 5 year study period the calculated overall survival, death and loss to follow-up was 38.9%, 24.5% and 36.6% respectively. The calculated mean time to progression was 18months ± 6 months. Only 14.4% of the study population had a total remission (Table 4.9).

Table 4.9: Summary of calculated outcome for overall death, survival and loss to follow-up

Outcome	**No of cases**	**Percentage %**
Percentage survival	84	38.9%
Percentage death	53	24.5%
Percentage lost to follow up	79	36.6%
Complete remission ≥5 years	31	14.4%
Mean TTP	18 months ± 6 months	

CHAPTER FIVE

5.0 DISCUSSION

This study conducted at the Oncology and Radiotherapy unit (National Cancer Registry) of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria was designed to access the characteristics, management and outcome of treatment for breast cancer patients that attended the clinic / unit between the periods of January 2004to December 2009.

The information obtained from the cancer registry's disease index cards and the 216 folders of patients that fulfilled study criteria as designed in the data capturing form include: cancer types (prevalence and incidence), socio-demographic characteristics, predisposing risk factors, expression pattern of breast cancer and involved metastatic organs at diagnostic stages, management strategies, disease free intervals and frequency of reoccurrence on completion of regimens, change in chemotherapy regimens used and outcome of treatment.

Out of the total number of registered cases of the various types of cancers across the 5 year study period, breast cancer had the highest number of patients over the period (Table 4.1) with increasing number of presenting cases across the years (Fig. 4.1). Global studies reported by Parklin *et al*. (1999) and Cancer Facts and Figures (ACS, 2012B) has lung cancer as the most common type of cancer, followed by breast cancer. The ranking of breast cancer as first in this study and probably other studies within Nigeria could be related to the societal cultures that restrict women from smoking and /or frowns at it. Anyanwu (2000) noted a steep rise in the incidence of breast cancer in Nigeria and other low-income countries. Such increase in breast

cancer cases was also reported by Ankarolol-Anthony *et al.* (2010) who projected a continued increase to up to 2020. However, this study observed a slight decrease in incidence in 2009 and it is not known if such decrease continued beyond 2009 since this study was only for 2005 – 2009. There may be need for a further study that would confirm this purported projected increase. The information on the socio-demographic characteristics revealed that most of the patients with breast cancer were within the age range of 36 – 45 years (34%) and that 45 of the 216 patients were less than 35 years. Breast cancer in both males and females is strongly related to age. The incidence is said to rise as from ages 35-39 years for women and reducing at about 50 years, to rise again around ages 65-69; while for males, 66% of all cases of breast cancer were diagnosed at 65 years and above (Yankaska, 2006; Westlake and Cooper, 2008; ACS, 2013). In this study, the earliest diagnosed male breast cancer was 55 years against 28 years for the female; and the majority of the cases (208 out of 216 = 96.3%; 27:1) were women. The prevalence age of 36 – 45 years was found, but consisting of only women (Table 4.2). This study also observed the reduction in breast cancer cases to be within the age range of 46-55, which is in line with the findings of Yankaska (2006), Westlake and Cooper (2008) and ACS (2013). Breast Cancer Facts and Figures (ACS, 2012A) stated that breast cancer is the second most common cancers in females after lung cancer and accounts for a high rate in cancer related deaths. This high breast cancer mortality rate in women can also be inferred from the observation in this study.

The 8 male cancer cases (3.7%) out of the total of 216 in this study was lower than the observation of 9% of cases by Hassan and Mabogunje (1999) in the same study center. It was also lower than that from the analysis of male cancer cases in all cancer registries across Nigeria by Abdulkareem (2009) and similar studies conducted in eastern Nigeria (Ezeoma, *et al.*, 2010). However, the 3.7% result obtained of this study was in line with the finding of Dogo *et al.*

(2006) in Maiduguri but was higher than the 1% reported from United States (Giordons, *et al.*, 2004; ACS, 2012). Anyanwu (2000) reported a male to female ratio of 1:67 which was much higher than the 1:27 obtained from this study.

The relationship of occupation, marital status and educational level to cancer occurrence and / or presentation has not been well documented. Majority of patients with breast cancer in this study were civil servants followed by housewives. Married subjects and those with the highest educational level (tertiary education) also presented the highest number of cases. Their presentation to the clinic could be related to better financial disposition and / or support from spouses.

The Predisposing risk factors of breast cancer could be related to the level and duration of exposure to endogenous hormones at the ages of menarche and full term birth, parity (number of pregnancies), menopausal status, as well as to exogenous exposure in contraceptives and replacement therapies use, and also to family history and environmental factors.

Majority of females (90 patients) in this study had their age at menarche within the range of 13-16 yrs. It has been reported that the earlier the onset of menstrual cycle, the longer the duration of exposure to endogenous hormones which could result in an increase in the risk of breast cancer occurrence (Grumbach and Styne, 2003). A 50% likelihood increase in risk of breast cancer at menarche ages of 12 and below has also been reported (Grumbach and Styne, 2003). Only 15 patients reported late menarche age (17-20) in this study of which Boyle (1988) reported as a protective factor.

This study found that women who had their first full-term birth within 16-20 years of age were more (35) disposed to breast cancer and this was contrary to earlier studies that the older a women is at first full term birth, the higher the risk of breast cancer (Lagde *et al.,* 1989; Lambe *et al.*, 1996; Kumle, 2002A, B). The reported view was that breast cancer risk increases by 13% for every 5 year increment in age at first full-term birth, attributing more of the risks to older subjects. It was also reported that increase in parity (more children) results in pronounced decrease in the risk of breast cancer with additional birth conferring 10% risk reduction / decrease (Lambe *et al.*, 1996). Reduced parity (fewer children) and reduced duration of breastfeeding had also been reported to increase the risk of breast cancer development (Boyle, 1988; Lagde *et al.,* 1989). Boyle (1988) also attributed early age at first full-term pregnancy to be a protective factor, of which aside 16-20 years that is of majority, the earliest age range was 11-15 years that had 7 patients. The question then is whether this childhood pregnancy that could be regarded as child abuse actually confers protection!

Menopause (45-50 years) – is a period of cessation of the menstrual cycle which also is a contributing risk factor to breast cancer. This study found only 37.5% (77 patients) to be of postmenopausal status. The reasons for the 60.5% of premenopausal subjects found in this and other studies within Nigeria being more at risk are not known, but could be because the majority of cases presented within the younger age group which was similar to studies conducted in other parts of Nigeria (Anyanwu *et al.*, 2010). It is assumed and also reported elsewhere that post-menopause should be of greater predisposing risk factor, being of older age status and the fact that postmenopausal age is usually associated with obesity and / or exogenous hormone replacement therapies. Lambe *et al.* (1996) had previously reported that breast cancer risk increases by 13% for every 5 yr increment in age of first full term birth and the low parity

commonly of this status also increases risk of breast cancer (Paffenberger *et al*., 1980; Zeeshan *et al.,* 2012).

Majority (83) of the patients had less or equal to 5 (≤ 5) children. Thus, this is in line with previous reports that low parity predisposes one to breast cancer. The patients with 6-10 children were only 29, while those with 11-15 children were only 5. This observation was actually in support of high parity as a factor that confers protection against breast cancer development (Boyle, 1988; Lagde *et al.,* 1989).

The use of oral contraceptives as a risk factor was found in 36.1% of the female study population. Most times, oral contraceptives are used for family planning as to reduce chances of unwanted pregnancies and / or improve maternal health, but its use is often associated with after effects including increased risk of breast cancers.

The patients with family history of breast cancer were 12% of the study population. Other studies had also reported family history as a predisposing risk factor of breast cancer (Yang *et al.,* 1998). Breast cancer had been traced to some abnormality in specific genes or gene mutations and so run in families suggesting genetic influence of the disease. However, it is increasingly clear that genetic abnormalities might only increase a person's susceptibility triggered by environmental factors (ACS, 2002). Other types of cancers were also observed to run in the families of some of the patients, the extent to which these are related to breast cancer risk is not known.

The patients that presented at stage IV of the disease were more in all the age groups (Fig. 4.2a). The reason for allowing this disease to deteriorate before presentation to the clinic is not known.

However, the stage at which breast cancer is detected ultimately plays a role in its management and prognosis. For breast cancers detected early (stages 0 and I), therapy may be curative and this was observed in this study. Only very few patients presented at the clinical diagnostic stage I, when the cancer is easily cured or controlled. In advanced or metastatic stage (III – IV) of the breast cancer, therapy can only be palliative for controlling the symptoms and improving the patient's quality of life (Karamouzis *et al*., 2007; NCCN, 2013; WHO, 2013).

Across the 4 stages of clinical diagnosis, patients of tertiary level of education had the highest presentation followed by those of secondary level; and both represent not only the majority of the diagnosed cases, but also of late stage presentation (Fig. 4.2b). The reason for these groups of patients not presenting to the clinic on time is not known and late presentation of the highly educated patients is also a puzzle as well. With the increased awareness programmes on breast cancer, one would have expected educated patients to be more prompt in presenting to clinics. However, their high levels of turn out could probably be related to their levels of education and the desired need to seek medical attention. Level of education however, has no role to play in response to chemotherapeutic regimens.

From this study, most (83%) of the breast cancers cases was of the invasive ductal (infiltrating) type. Few (20) patients were of the invasive lobular type and 15 patients were of the medullary type, while invasive ductal-lobular was only 2 patients. The invasive ductal carcinoma had been recorded the most common global type of breast cancer accounting for about 70 to 80% (Abdulkareem, 2009; NCI, 2014). This study also found that only 5 patients had the cancer on both breasts (bilateral) and that breast cancer occurred mostly on one breast of either the right (50.9%) or the left side (46.8%).

In this study, 11 patients (5.10%) had their excised tumours screened for tumor cell surface receptor types and of which 7 patients (63.30%) had triple negative breast cancer (HER_{-ve} ER_{-ve} PR_{-ve}). Tumour cell surfaces have receptor binding sites which characterize the cells into hormone types of either ER_{+ve} – if the receptor site binds estrogen; or PR_{+ve} - if it binds progesterone. The tumour cells may also have an over expression of the human epidermal growth factor rexptor-2neu genes (HERs-2 neu receptors) which can also be either positive or negative (normal levels). Thus, a tumour could be of ER positive, PR positive or HERs-2neu positive; and/or their negatives as was found in seven of the patients who had triple negatives **(**HER_{-ve} ER_{-ve} PR_{-ve}), and in two patients who also had tripled positives (HER_{+ve} $ER_{+ve}PR_{+ve}$). Varied receptor type combinations can also occur for a particular tumor such as HER_{+ve} ER_{+ve} PR_{-ve} and HER_{+ve} ER_{-ve} PR_{-ve} as seen in two patients respectively (Abeloff, 2008). When a tumor cell express hormone receptor negatives, such tumor may not be effectively managed by hormonal and targeted therapies and may rather require chemotherapy of various combinations and vice versa. Thus, triple-negative breast cancers often have poor prognosis and exhibit difficult clinical management (Verma *et al.*, 2011), while triple positive types are usually more responsive to hormonal and targeted therapies.

According to the National Cancer Institute (NCI), triple negative breast cancers accounts for 10-20% of all diagnosed cases of breast cancer. They are aggressive in nature and difficult to treat. A triple negative diagnosis for breast cancer refers that the cells have been tested negative for hormonal epidermal growth factor receptor (HER-2neu), oestrogen receptors (ER) and progesterone receptors (PR). This means that these groups of patients would most likely not

benefit from any form of targeted or hormonal therapy and / or the use of monoclonal antibodies (as the growth of the cancerous cells is not supported by either oestrogen or progesterone).

It is known that cancer tends to spread when left untreated (metastasis) and thus, the observation in this study is not surprising except that most of the affected organs are those of important functions in the homeostatic up-keep of the body system. The reason for the highly involvement of the lungs in metastasis is not known as this had also been reported by Adisa *et al*. (2012).

Prior to presentation at ABUTH, majority of the study population had undergone one or more forms of surgery (lumpectomy or mastectomy) and had chemotherapy (62 patients). At ABUTH, Zaria, chemotherapeutic, radiotherapy and hormonal combination (79 patients) and chemo- and radio-therapies combination (47 patients) were the most used treatment protocols. The primary goal / aim of surgeries in breast cancer management are the removal of the cancerous cells / tissues from the breast and this could be a conservative surgery (BCS). This is an attempt made to preserve the breast by removing only the diseased tissues or lumps (lumpectomy). Otherwise mastectomy is performed, whereby the breast is completely removed. In this study, majority of the patients that presented to ABUTH were found to be at the advanced stage of the disease, and this probably might be the reason for the reduced number of surgical cases for the fact that many had previously undergone surgery. It was also noted that radiotherapy was used to a large extent. Radiotherapy is often used as an adjunct therapy in patients who have had breast conservative surgery (BCS) or mastectomy; and as majority of the patients had done this prior to referral; only chemotherapy, radiotherapy and other forms of treatment modalities were required. Radiotherapy utilizes high energy rays (x-rays or gamma rays) to destroy cancerous cells. It is based on the

principle that abnormal/cancerous cells are unable to repair radiation induced cellular damage unlike normal/healthy cells.

Regimens prior to presentation to ABUTH were found to be of 12 types; of which Cyclophosphamide-Methrotexate-5-Flourouracil (CMF- 37) and Cyclophosphamide-Doxorubicin-5-Flourouracil (CAF- 27) were the most used regimens. The others were used to the extent of less than 10%. However, on presentation to ABUTH, out of the 14 regimens prescribed, CAF (78 patients) was found to be the most prescribed regimen followed by 5-Flourouracil-Epirubicin-Cyclophosphamide (FEC- 48 patients) and then paclitaxel (37 patients) before CMF (18patients).

The selection of chemotherapeutic regimens often depends to a large extent on a number of factors such as stage at diagnosis, histological characteristic of the tumor, patients' tolerability, refractoriness to drug as well as accessibility to drugs in terms of availability and affordability. CMF was found to be most used prior to presentation to ABUTH probably because it was one of the earliest used chemotherapeutic regimens, in addition to its low cost and readily availability. CAF which was almost used to the same extent may also have been due to its preference for recurrent and metastatic breast cancer as well as its relatively low cost and availability (NCCN, 2014). Newer regimens such as paclitaxel or docetaxel (Taxens) and Doxorubicin-Cyclophosphamide (AC-based) are the recommended first-line therapy by National Comprehensive Cancer Network (NCCN) (Appendix V) probably because these are deemed to be therapeutically more effective and superior to the CMF regimen (Peto *et al.,* 2012). However, the National Guidelines for Breast Chemotherapy in Nigeria recommended CMF as first-line, followed by AC- based (second line) and then paclitaxel based (third line) (Appendix

IV). It was found from this study that at ABUTH, CMF was the fourth used (8.4%) after CAF (the second line) and FEC which is not in the guideline at all, and then paclitaxel (a third line drug) .The high use of paclitaxel in the management of breast cancer nationwide may be related to its efficacy and tolerability as well as its lack of cross-resistance with anthracyclines based regimens such CAF and VAC.

In all, CAF was the drug of first choice irrespective of the stage at presentation, FEC was the second most prescribed drug at stages 1, 2 and 3 of presentation, but at stage 4, paclitaxel was the second prescribed after CAF. CAF is one of the most cost effective regimens for breast cancer, although it is a second line drug. CMF which is the first line regimen was sparsely used which could be attributed to the late presentation of breast cancer cases. It has been widely reported that cancer cells have the ability to spread to many organs of the body if left untreated. This is because at this terminal stage (III-IV), micro-metastasis from the primary disease site / organ tends to involve other organs of the body resulting in progressive disease condition that is not responsive to drug regimens.

From this study, many of the patients were found to present at late stages of the disease and thus, none responsiveness to treatment regimens was the major observation at these stages (Fig. 4.5). Treatment for patients in this terminal stage will only be of palliative type, to improve quality and prolong patients' life. The complete remission / response demonstrated at the stage I and early stage II showed the extent of efficacy of the available chemotherapeutic regimens for breast cancer management, and thus, rules out the thought of ineffective or non-availability of drugs for this ailment. The problem therefore lies in the attitude of patients in late presentation and none

compliance to therapy even though there may be cases of resistance to drugs and / or mismatch of the drugs with cancer types.

Forty-four patients (20.4%) of the 216 patients that constituted the study population had one or more side effects of their prescribed regimens / drugs. The overall finding suggested that majority of the patients tolerated their chosen drug regimens well, except for occasional gastrointestinal tract and blood related side effects. Ketiku and Ajekigbe (1990) had also previously noted the high tolerability of cancer patients to anti-neoplastic agents in Africa.

The four most prescribed regimens for breast cancer remission at ABUTH, Zaria produced a disease free interval (DFI) in some patients, but there was progressive reduction in the number of patients that maintained this status. Many of the patients showed reoccurrence, while many were lost to follow up. No additional benefit was observed on the overall survival of patients placed on the newer regimen (paclitaxel) as against those on older regimens.

Cost is usually a major factor in the choice of drug regimens. Most times, the newer drugs like paclitaxel are more expensive than the older types. Such new drugs are often thought to be more superior or effective, but some older drugs of lesser cost could also be as effective. The changes due to disease progression could only be as a result of inadequate relief of symptoms from the previously recommended regimen, while intolerance or side effects also necessitated changes from one regimen to another.

Many of the patients either died in the course of treatment or were lost to follow up (probably due to financial implications or unwillingness to maintain treatment or routine checkup strategies). However, quite a number of the patients (84) maintained disease free interval

remission up to 5 years from the time of completion of prescribed therapeutic regimens. The patients that survived could most likely be those that presented to the clinic at the early stage of the disease.

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary

Data on breast cancer in this part of the country are currently limited. The burden of the disease on both the Nigerian woman as well as the Nigerian public health system will continue to increase as incidence increases with progressive years. Breast cancer is a frequently occurring disease which has shown increased prevalence in premenopausal Nigerian women.

The outcome of the use of chemotherapy in curtailing the rampant micro-metastases as adjuncts to surgery and / or radiation therapies was evaluated retrospectively with other characteristic indices of breast cancer at Ahmadu Bello University Teaching Hospital (ABUTH), Zaria within January 2005 to December 2009.

Breast cancer prevalence in male was higher than documented in developed countries and previous studies at the same centre with a male to female incidence ratio of 1:27, more prevalent in the educated, premenopausal and multi-parous women. Breast cancer incidence in this study group did not show any familial aggregation. It was found to be prevalent amongst the economic / productive class of the society. The average age of breast cancer patients was lower for the study population than what was obtained in documented literature for breast cancer. Invasive

ductal carcinoma was the most prevalent subtype of breast cancer encountered with no preference for any breast.

Unpreventable risk factors-age at menarche, age at first full term birth was demonstrated for the incidence of breast cancer amongst the female patients. Majority of patients presented at the terminal stage of the disease irrespective of level of education as demonstrated by other studies conducted in middle / low income countries. More than half the patients diagnosed as having breast cancer presented with signs and symptoms of metastasis to vital organs –lungs, brain,bone etc.

Differences were observed between literature, published study results and findings from retrieved data on management of breast cancers patients in ABUTH. Although the established protocol for the selection of suitable chemotherapeutic regimen was readily followed, final chemotherapeutic drug management selection was based on the accessibility of the selected regimens in terms of availability and affordability. Drug regimen preferences were for cyclophosphamide, adriamycin (Doxorubicin) and 5-flourouracil (CAF) and 5-flourouracil, epirubicin and cyclophosphamide (FEC) regimens. Other drugs regimens encountered include T-based regimens and cyclophosphamide, methotrexate 5-flourouracil (CMF).

Drug use was associated with side effects in relatively small number of patients and side effects encountered were mainly generalized side effects with less 4% demonstrating drug specific side effects which where managed by either the use of other drugs which cancel out such effects, or discontinuation of drug used. Based on the fact that a vast majority presented at the terminal

stage of the disease hence the high proportion of progressive disease as the end point of study with those presenting at the earlier stages (stage I and II) having complete remission as their primary outcome of study. Calculated survival rate was less than 14% of the study population.

6.2 Conclusion

This study as with other studies had confirmed that lack of early detection programs and / or late presentations to clinics as attributes of low survival rates. Breast cancer responds well to treatment if detected early (stage I and early stage II) during which complete remission is possible, while late presentation at the advanced stage is associated with poor prognosis. Low survival rates often reported of in developing countries may be as a result of lack of adequate diagnostic measures or facilities, cost of management and chemotherapeutic regimens.

It may not be possible from this type of study to ascertain the pathologic complete remission (pCR) of the patients that maintained progression free survival to the end of the 5 years study.
The complete response rate with no reoccurrences obtained at stage I and early stage II as well as the progression free survival (PFS) of 2-5 years in late presentations from these commonly used chemotherapeutic regimens may suffice for good therapeutic outcome if not for the associated early reoccurrence from 18 months (± 6 months) of disease free interval remission.

6.3 Recommendations for Further Study

Detailed prospective study of the outcome of use chemotherapy in the various receptor expression patterns of breast cancer is required as to ascertain the exact effect of the regimens and the extent of their pathologic free remission and / or disease free interval patterns such that those with effects on overall patient survival would be used.

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APPENDIX I

Ahmadu Bello University Teaching Hospital

P.M.B. 06, Shika - Zaria, Kaduna State, Nigeria. 069-876305

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Chairman of Board:

Chief Medical Director: **DR. LAWAL KHALID,** ***MBBS, FMCS, FWACS, FRCS(ED) mni***

Chairman, Medical Advisory Committee: **DR. ABDULLAHI MOHAMMED,** ***MBBS, FWACP FICS***

Director of Administration: **BARR. ISHAK BELLO,** ***LL.B, BL, LL.M, PGDM, AHAN, FCAI***

Our Ref:

ABUTH/HREC/TRG /36 28th June, 2013

FULL ETHICAL CLEARANCE AFTER COMMITTEE REVIEW

Re: *"Evaluation of Chemotherapeutic Outcome of Breast Cancer at Ahmadu Bello University Teaching Hospital, Zaria"*

ABUTH Ethics Committee assigned number:	-	ABUTH/HREC/F02/2013
Name of the principal Investigator:	-	Ajagu, Ebele Joan
Address of the Principal Investigator:	-	Dept. of Pharmacology and Therapeutic, A.B.U Zaria
Date of receipt of valid application:	-	10th June, 2013
Date of meeting when final determination on ethical approval was made:	-	19th June, 2013

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and ***given full approval by the ABUTH Ethics Committee.***

Please note: this approval dates from ***28th June, 2013*** to ***28th June , 2014***.

No participant recruitment into this research may be conducted outside these dates.

All informed consent forms in this study must carry the ABUTH HREC number assigned to this research and the duration of ABUTH HREC approval of the study.

This HREC expects that you submit your application as well as an annual report for ethical clearance renewal 3 months prior to expiration of study dates. This is to enable you obtain renewal of your approval and avoid interruption of your research.

If there is delay in starting the research, please inform the ABUTH HREC so that starting dates can be adjusted accordingly.

No changes are permitted in the research without prior approval by ABUTH HREC, except in circumstances outlined in national code for Health Research Ethics:http://www.nhrec.net.

ABUTH HREC reserves the right to conduct compliance assessment visits to your research site without prior notification.

Mr Agboola, I/c oncology Himdg

Pls deal.

By retrieving my batches records btw 2005 and 2009

APPENDIX II: Classification of Breast Cancer

TNM CLASSIFICATION OF BREAST CANCER

TNM class	Criteria
T0	no evidence of primary tumor
T1a	carcinoma in situ
T1	< or = 2 cm
T1m1c	microinvasion .1 cm or less
T1a	>.1 to .5 cm
T1b	>.5 to 1 cm
T1c	>1 to 2 cm
T2	>2 to 5 cm
T3	>5cm
T4	any size tumor with direct extension to : a) cheat wall or b) skin
T4a	chest wall, not including pectoral muscle
T4b	skin edema, ulceration, satellite skin nodule
T4c	4a and 4b (chest wall and skin wall involvement)
T4d	inflammatory carcinoma
Nx	regional lymph nodes cannot be assessed
N0	no regional lymph node metastasis
N1	metastasis to movable ipsilateral axiliary lymph nodes
N2	metastases in ipsilateral axillaries lymph nodes fixed of matted (N2a) or met. Only in clinically apparent ipsilateral mammary nodes without clinically evident axiliary lymph nodes. (N2b)
N3	Metastases in ipsilateral infraclavicular lymph nodes (N3a) or clincially apparent ipsilateral internal mammary lymph nodes (N3b) or ipsilateral supraclavicular lymph nodes (N3c)
MX	distant metastasis cannot be assessed
M0	no distant metastasis
M1	distant metastasis

Adapted from AJCCs' cancer staging manual, 2002. Sixth Edition.

PATHOLOGIC CLASSIFICATION OF BREAST CANCER

P classification	Criteria
pNx	Regional lymph nodes cannot be assessed, No regional l. node metastasis histologically, Metastasis in 1-3 axillary lymph nodes
pN1mi	Micrometastasis > 0.2 mm to < 2 mm
pN1a	Metastasis > 0.2 mm + at least one node > 2 mm
pN1b	Metastasis in internal mammary l. nodes detected by SLN
pN1c	Metastasis in 1-3 axill. + internal mammary l. nodes by SLN
pN2	Metastases in 4-9 ipsilateral lymph nodes
pN2a	Metastases in 4-9 axillary + at least one > 2 mm
pN2b	Metastasis in clinically apparent internal mammary l. nodes without axillary lymph nodes metastasis
pN3a	Metastases in 10 or more ipsilateral axillary lymph nodes or ipsilateral infraclavicular
pN3b	clinically apparent internal mammary l. nodes with 1 or more axillary l. nodes or more than 3 axillary lymph nodes with microscopic met. in internal mammary l. nodes
pN3c	ipsilateral supraclavicular l. Nodes

ANATOMIC STAGE OF BREAST CANCER

Stage	**T**	**N**	**M**
0	Tis	N0	M0
IA	T1[b]	N0	M0
IB	T0	N1mi	M0
	T1[b]	N1mi	M0
IIA	T0	N1[c]	M0
	T1[b]	N1[c]	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[b]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

APPENDIX III: Data Capturing Form

CODE NO.-_____

This is a postgraduate research intended for the award of M.Sc. Pharmacology in the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria.
This research titled '**Evaluation of Chemotherapeutic Outcome of Breast Cancer at Ahmadu Bello University Teaching Hospital, Zaria** 'is intended to retrospectively assess the prevalence, incidence, predisposing risk factors, management and outcomes of treatment of breast cancer patients attending the Oncology and Radiotherapy clinic of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria.

BIODATA (tick where appropriate)

1. Age :- _____
2. Sex:- _____
3. Occupation:- _____
4. Level of education: – illiterate Primary Secondary Tertiary Islamic education
5. Marital status :– Single Married Divorced Widowed

PREDISPOSING RISK FACTORS

1. Age at menarche:- _____
2. Age at first full term birth:-_____
3. Menopausal status: Pre-menopause Post-menopause
4. Age at menopause:- _____
5. Number of pregnancies:-_____
6. Parity :-_____
7. Age at diagnosis:-_____
8. History of contraceptive use:-_____
9. Positive first degree familial history:- _____
10. Familial history of any type of cancer:-_____

CLINICAL FEATURES

1. Clinical diagnosis:-_____

2. Histological type: - _____

3. Presence of cofactors Y/N

Cardiovascular Endocrine Renal Others

4. Presence of mass: - Y/N

ii. Breast involved: - L/R

5. Presence of ulcers: - Y/N

6. Presence of infection: - Y/N

7. Lymph node involvement: - Y/N

i. Auxiliary: - Y/N

ii. Supraclavicular: - Y/N

iii. Internal mammary: - Y/N

8. Distant metastasis: - Y/N

i. Contralateral breast- Y/N ii. LN -Y/N iii. Bone- Y/N

iv. Liver- Y/N v. Lung- Y/N vi. Brain - Y/N

9. Present status: - Primary Metastasis

PRESENT MANAGEMENT

1. Surgery Y/N
2. Radiotherapy Y/N
3. Chemotherapy Y/N
4. Hormonal therapy Y/N
5. Targeted therapy Y/N
6. Treatment combinations _____

CHEMOTHERAPEUTIC REGIMEN

1. Aim of chemotherapy: - Palliative Curative

2. Drug regimen selected: - _____

3. Number of cycles:-_____

4. Change in drug regimen: - Y/N 2^{nd} line Y/N 3^{rd} line Y/N

5. Addition of drug to regimen: - Y/N

i. Drug added:-_____

6. Removal of drug from regimen: - Y/N

i. Drug removed: -_____

7. Completely new regimen: - Y/N

i. Drugs: -_____

8. Duration between each visit: - _____

PREVIOUS MANAGEMENT

1. Previous management Y/N
2. Surgery Y/N
   Type: - _____
3. Radiotherapy Y/N
4. Chemotherapy Y/N
5. Chemotherapeutic agents used:-
   i._____
   ii. _____
   iii._____
   iv._____
6. Hormonal therapy
7. Targeted therapy

7. Toxicities: - Y/N

OUTCOMES

1. Complete response Partial response No response Progressive disease
2. Disease free interval:-_____
i. Loss to follow-up:-_____
ii. Survived:- _____
iii. Death :- _____

APPENDIX IV

NATIONAL GUIDELINES FOR BREAST CANCER CHEMOTHERAPY (2007) FOR NIGERIA

Treatment guidelines depend on the disease stage at diagnosis and are as shown below:

1. Stage 1 breast cancer

Surgery plus adjuvant radiotherapy and or chemotherapy

a. Breast conserving surgey

Lumpectomy, Quadrantectomy plus Radiotherapy

i) Unifocal breast cancer.

ii) Well differentiated breast cancer.

iii) Availability of radiotherapy.

iv) Not used for subareolar tumor.

b. Modified radical mastectomy, chemotherapy, radiotherapy if:

i) Family history of breast cancer.

ii) Early stage of onset < 40 years.

iii) Poorly differentiated.

iv) Poor histological variants.

2. Stage II Breast cancer

i) Modified radical mastectomy plus adjuvant chemotherapy/radiotherapy

ii) Neoadjuvant chemotherapy followed by surgery and then chemotherapy may be used in some cases

iii) If tumor is estrogen receptor positive, progesterone positive: hormonal therapy (tamoxifen) plus chemotherapy (6 cycles) administered together.

3. Stage III Breast Cancer

i) Neoadjuvant chemotherapy followed by surgery

ii) Radiotherapy for unresectable tumor

iii) Herceptin/Trastuzumab for HER/2 neu positive cancers

iv) Hormonal therapy for ER+/PR+ tumor

4. Stage 4 Breast Cancer

i) Radical surgery is not usually indicated

ii) Palliative care including

- Tube insertion or pleural effusion
- Radiotherapy to the spine for spinal metastasis
- Internal fixature for pathological failure
- Compression elastic sleeve or bandage or jobst pump for lymphoedema of the arm
- Biphosphonates in malignant hypercalcemia and metastatic tumors

NEOADJUVANT/ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER

First line

CMF (28 day cycle for 4-6 weeks)

Cyclophosphamide	100mg/m^2	PO days 1-14
Methotrexate	40mg/m^2	IV days 1-8
5-fluorouracil	600mg/m^2	IV days 1-8

Second line

VAC P (21 day cycle for 4-6 weeks)

Vincristine	1.4mg/m^2	IV day1
Adriamycin	50mg/m^2	IV day 1
Cyclophosphamide	200mg.m^2	PO days 3-6
Prednisolone	40mg/m^2	PO days 1-5

CAF (21-28 day cycle for 4-6 weeks)

Cyclophosphamide	600mg/m^2	IV day 1
Adriamycin	60mg/m^2	IV day 1
5-fluorouracil	600mg/m^2	IV day 1

AC (21 day cycle for 4-6 weeks)

Cyclophosphamide	600mg/m^2	IV day 1
Adriamycin	60mg/m^2	IV day 1

Third line

PA (28 day cycle for 4-6 weeks)

Paclitaxel	175mg/m^2	IV day 1
Adriamycin	50mg/m^2	IV day 1

Capecitabine 1000mg/m^2

Hormonal Therapy

Tamoxifen 20mg PO daily for 5 years

APPENDIX V

NATIONAL COMPREHENSIVE CANCER NETWORK PRACTICE GUIDELINES IN ONCOLOGY FOR BREAST CANCER

1. Preferred Adjuvant Regimens

TAC Chemotherapy (every 21 days for 6 cycles)

Docetaxel 75mg/m^2 IV day 1

Doxorubicin 50mg/m^2 IV day 1

Cyclophosphamide 500mg/m^2 IV day 1

Dose dense AC followed by Paclitaxel chemotherapy

Doxorubicicn 60mg/m^2 IV day 1

Cyclophosphamide 500mg/m^2 IV day 1

Every 14 days for 4 cycles

Followed by

Paclitaxel 175mg/m^2 by 3hrs IV infusion day 1

Every 14 days for 4 cycles

AC followed by Paclitaxel chemotherapy

Doxorubicin 60mg/m^2 IV day 1

Cyclophosphamide 600mg/m^2 IV day 1

Every 21 days for 4 cycles

Followed by Paclitaxel 80mg/m^2 by 1hr IV infusion weekly for 12 weeks

TC Chemotherapy

Docetaxel 75mg/m^2 IV day 1

Cyclophosphamide 600mg/m^2 IV day 1

Every 21 days for 4 cycles

AC Chemotherapy

Doxorubicin 60mg/m^2 IV day 1

Cyclophosphamide 600mg/m^2 IV day 1

Every 21 days for 4 cycles

2. Other Adjuvant Regimens

FAC Chemotherapy

5-Fluorouracil 500mg/m^2 IV days 1 and 8 or days 1 and 4

Doxorubicin 50mg/m^2 IV day 1

Cyclophosphamide 500mg/m^2 IV day 1

Every 21 days for 6 cycles

CAF Chemotherapy

Cyclophosphamide 100mg/m^2 IV day 1

Doxorubicin 30mg/m^2 days 1 and 8

5-Fluorouracil 500mg/m^2 IV days 1 and 8

Every 28 days for 6 cycles

CEF Chemotherapy

Cyclophosphamide 75mg/m^2 IV day 1

Epirubicicn 60mg/m^2 days 1 and 8

5-Fluorouracil 500mg/m^2 IV days 1 and 8

Every 28 days for 6 cycles

CMF Chemotherapy

Cyclophosohamide 75mg/m^2 IV day 1

Methotrexate 40mg/m^2 IV days 1 and 8

5-Fluorouracil 600mg/m^2 IV days 1 and 8

Every 28 days for 6 cycles

AC followed by Docetaxel chemotherapy

Doxorubicin 60mg/m^2 IV day 1

Cyclophosphamide 600mg/m^2 IV day 1

Every 21 days for 4 cycles

Followed by

Docetaxel 100mg/m^2 IV day 1

Every 21 days for 4 cycles

EC Chemotherapy

Epirubicicn 100mg/m^2 IV day 1

Cyclophosphamide 830mg/m^2 IV day 1

Every 21 days for 8 cycles