Determination of cardiotoxic effects of chemotherapy drugs used in breast cancer patients at Dr George Mukhari Academic Hospital using Multigated Acquisition scans

A mini-dissertation submitted by

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School of Pharmacy

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M Kahts Lundie

2017
DECLARATION

I declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Pharmacy, in the Faculty of Health Sciences, School of Pharmacy has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

Sibanda, UM (Miss)

__________________________________    __________________
Surname, Initials (Title)     Date
DEDICATION

To God Almighty, thank you for guiding each and every step of the way and giving the strength to accomplish my work. I would also like to thank my dear parents for believing in me, I appreciate all the sacrifices you made for me to be where I am today, I am truly grateful.
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<td>BOC</td>
<td>Breast Oncology Clinic</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DGMAH</td>
<td>Dr George Mukhari Academic Hospital</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ED</td>
<td>End Diastolic</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection Fraction</td>
</tr>
<tr>
<td>ES</td>
<td>End Systolic</td>
</tr>
<tr>
<td>LAO</td>
<td>Left Anterior Oblique</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multigated Acquisition scan</td>
</tr>
<tr>
<td>PACS</td>
<td>Picture Archiving and Communication Systems</td>
</tr>
<tr>
<td>RBCs</td>
<td>Red Blood Cells</td>
</tr>
<tr>
<td>RNVG</td>
<td>Radionuclide Cardiac Ventriculograms</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<tr>
<td>TNM</td>
<td>Tumor, Nodes and Metastases</td>
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ABSTRACT

Abstract

Introduction: The aim of this study was to assess cardiotoxicity in breast cancer patients at Dr George Mukhari Academic Hospital by monitoring cardiac function before commencement of chemotherapy and during the course of treatment, by determining the change in Left Ventricular ejection fraction (LVEF) using Multi-gated Acquisition (MUGA) scans.

Breast cancer is one of the most common cancers in women. It is prevalent worldwide and also in South Africa. Different chemotherapy agents such as anthacyclines have been associated with chemotherapy-induced cardiotoxicity, hence a patient receiving breast cancer chemotherapy might also be faced with increased mortality and morbidity due to cardiovascular side effects. It is therefore important to monitor these cardiotoxic effects especially in patients with pre-existing cardiac conditions and those at risk of developing cardiac conditions by measuring the left ventricular ejection fraction (LVEF) using Multi-gated Acquisition (MUGA) scans.

The non-invasive imaging methods currently available to measure LVEF, include MUGA scan, 2-D and 3-D echocardiography, Tissue Doppler imaging, cardiac Magnetic Resonance Imaging, electrocardiography and radiographic contrast angiography. The most commonly accepted methods of evaluating LVEF to assess cardiac function are echocardiography and MUGA scans.

Multigated acquisition (MUGA) scans are used to monitor cardiac capacity by measuring the left ventricular ejection fraction (LVEF). This approach is highly reproducible and is used as an early warning diagnostic process to monitor the cardiotoxic effects of chemotherapy agents.

Objectives:

• Obtain demographic, clinical and laboratory data, as well as details of current and previous therapy for prospective patients about to receive chemotherapy at the Breast Oncology Clinic DGMAH (new patients enrolled over a period of approximately two months) and also for retrospective patients from hospital files.
• Measure LVEF (via MUGA scans) in breast cancer patients at DGMAH prior to commencement of chemotherapy treatment and at set points during the chemotherapy treatment cycle.

• Compare the change in LVEF levels between the time points and identify variables that may be associated with the change in LVEF (e.g. chemotherapy regimen, age, concomitant treatment and disease).

**Method:** A descriptive prospective and retrospective study was performed in 40 breast cancer patients at Dr George Mukhari Academic Hospital (DGMAH). Patient demographic and cardiovascular assessment data, laboratory and breast cancer data and MUGA scan data were collected using Appendix 6, 7 and 8, respectively. Data were entered into an Excel™ spreadsheet, expressed in terms of percentages, distribution mean values, and standard deviations. Tables, graphs and figures were used to present the results. Data were analysed statistically using the paired t-test with Microsoft Excel 2016 data analysis tool.

**Results:** The Mean and Standard Deviation SD for the first MUGA scan was 64,2 ± 7,7 and the Mean and SD for the last MUGA scan was 60,5 ± 8,5. There was a drop in LVEF in 25 out of 40 (62.5%) of all patients. Fifteen out of 40 (37.5%) retrospective and prospective patients had a drop in LVEF of more than 10% from the first MUGA scan to the last MUGA scan. Six out of 40 (15%) of the patients met the criteria of chemotherapy-induced cardiotoxicity (10% drop in LVEF and a LVEF <55%). The proportion of cardiotoxicity cases was 1/6 and 5/6 for prospective and retrospective patients, retrospectively. The difference between the first MUGA scan and last MUGA scan was statistically significant (p < 0,04).

**Conclusion:** A decline in LVEF during a 6-month period of chemotherapy is evident as seen from the study. This shows that signs of cardiotoxicity manifest at an early stage during chemotherapy treatment comparable with a study by Cardinale et al., (2015) which investigated the early detection of anthracycline-induced cardiotoxicity. In the latter study, the incidence cardiotoxicity was 9% in a study population of 2625 patients, and most cases of cardiotoxicity in this study occurred within a year.

**Recommendations:** Protocols on when to monitor LVEF at set point intervals should be written. All patients should undergo a baseline MUGA scan and at least two subsequent MUGA scans: in the middle of chemotherapy treatment and after chemotherapy treatment. Patients follow up should also be long term in order to identify late cardiotoxic effects that may develop and treat them before they progress..
1.1 INTRODUCTION

This introductory chapter gives the background, rationale and importance of this study. The research question, aim, objectives and outline of this study are also covered in this chapter.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Breast cancer in women is one of the most common cancers. It is prevalent worldwide and also in South Africa. According to the National Cancer Registry (NCR) report in 2010, breast cancer accounted for 20.62% of all the cancers affecting women in South Africa. (National Cancer Registry, 2010).

Different chemotherapy agents have been found to be effective in the treatment of breast cancer. However, some chemotherapy drugs such as anthracyclines have been shown to induce cardiotoxicity. (De Geus-Oie et al, 2011). These cardiotoxic effects may be exacerbated when anthracyclines are given in combination with other chemotherapy agents that have the potential to cause cardiotoxic effects (De Geus-Oie et al, 2011).

The aim of chemotherapy treatment is to reduce mortality and morbidity. A patient receiving breast cancer chemotherapy might also be faced with increased mortality and morbidity due to cardiovascular side effects. It is therefore important to monitor these cardiotoxic effects especially in patients with pre-existing cardiac conditions and those at risk of developing cardiac conditions (Bovelli et al, 2010). Patients react differently to treatment, therefore it is hard to determine which patient will experience cardiac side effects (Sorrentino et al, 2012).

Multigated acquisition (MUGA) scans are used to monitor cardiac capacity by measuring the left ventricular ejection fraction (LVEF). This approach is highly reproducible (Hershman and Shao, 2009) and is used as an early warning diagnostic process to monitor the cardiotoxic effects of chemotherapy agents (Gulati et al, 2014). Cardiac dysfunction is normally preceded by a decrease in LVEF without any symptoms (Wei, 2014). MUGA scans involve labelling red blood cells (RBCs) with $^{99m}$Technetium ($^{99m}$Tc) pertechnetate (Nicol et al, 2009).

Labelling efficiency is crucial in quality monitoring (De Vries et al, 2010) and to obtain high quality images (Hambye et al, 1995). The labelling efficiency of the $^{99m}$Tc labelled RBCs
used in the MUGA scans and other quality control aspects were covered in a parallel study (Bonisile Nkosi, MPharm candidate).

The majority of MUGA studies to monitor cardiotoxicity in breast cancer patients have been performed in developed countries (Reuvekamp et al, 2015; Ganz et al, 2008). There is a lack of literature on studies performed in developing countries such as South Africa. No such studies could be identified from literature searches.

1.3 RESEARCH QUESTION

The research question was:

Does chemotherapy in breast cancer patients at DGMAH (Dr George Mukhari Academic Hospital) result in cardiotoxicity, as measured by changes in LVEF, assessed with the use of MUGA scans?

1.4 AIM OF THE STUDY

The aim of the study was to assess cardiotoxicity in breast cancer patients by monitoring cardiac function before commencement of chemotherapy and during the course of treatment, by determining the change in LVEF using MUGA scans.

1.5 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- Obtain demographic, clinical and laboratory data, as well as details of current and previous therapy for prospective patients about to receive chemotherapy at the Breast Oncology Clinic DGMAH (new patients enrolled over a period of approximately two months) and also for retrospective patients from hospital files.

- Measure LVEF (via MUGA scans) in breast cancer patients at DGMAH prior to commencement of chemotherapy treatment and at set points during the chemotherapy treatment cycle.

- Compare the change in LVEF levels between the time points and identify variables that may be associated with the change in LVEF (e.g. chemotherapy regimen, age, concomitant treatment and disease).
1.6 IMPORTANCE OF THE STUDY

Chemotherapy agents are known to induce cardiotoxicity. Many breast cancer patients at Dr George Mukhari Academic Hospital (DGMAH) are given such agents. The cardiotoxic effect of these agents has not been formally studied in this patient group.

A study of this nature will help monitor cardiotoxicity of chemotherapy drugs by measuring the changes in LVEF using MUGA scans and therefore may detect cardiotoxicity in its early stages and help the physician decide on the appropriate chemotherapy for the patient.

1.7 OUTLINE OF THE DISSERTATION

Chapter 1 is an introductory chapter of the dissertation, which provides the background, rationale, aims and objectives of the study. The literature review on the study is discussed in Chapter 2. The methodology adopted in this study is described in Chapter 3. In Chapter 4, the results are presented and discussed in the form of a draft publication. The dissertation is summarised, concluded and recommendations are made in Chapter 5.
2.1 INTRODUCTION

The literature review in this chapter covers breast cancer and its chemotherapy agents and methods of monitoring cardiotoxicity due to chemotherapy, in particular, Multigated Acquisition (MUGA) scans. Aspects of labelling red blood cells with $^{99m}$Tc for MUGA scans, imaging modalities and the Picture Archiving and Communication Systems (PACS) are also discussed.

2.2 BREAST CANCER

Breast cancer involves the abnormal growth of cells lining the ducts and lobules of the female breasts. Such growths have the potential to metastasize to other distal areas such as the axillary lymph nodes. Not all breast cancers will present with a lump in the breast (Ades et al., 2006).

Breast cancer can be classified as invasive or non-invasive/carcinoma in situ. Non-invasive breast cancer means that the cancer is at a very early stage and is restricted to the lobules or ducts and has not spread to other distant organs of the body and areas such as fatty tissue, which surround the breast (Ades et al., 2006).

There are two types of non-invasive breast cancer, namely; lobular carcinoma in situ, which means that the cancer originated from the lobules, and ductal carcinoma in situ, which originated from the ducts (Ades et al., 2006).

Breast cancer that has spread beyond the lobules or ducts to other organs is referred to as invasive breast cancer. There are different types of invasive cancers, namely: infiltrating ductal carcinoma, infiltrating lobular carcinoma, mixed tumours, inflammatory breast cancer, medullary cancer, colloid carcinoma, metaplastic carcinoma and tubular carcinoma (Ades et al., 2006).

Breast cancer diagnosis and screening involves the following processes; medical history, physical examination, breast imaging and biopsy. When taking the medical history, the patient will be asked to describe the symptoms experienced and questions relating to factors contributing to breast cancer such as family history, early menarche and alcohol...
consumption will be asked. Physical examination involves palpating the breast, evaluating the texture and size of the breasts and determining whether any lumps are present. Other areas assessed when examining the patient are the nipples and skin of the breasts. There is also an assessment to see if any abnormal lymph nodes are present under the armpit or found above the collarbone (Ades et al, 2006). Breast cancer clinical signs and symptoms are as follows:

- Distinct lumps or masses,
- Breast pain,
- Abnormal discharge from the nipple, e.g. blood,
- Skin changes,
  - Discoloration, e.g. redness
  - Texture which is like orange peel
- Dimpling and retraction of the nipple (Goldberg and Thompson, 2004),
- Enlargement and swelling of the breast,
- Indescribable thickening in the breast,
- Lump which is fixated on the chest wall (Porter and Kaplan, 2011)

Initial diagnostic imaging is done using a mammogram, ultrasound or magnetic resonance imaging (MRI). A mammogram will give information on the area of interest, such as the size of the lump or any suspicious symptom that may be seen. An ultrasound, which makes use of high frequencies, further examines a lump or any finding on the mammogram but most importantly, checks to see if there might be a cyst filled with fluid, which is not cancerous, or a solid tissue, which is cancerous. Tumours not found on the mammogram can be identified using MRI, which also outlines the size and extent of the cancer. If any lump is present on the breast or cancer is suspected, a biopsy is performed. Biopsy procedure involves removing tissue from the breast using a needle or surgery to be examined under a microscope by a pathologist to establish if cancer is present (Ades et al, 2006).

Once breast cancer is diagnosed other tests may be performed, such as; chest x-rays to check if cancer has spread to the lungs, bone scans, Positron Emission Tomography (PET) scans, MRI, blood tests and tumour tests. Three types of receptors are tested for on tumours: oestrogen, progesterone and HER-2/neu receptors. Oestrogen and progesterone
promote the normal growth of breast cancer cells and play a role in breast cancers. If progesterone or oestrogen receptors are found on a tumour cell, the former is said to be PR positive and the latter ER positive. To suppress the tumour by inhibiting growth, drugs that block these hormones are given such as tamoxifen. When high levels of HER-2/neu, a protein promoting growth, are found in a tumour it is said to be HER-2/neu positive and contribute to the growth and rapid spread of the tumour. Trastuzumab is given to block the HER-2/neu receptor (Ades et al., 2006). Breast cancer chemotherapy can be administered either before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy) (Green and Hortobagyi, 2002).

2.2.1 Breast cancer staging

Breast cancer is staged according to the TNM system according to the American Joint Committee on Cancer, where T is the primary tumour size, N is for regional lymph nodes affected and M is for distant metastases (Cancer.org, 2017). In the TNM system, T is on a scale of zero to four, N is zero to three and M is zero or one; see Table 2.1 (Edge, 2010). The TNM staging is also describe in Appendix 1.

Table 2.1: TNM staging

<table>
<thead>
<tr>
<th>Tumours</th>
<th>T0 or Tis</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Tumour</td>
<td>T0 – there is no primary tumour</td>
<td>0 to 2 cm</td>
<td>2 to 5 cm</td>
<td>Size of tumour more than 5 cm</td>
<td>Tumour that has extended to skin or wall of the chest. Ulceration. Inflammatory cancer.</td>
</tr>
<tr>
<td></td>
<td>Tis – tumour is confined to ducts or lobules of the breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodes</td>
<td>N0</td>
<td>N1</td>
<td>N1mi</td>
<td>N2</td>
<td>N3</td>
</tr>
<tr>
<td></td>
<td>Lymph node metastases not present</td>
<td>Cancer cells are found in 1 to 3 axillary lymph nodes</td>
<td>Tumour of the lymph node is more than 2 mm</td>
<td>Cancer cells found in 4 to 9 axillary lymph nodes</td>
<td>Cancer cells found in more than 10 axillary lymph nodes or they may be found in infra and supraclavicular lymph nodes</td>
</tr>
<tr>
<td>Metastasis</td>
<td>M0</td>
<td>M1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No cancer cell metastases present</td>
<td>Cancer cells present in other organs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 2: Literature Review

Source: (Edge, 2010)

Different combinations of T, N and M are then grouped to form a stage, from stage 0 to IV as shown in Table 2.2. Stages 0 to 2B are classified as early breast cancer and stages 3A to 4 are advanced breast cancers.

Table 2.2: Breast cancer stages

<table>
<thead>
<tr>
<th>Classification</th>
<th>Stage</th>
<th>TNM Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early breast cancer</td>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 1A</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 1B</td>
<td>T0-T1, N1mi, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 2A</td>
<td>T0, N1 but not N1mi, M0 OR T2, N0, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 2B</td>
<td>T2, N1, M0 OR T3, N0, M0</td>
</tr>
<tr>
<td>Advanced breast cancer</td>
<td>Stage 3A</td>
<td>T0-T2, N2, M0 OR T3, N1/N2, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 3B</td>
<td>T4, N0-N2, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 3C</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td></td>
<td>Stage 4</td>
<td>Any T, any N, M1</td>
</tr>
</tbody>
</table>

Source: (Shah, 2014)

2.2.2 Breast cancer treatment by stage

Treatment of each cancer stage is shown in Table 2.3.

Table 2.3: Treatment of breast cancer

<table>
<thead>
<tr>
<th>Classification</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular carcinoma in situ</td>
<td>Primary: Observation or bilateral mastectomy</td>
</tr>
<tr>
<td></td>
<td>Adjuvant: Tamoxifen for a period of 5 years</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>Primary: Mastectomy without lymph node dissection</td>
</tr>
<tr>
<td></td>
<td>Adjuvant: Tamoxifen for a period of 5 years</td>
</tr>
<tr>
<td>Stage 1A to 2B</td>
<td>Primary: Lumpectomy, axillary dissection, radiation therapy or modified</td>
</tr>
<tr>
<td></td>
<td>radical mastectomy</td>
</tr>
<tr>
<td></td>
<td>Systemic: No nodes and tumour size less than 1 cm –adjuvant</td>
</tr>
</tbody>
</table>
# Chapter 2: Literature Review

## 2.3 Breast Cancer Chemotherapy Agents

The following chemotherapy agents, used for the treatment of breast cancer, have cardiotoxic side effects: anthracyclines, taxanes, cyclophosphamide and 5 fluorouracil.

<table>
<thead>
<tr>
<th>Stage 3A</th>
<th>Primary:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T4 is less than 4 cm and there is no skin involvement</td>
</tr>
<tr>
<td></td>
<td>Lumpectomy, axillary dissection</td>
</tr>
<tr>
<td></td>
<td>If inoperable doxorubicin based chemotherapy is given</td>
</tr>
<tr>
<td></td>
<td>Response to treatment: modified radical mastectomy, post-operative radiotherapy</td>
</tr>
<tr>
<td></td>
<td>No response to treatment: preoperative radiation therapy / second line chemotherapy, modified radical mastectomy and adjuvant chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3B</th>
<th>Primary:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If operable, Doxorubicin based chemotherapy for induction is given, modified radical mastectomy, radiation therapy and chemotherapy is given further</td>
</tr>
<tr>
<td></td>
<td>If inoperable, see stage 3A</td>
</tr>
<tr>
<td></td>
<td>For inflammatory cancer, Doxorubicin based chemotherapy for induction is given</td>
</tr>
<tr>
<td></td>
<td>Response to treatment: modified radical mastectomy, radiation therapy and further chemotherapy is given</td>
</tr>
<tr>
<td></td>
<td>No response to treatment: / second line chemotherapy and third line chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV</th>
<th>ER/PR +ve and metastases are present in bone or soft tissue and no symptomatic visceral disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st line: Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>2nd line: Aromatase inhibitors</td>
</tr>
<tr>
<td></td>
<td>3rd line: Androgens</td>
</tr>
<tr>
<td></td>
<td><strong>ER/PR-ve Symptomatic visceral disease</strong></td>
</tr>
<tr>
<td></td>
<td>1st line: FAC (5-Fluorouracil, Adriamycin and Cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td>2nd line: Navelbine/Taxotere/Taxol</td>
</tr>
</tbody>
</table>

Source: (Gezairy, 2006)
2.3.1 Anthracyclines

Anthracyclines promote the formation of free radicals. Cardiotoxic effects result from the iron-catalyzed formation of free radicals. Acute toxicity may occur within 24 hours after initiation of therapy and presents with sinus tachycardia. Chronic toxicity leads to congestive cardiomyopathy (Brenner and Stevens, 2017). The incidence of doxorubicin-induced cardiotoxicity is 4% to over 36%, in patients receiving a cumulative dose of 500-550 mg/m² of their body surface area. The incidence of developing heart failure is lower with epirubicin. Risk factors include; female gender, young and old age, prior irradiation, use of anthracyclines in combination with other chemotherapy agents, cumulative dose given and any pre-existing cardiovascular disease (Bovelli et al, 2010).

2.3.2 Taxanes

Taxanes, such as paclitaxel, reduce the uptake of free fatty acids by the mitochondria, as a result of microtubular transport impairment in cardiomyocytes. Clinical manifestations are heart failure, arrhythmias and ischemia (De Geus-Oei et al, 2011). Incidence of developing bradyarrhythmias is low at 0.1% (Feenstra et al, 1999). Risk factors include treatment with other chemotherapy agents, underlying cardiovascular disease and chest irradiation (Bovelli et al, 2010)

2.3.3 Cyclophosphamide

Cyclophosphamide metabolites are toxic and thereby lead to the breakdown of the endothelial cells, thus causing damage to the myocardium and capillary blood vessels. As a result there is formation of micro thrombi, oedema and interstitial haemorrhage. Clinical manifestations are arrhythmias and acute heart failure and may occur within 10 hours after initiation of therapy. In patients receiving a dose of >150 mg/kg and 1.5 g/m²/day, the incidence of cyclophosphamide-induced cardiotoxicity ranges from 4% to 28%. Risk factors include; prior anthracycline administration, mediastinal irradiation and symptomatic heart failure (Bovelli et al, 2010)

2.3.4 5-Fluorouracil

5-Fluorouracil may induce cardiotoxicity by several mechanisms; accumulation of toxic metabolites, endothelial dysfunction, coronary vasospasm and direct injury to myocardium. Clinical manifestations such as angina, silent ischemia and myocardial infarction, myocarditis and heart failure may occur within 12 hours after administration of the first dose.
(Sorrentino et al, 2012). The incidence of 5-fluorouracil-induced cardiotoxicity ranges from 1% to 68%. Risk factors include; pre-existing cardiovascular disease and heart failure, treatment with other chemo agents, mediastinal irradiation and impaired renal function (Bovelli et al, 2010)

2.3.5 Trastuzumab

Trastuzumab, a monoclonal antibody, is given either alone or in combination with other chemotherapy drugs. When given alone the incidence of heart failure in women reported was 7%. The incidence of cardiac dysfunction observed when Trastuzumab was given in combination with anthracyclines was 28% (Schimmel et al., 2004). The exact mechanism of Trastuzumab-induced cardiotoxicity is not known however, it may be through the blocking of pathways that respond to stress for myocardial survival (Kang, n.d.)

2.3.6 Combined chemotherapy in breast cancer

Adjuvant chemotherapy regimens for HER2-negative Breast Cancer (NCCN guidelines, 2014) are shown in Table 2.4 and 2.5 HER2-positive Breast Cancer regimens are shown in Appendix 3a and Appendix 3b (NCCN guidelines, 2014).
Table 2.4: HER2-negative Breast Cancer preferred regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adriamycin/doxorubicin</th>
<th>Cyclophosphamide</th>
<th>Docetaxel</th>
<th>Epirubicin</th>
<th>5-Flourouracil</th>
<th>Methotrexate</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-P (dose-dense)</td>
<td></td>
<td>60 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>175 mg/m² by three hour IV infusion, Day 1</td>
</tr>
<tr>
<td>AC every two weeks for four cycles, Followed by; P every two weeks for four cycles</td>
<td></td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC-P (dose dense)</td>
<td></td>
<td>60 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 mg/m² by one hour IV infusion, weekly</td>
</tr>
<tr>
<td>AC every two weeks for four cycles, Followed by; P weekly for 12 weeks</td>
<td></td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC every three weeks for four cycles</td>
<td></td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td>75 mg/m² IV , Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(NCCN guidelines, 2014)
## Table 2.5: Other regimens for HER2-negative Breast Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adriamycin/ doxorubicin</th>
<th>Cyclophosphamide</th>
<th>Docetaxel</th>
<th>Epirubicin</th>
<th>5-Flourouracil</th>
<th>Methotrexate</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC (dose dense) Every two weeks for four cycles</td>
<td>60 mg /m² IV, Day 1</td>
<td>600 mg /m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC every three weeks for four cycles</td>
<td>60 mg /m² IV, Day 1</td>
<td>600 mg /m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC every three weeks for six cycles</td>
<td>50 mg /m² IV, Day 1</td>
<td>500 mg /m² IV, Day 1</td>
<td>75 mg /m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC every three weeks for six cycles</td>
<td>50 mg /m² IV, Day 1</td>
<td>500 mg /m² IV, Day 1</td>
<td></td>
<td></td>
<td>500 mg /m² IV, Days 1 and 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAF every four weeks for six cycles</td>
<td>30 mg /m² IV, Days 1 and 8</td>
<td>100 mg /m² orally, Days 1 to 14</td>
<td></td>
<td></td>
<td>500 mg /m² IV, Days 1 and 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEF every four weeks for six cycles</td>
<td></td>
<td>75 mg /m² orally, Days 1 to 14</td>
<td>60 mg /m² IV, Days 1 and 8</td>
<td>500 mg /m² IV, Days 1 and 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMF every four weeks for six cycles</td>
<td></td>
<td>100 mg /m² orally, Days 1 to 14</td>
<td></td>
<td></td>
<td>600 mg /m² IV, Days 1 and 8</td>
<td>40 mg /m² IV, Days 1 and 8</td>
<td></td>
</tr>
<tr>
<td>EC every three weeks for eight cycles</td>
<td></td>
<td>830mg/m² IV, Day 1</td>
<td>100mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC-T AC every three weeks for six cycles, followed by T every three weeks for four cycles</td>
<td>60 mg /m² IV, Day 1</td>
<td>600 mg /m² IV, Day 1</td>
<td>100 mg /m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2.5: Other regimens for HER2-negative Breast Cancer (Continued)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adriamycin/doxorubicin</th>
<th>Cyclophosphamide</th>
<th>Docetaxel</th>
<th>Epirubicin</th>
<th>5-Flourouracil</th>
<th>Methotrexate</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-P</td>
<td>60 mg/m² IV, Day 1</td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 mg/m² by one hour IV infusion, weekly</td>
</tr>
<tr>
<td>AC every three weeks for four cycles, followed by P weekly for 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC-T</td>
<td>500 mg/m² IV, Day 1</td>
<td>100 mg/m² IV, Day 1</td>
<td>100 mg/m² IV, Day 1</td>
<td>500 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC every three weeks for three cycles, followed by T every three weeks for three cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC-P</td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td>90 mg/m² IV, Day 1</td>
<td>600 mg/m² IV, Day 1</td>
<td></td>
<td></td>
<td>100 mg/m² weekly by IV infusion</td>
</tr>
<tr>
<td>FEC every three weeks for four cycles, followed by P weekly for eight weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC-P</td>
<td>50 mg/m² IV, Day 1</td>
<td>500 mg/m² IV, Day 1</td>
<td></td>
<td>500 mg/m² IV, Days 1 and 8</td>
<td></td>
<td></td>
<td>80 mg/m² by one hour IV infusion, weekly</td>
</tr>
<tr>
<td>FAC every three weeks for six cycles, followed by P weekly for 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(NCCN guidelines, 2014)
Chapter 2: Literature Review

Concomitant use of cardiotoxic chemotherapy and other cardiotoxic agents, such as antiarrhythmics, antidepressants and calcium channel blockers, may increase the cardiotoxic effects that will result in congestive heart failure (Feenstra et al, 1999).

2.4 METHODS OF MONITORING CARDIOTOXICITY

Cardiac ejection Fraction (EF) is classified as normal when it falls in the range of 50-75%, or decreased, where the function is impaired (mild: <50%, moderate: <40% and severe: <30%) (Milne et al, 2007).

Chemotherapy-induced cardiotoxicity according to Saidi and Alharethi (2011) is,

“Decline in Left Ventricular Ejection Fraction (LVEF) of at least 5% to below 55% with accompanying signs or symptoms of HF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms”.

The non-invasive imaging methods currently available to measure LVEF include MUGA scan, 2-D and 3-D echocardiography, Tissue Doppler imaging, cardiac Magnetic Resonance Imaging, electrocardiography and radiographic contrast angiography. The most commonly accepted methods of evaluating LVEF to assess cardiac function are echocardiography and MUGA scans (De Geus-Oei et al, 2011).

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>MUGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in LVEF may be seen when cardiotoxicity has already occurred</td>
<td>Can determine changes in LVEF at an early stage before cardiac side effects manifest</td>
</tr>
<tr>
<td>Less sensitive and poor specificity</td>
<td>Gold standard and high specificity</td>
</tr>
<tr>
<td>Poor reproducibility</td>
<td>High reproducibility</td>
</tr>
<tr>
<td>High interobserver and intraindividual variability</td>
<td>Low interobserver and intraindividual variability</td>
</tr>
<tr>
<td>Variable operator skill</td>
<td>Simple and effective approach</td>
</tr>
<tr>
<td>No ionising radiation</td>
<td>Ionising radiation</td>
</tr>
<tr>
<td>Cheap</td>
<td>Expensive</td>
</tr>
<tr>
<td>Widely available</td>
<td>Not widely available</td>
</tr>
<tr>
<td>Can be done at patient’s bedside</td>
<td>Cannot be done at patient’s bedside</td>
</tr>
<tr>
<td>No special equipment need</td>
<td>Special equipment used e.g. gamma camera</td>
</tr>
</tbody>
</table>

Source: De Geus-Oei et al, 2011; Gutta, 2016 personal communication.
2.4.1 MUGA scan

MUGA scans are also known as radionuclide cardiac ventriculograms (RNVG). They allow for the assessment of LVEF and observation of left ventricle wall motion. $^{99m}$Tc-labelled RBCs are used in this study. RBCs are labelled using three methods: in vitro, modified in vivo and in vivo (Nicol et al, 2009).

The electrocardiogram (ECG) is connected to the patient to pick up the cardiac R-wave and sends impulses to the gamma camera.

![Figure 2.1: ECG showing R-R interval](Ni.com, 2012)

The camera will then obtain multiple images which are synchronized with the ventricular contraction (Zeissman et al, 2014). The left anterior oblique (LAO) shows the optimal septal separation between left ventricle and right ventricle, an angle of 45° displays the best septal view (Corbett et al., 2006). Images acquired should have more than 24 frames per cycle (Nicol et al, 2009); 300 cardiac cycles are imaged in five minutes and the computer combines all the images to one average representative cycle (Zeissman et al, 2014).

From representative cycle scans, regions of interest (ROI) on the left ventricle are identified. The defined regions are the end diastolic (ED) and end systolic (ES) cardiac blood pool; they are drawn manually or automatically. Based on the counts projected by the ED and ES, the ejection fraction (EF) is calculated using the following equation:

$$EF\% = \frac{(ED\ counts – ES\ counts)}{ED\ counts}\ (Nicol\ et\ al,\ 2009)$$
2.4.2 **$^{99m}$Tc RBC Labelling Methods**

Labelling of RBCs involves treating the RBCs with stannous chloride (a reducing agent), removing any excess stannous ion and the addition of $^{99m}$Tc pertechnetate (Callahan, 2006). In the labelling of RBCs with $^{99m}$Tc, $^{99m}$Tc pertechnetate is reduced by the presence of stannous ions inside the RBCs. The reduced $^{99m}$Tc pertechnetate binds mainly to the β chain of the globin part of haemoglobin. The stannous ions and reduced $^{99m}$Tc pertechnetate have the ability to diffuse into RBCs (Schwochau, 2009). Stannous ions are susceptible to hydrolysis and precipitation under physiological pH and as a result, they are rapidly cleared from the bloodstream. However, when stannous ions are bound to pyrophosphate they are not easily susceptible to these effects (Callahan, 2006).

2.4.2.1. **In vitro:**

In this method, blood is removed from the patient. The RBCs are then separated from other blood components by centrifugation or washing. The separated RBCs are then incubated in stannous citrate and excess stannous ion is washed out. The RBCs (incubated in stannous citrate) are then incubated with $^{99m}$Tc pertechnetate (Saha, 2010).

2.4.2.2. **In vivo:**

In the in vivo method, the patient is injected with stannous pyrophosphate. After 20 to 30 minutes, the patient is injected with $^{99m}$Tc pertechnetate and the labelling process takes place in the patient’s bloodstream (Callahan, 2006).

2.4.2.3. **Modified in vivo:**

The modified in vivo method makes use of a three-way stopcock. A syringe with heparinised normal saline is connected to one port of the stopcock and the other port is connected to a syringe containing $^{99m}$Tc pertechnetate. Twenty to thirty minutes after injection of stannous pyrophosphate, 3 ml of blood is drawn into the syringe containing $^{99m}$Tc pertechnetate. The blood is then incubated for 10 minutes while shaking gently before it is re-injected into the patient (Saha, 2010).

2.4.3 **Imaging modalities**

2.4.3.1. **SPECT (Single photon emission computed tomography)**

SPECT images the distribution of the radionuclide by detecting the gamma photons generated by the radionuclide. The main goal of SPECT is to produce emission tomography...
images that represent the radiotracer distributed within the body. The detectors of the gamma camera rotate or orbit around the patient and image "slices" are acquired simultaneously. A SPECT gamma camera can comprise of single-, dual- and triple-head detectors (Kirks and Griscom, 1998).

Most SPECT studies have 360° orbits, with the exception of cardiac anterior imaging at 180°. A SPECT gamma camera creates slices of two dimensional (2-D) images or volume images, which are three-dimensional (3-D). The 3-D volume images are obtained from the 2-D planar image (Aarsvold and Wernick, 2004). 3-D reconstructed images in MUGA scans are employed for quantification of left ventricular volumes (Corbett et al., 2008).

2.4.3.2. CT (Computed tomography)

In CT, X-rays produced from the X-ray tube are transmitted through the body. The photons transmitted are then detected. An image is processed and reconstructed. CT as compared to projection radiography has the ability to gain information in-depth from a single image by separating the anatomical details, which are superimposed and thus produce slices of images which have very good tissue contrast (Aichinger et al., 2011).

2.4.3.3. SPECT/CT

Due to poor spatial resolution of SPECT images, imaging systems have been improved and CT has been incorporated into the same gantry system. This allows both functional and anatomical images to be acquired (Aarsvold and Wernick, 2004). As a result there is better localisation and scintigraphic findings can be defined properly (Buck et al., 2008). CT also helps in attenuation correction of SPECT images (Aarsvold and Wernick, 2004).

2.4.4 PACS (Picture archiving and communication systems)

In many hospitals, hard film copies have been replaced by digital images with the use of PACS. PACS allows images to be seen simultaneously by medical professionals. PACS combines both hardware and software and is used in retrieving, storing, distributing, presenting and managing images (Cruz-Cunha et al, 2013). The PACS system has been recently introduced at Dr George Mukhari Academic Hospital.
2.5 SUMMARY

Breast cancer aspects discussed in this chapter are as follows;

- Overview of breast cancer; types, diagnosis and screening and clinical signs and symptoms
- Staging; TNM classification and treatment of each stage
- Treatment; Mechanisms of cardiotoxicity of each class or types of chemotherapy drugs and the combination regimens.
- Assessment of LVEF to measure the extent of cardiotoxicity is included as well as the different ways to measure LVEF with MUGA scans being the main focus.
- $^{99m}$Tc labelling techniques with pyrophosphate; in vitro, in vivo and modified in vivo.
- Description of Imaging systems using gamma cameras and the PACS system.
CHAPTER 3
METHODOLOGY

3.1 INTRODUCTION

This chapter presents the method of the study. The sections covered are the study design, site, population and sample. The data collection description includes the period of study, training, instruments used, entry and analysis of data. Other sections include the pilot study, reliability and validity of the study and the ethical considerations.

3.2 STUDY DESIGN

A descriptive prospective and retrospective study was performed. Patients acted as their own controls. This study was an exploratory study. The prospective study design is shown in Figure 3.1 and the retrospective study design is shown in Figure 3.2. Due to slow recruitment in the prospective study, a retrospective component had to be added via an approved protocol amendment (Appendix 2) in order to achieve an adequate sample size.
Chapter 3: Methodology

*Note: The duration of each chemotherapy treatment cycle is 4 weeks

Figure 3.1: Prospective MUGA study flow
Figure 3.2: Retrospective MUGA study flow

3.2.1 MUGA scan procedure

Scans obtained for prospective patients include; baseline scan (before initiation of chemotherapy), 2nd scan (at 8 weeks, before the 3rd cycle) and 3rd scan (at 16 weeks, before the 5th cycle).

For the retrospective patients the MUGA scans were not at set specific intervals.

For this study, labelling of red blood cells with $^{99m}$Tc was done using the in vivo method discussed in Chapter 2. The process is as follows:

- 20mg of sodium pyrophosphate which is sterile, pyrogen-free and freeze-dried was reconstituted by adding 4.5 ml of water for injection.

- On one of the patient’s hands, an injection needle was inserted intravenously (IV), with a three-way stopcock inserted on injection hub. The three-way stopcock was flushed with normal saline using a syringe. A syringe containing 2.5 ml of sodium pyrophosphate was
inserted on one of the ports of the three-way stopcock and infused into the patient. Normal saline was used to flush the IV line after the infusion.

- 20 min after administration of sodium pyrophosphate, 555 - 1110 MBq activity of \(^{99m}\text{Tc}\) was injected intravenously on the opposite hand by inserting the syringe filled with technetium on the three-way stopcock inserted on the injection hub. Normal saline was used to flush the IV line.

- Two cameras were used in the acquisition of images; GE (SPECT/CT gamma camera) and Ecam (SPECT gamma camera). Initially one camera was supposed to be used for repeatability and consistency, but due to time constraints and patient logistics two cameras were utilised.

- After injection of \(^{99m}\text{Tc}\), the patient lay on the imaging couch in a supine position. Three electrodes connected to the ECG were placed on the chest: right shoulder (below clavicle), left shoulder (below clavicle) and lower left chest.

- Three Static images were obtained
  - One anterior view – approximately seven minutes
  - One Left Anterior Oblique (LAO) view – approximately seven minutes
  - One lateral view – approximately seven minutes

- The researcher took note of the LAO angle during imaging, which was of importance to check if there was adequate image separation between the right ventricle and left ventricle

- 24 frames were obtained for 480 sec per view

- Images were sent to the PACS system for processing

- In the processing unit, the LAO and LAO gated images were selected under the cardiac category, one representative cardiac cycle image was generated and the LV centre was determined taking the background into account. The ROI was automatically drawn. The LVEF was calculated from the background corrected counts, which are within the left ventricle at end diastolic and end systolic, as discussed in section 2.4.1

- When the processing was complete the researcher obtained the scan results from the flexible display on the computer and recorded the EF and the ED and ES counts.
3.3 STUDY SITE

The study was performed at the Breast Oncology Clinic of the Department of Surgery and at the Nuclear Medicine Department at Dr George Mukhari Academic Hospital, Ga-Rankuwa, South Africa.

3.4 STUDY POPULATION AND SAMPLE

3.4.1 Study population

The prospective study population consisted of newly enrolled female breast cancer female patients who were 18 years and older. The prospective study population consisted of breast cancer patients who were scheduled to be initiated on chemotherapy at the Breast Oncology Clinic at DGMAH.

The retrospective study population consisted of breast cancer patients who had completed chemotherapy treatment and had at least two MUGA scans.

3.4.2 Sample selection

The sample included all patients visiting the Breast Oncology Clinic for initiation of chemotherapy for a period of approximately two months and retrospective patients who had completed chemotherapy. Follow up of each patient took a further four months, hence the total study duration was six months for data collection. Approximately five new patients were seen weekly, hence the number of patients recruited in the first two months was anticipated to be 40. As this study was part of a master’s degree by minor dissertation and coursework, linked to an academic internship, the study could only be an exploratory study of approximately 40 patients due to time constraints.

3.4.2.1 Inclusion criteria

The following inclusion criteria applied:

Retrospective patients

- Female patient, >18 years
- Patients that had completed chemotherapy treatment
- Patient had a negative pregnancy test before study
Chapter 3: Methodology

- Minimum of two MUGA scans

**Prospective patients**

- Female patient, >18 years
- Breast cancer patient who was newly scheduled to receive chemotherapy
- Patient had a negative pregnancy test before study
- Able to understand the study requirements
- Willing to sign informed consent for inclusion in the study
- Minimum of two MUGA scans

**3.4.2.2. Exclusion criteria**

The following exclusion criteria applied:

**Retrospective patients**

- Patients who were pregnant or breastfeeding
- Patients who had received blood within four weeks prior to the study

**Prospective patients**

- Existing patients already undergoing chemotherapy
- Patients who were pregnant or breastfeeding
- Patients who had received blood within four weeks prior to the study

**3.5 DATA COLLECTION**

**3.5.1 Data collection period**

The study ran from February 2017 to October 2017.
3.5.2 Data collection training

The researcher was capable of collecting data based on previous data collection training experience during her undergraduate degree where she was involved in a research project. Further training occurred during the pilot study.

3.5.3 Enrolment and data collection

Patients with suspected breast cancer are referred to the Breast Oncology Clinic for an appointment. On the day of appointment breast examination, history taking, laboratory investigations and breast cancer staging are performed. Results from the x-ray and biopsy are sent to breast clinic. Patients for initial chemotherapy workup are given request forms for both MUGA and bone scans to be booked at the Nuclear Medicine department.

3.5.3.1. Enrolment

Prospective

The researcher obtained the names and hospital numbers of newly diagnosed breast cancer patients at the BOC and NM department. The new patients who attended over a period of two months were approached for recruitment into the study.

On the day that the patient was having their MUGA baseline scan, the researcher informed the patient of the study and gave a Patient Information Leaflet (Appendix 4) to the patient. If the patient fully understood the information on the leaflet and was willing to participate in the study, she signed a Patient Informed Consent Form (Appendix 5).

After signing the consent form, a Patient Demographics, Cardiovascular Risk Assessment and Clinical Data Form (Appendix 6) were completed by the researcher from information obtained from the BOC patient notes and from the patients themselves via interviews. Some questions on Appendix 6 were repeated at each scan, as some of the answers were subject to change (for example weight, concomitant drugs and adjuvant therapy).

Retrospective

Retrospective Breast Cancer patients who had completed their chemotherapy treatment would be selected from Breast Oncology Clinic files as well as from the Nuclear Medicine Department’s Picture Achiving and Communication system (PACS). Patients selected would be from 1 January 2014 to 30 September 2017.
3.5.3.2. Data collection

Prospective

The completion of Appendices 4, 5 and 6 was done before the baseline MUGA scan.

Laboratory and Breast Cancer Data Form (Appendix 7) were completed upon obtaining laboratory results after each chemotherapy cycle and breast cancer information was obtained on the appointment day and also from the BOC file. The researcher and the colleague who conducted the parallel blood-labelling efficiency study, collected patient data. The Patient MUGA Scan Form (Appendix 8) was used to record the results obtained from the baseline MUGA scan, 2nd MUGA scan and the 3rd scan, which included data on labelling efficiency (LE). LE is a quality monitoring measure which was performed in the parallel study. The results of the MUGA scan were sent to the BOC.

The bone scan followed the MUGA baseline scan, normally by two to four weeks, and the results we sent to the BOC.

The researcher followed up by contacting the patient to ask on which date they were returning, in order to keep track of when the patient would have their first chemotherapy cycle.

On the day of the first chemotherapy cycle, the researcher liaised with the doctor at BOC and obtained the request forms for the 2nd and 3rd MUGA scans. The researcher labelled the files of the patients in the study at BOC using coloured stickers to distinguish them from the other files.

The researchers booked the subsequent MUGA scans for the patients at the Nuclear Medicine Department and followed up on the patients at the Nuclear Medicine Department when they returned for the subsequent scans.

Retrospective

For the retrospective patients the information obtained from the breast clinic files would be used to complete Appendices 6, 7 and 8. The MUGA scan results obtained using the PACS would be used to complete Appendix 8 for the MUGA scan results.
3.5.3.3. **Data Collection Instruments**

The patient information leaflets and consent forms were in both English and Setswana, as Setswana is the other commonly spoken language by patients at DGMAH. The data collection forms are explained below;

**Appendix 6: Patient Demographics, Cardiovascular Risk Assessment and Clinical Data Form**

This form had different aspects: Demographics (age, height, weight, etc.), cardiovascular risk assessment and clinical data (includes factors that may contribute to cardiotoxicity, such as previous chest radiation exposure, comorbid conditions, social drug use, lifestyle and medications that the patient was taking).

**Appendix 7: Laboratory and Breast Cancer Data Form**

A full blood count was performed at each cycle. Information that was of interest in this study was the lipid and blood results of the patient. The information on breast cancer, such as stage and chemotherapy treatment regimen (including the dose), helped to give a background on the patient’s condition and helped link the treatment regimen and dose to the obtained LVEF values.

**Appendix 8: Patient MUGA Scan Form**

This form assisted in collecting the results obtained from the MUGA scan images, such as LVEF, ESV and EDV. Labelling efficiency results obtained from a parallel study were also included.

3.5.3.4. **Treatment cycles**

Patients normally undergo six cycles of chemotherapy. The study was designed to follow patients up over the first four cycles only, due to time constraints.

3.6 **PILOT STUDY**

A pilot test was performed at DGMAH on breast clinic patients receiving chemotherapy, on the data collection instruments prior to the main study, once the clearance certificate had been issued. The aim of the pilot study was to assess the study logistics as well as the content and use of the data collection instruments. The pilot test of the Patient
Demographics and Cardiovascular Assessment form (Appendix 6) and the Laboratory data form (Appendix 7) was conducted on three patients who were not eligible for inclusion in the study as they were already receiving chemotherapy. The two data collectors collected data from the three patients independently and then compared results for consistency of data collection and discussed with the supervisor and co-supervisors.

The MUGA scans are conducted routinely on a range of patients hence did not need to be pilot tested. Appendix 8 merely summarised key data from the existing report scans.

3.7 DATA ENTRY AND ANALYSIS

Demographic data, cardiovascular risk assessment and clinical data, as well as laboratory breast cancer data were entered into an Excel™ spreadsheet. The data were then expressed in terms of percentages, distribution mean values, and standard deviations. Tables, graphs and figures will be used to present the results.

Data from the MUGA scan such as, LVEF %, ESV and EDV, were analysed quantitatively and compared with other patient parameters that may affect cardiotoxicity (mentioned above). The LVEF data from the three MUGA scans were compared for each patient.

A statistician was consulted for data analysis. Data were analysed statistically using the paired t-test with the Microsoft Excel 2016 data analysis tool.

3.8 RELIABILITY AND VALIDITY

Reliability is defined as the consistency or reproducibility of a measure (Key, 1997).

The two data collectors collected data from the three patients in the pilot study independently and then compared results for consistency of data collection and this was done by discussing with the supervisor and co-supervisor.

MUGA scans have been shown to be reliable for a given patient, as stated in literature, they are highly reproducible (See Table 2.6).

For prospective patients, operator variability was decreased by having the same operator conduct every scan for a given patient and hence the ⁹⁹ᵐTc-RBCs for a given patient. Although it was intended that the same camera would be used throughout for a given patient, logistics made this action impossible. LVEF data is computer-generated, which
increases reliability. The software packages used to determine LVEF had been commercially validated. Two physicians interpreted the images in terms of consistency of the ROI of the scans.

The instruments used were calibrated and quality control tests will be performed.

Quality control tests were done on the radiopharmaceuticals used.

Validity refers to the ability of a test to measure what it claims to measure (Key, 1997).

Patient data collection forms were designed in collaboration with specialist clinicians and experienced researchers.

MUGA scans have been performed internationally and have shown to be efficient in measuring LVEF (Reuvekamp et al, 2015 and Ganz et al, 2008). MUGA scans will be performed according to internationally accepted procedure.

$^{99m}$Tc-RBC quality control methods were based on international guidelines and the process was validated in-house in the parallel study for the prospective patients.

3.9 ETHICAL CONSIDERATIONS

Permission to perform the study was obtained from the Chief Executive Officer of Dr George Mukhari Academic Hospital and the Nuclear Medicine Department. Ethical clearance will be obtained from the School of Health Sciences Research Ethics Committee (SREC) and the Sefako Makgatho University Research and Ethics Committee (SMUREC) before commencement of the study.

This study involved human subjects therefore informed consent was obtained from participants prior to the study. Participants were made aware that they could withdraw at any time of the study. Confidentiality was also maintained, only the researcher and supervisors had access to any raw data.
3.10 SUMMARY

This chapter outlined the study design, described MUGA scan procedure, patient enrolment, data collection instruments and data entry. The results are discussed in Chapter 4.
CHAPTER 4
RESULTS AND DISCUSSION

4.1 INTRODUCTION

The results and discussion in this chapter will be presented as one manuscript which will be submitted to an appropriate peer-reviewed journal.

4.2 MANUSCRIPT FOR PUBLICATION

Determination of cardiotoxic effects of chemotherapy drugs used in breast cancer patients at Dr George Mukhari Academic Hospital using Multigated Acquisition scans

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School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

Abstract

Introduction: Breast cancer is one of the most common cancers in women. It is prevalent worldwide and also in South Africa. Different chemotherapy agents such as anthacyclines have been associated with chemotherapy-induced cardiotoxicity, hence a patient receiving breast cancer chemotherapy might also be faced with increased mortality and morbidity due to cardiovascular side effects. It is therefore important to monitor these cardiotoxic effects especially in patients with pre-existing cardiac conditions and those at risk of developing cardiac conditions by measuring the left ventricular ejection fraction (LVEF) using Multigated Acquisition (MUGA) scans.

Aim: To assess cardiotoxicity in breast cancer patients by monitoring cardiac function before commencement of chemotherapy and during the course of treatment, by determining the change in LVEF using MUGA scans.

Method: A descriptive prospective and retrospective study was performed in 40 breast cancer patients at Dr George Mukhari Academic Hospital (DGMAH). Patient demographic and cardiovascular assessment data, laboratory and breast cancer data and MUGA scan
data were collected using Appendices 6, 7 and 8, respectively. Data were entered into an Excel™ spreadsheet, expressed in terms of percentages, distribution mean values, and standard deviations. Tables, graphs and figures were used to present the results. Data were analysed statistically using the paired t-test with Microsoft Excel 2016.

**Results:** The Mean and Standard Deviation SD for the 1st MUGA scan was 64.2 ± 7.7 and the Mean and SD for the last MUGA scan was 60.5 ± 8.5. There was a drop in LVEF in 25 out of 40 (62.5%) of the patients. Fifteen out of 40 (37.5%) retrospective and prospective patients had a drop in LVEF of more than 10% from the first MUGA scan to the last MUGA scan. Six out of 40 (15%) of the patients met the criteria of chemotherapy-induced cardiotoxicity (10% drop in LVEF and a LVEF <55%). The proportion of cardiotoxicity cases was 1/6 and 5/6 for prospective and retrospective patients, retrospectively. The difference between the first MUGA scan and last MUGA scan was statistically significant (p < 0.04).

**Conclusion:** A decline in LVEF during a 6-month period of chemotherapy is evident as seen from the study. This shows that signs of cardiotoxicity manifest at an early stage during chemotherapy treatment this comparable with a study by Cardinale et al. (2015) which investigated the early detection of anthracycline-induced cardiotoxicity. In the latter study, the incidence cardiotoxicity was 9% in a study population of 2625 patients, and most cases of cardiotoxicity in this study occurred within a year.

**Recommendations:** Protocols on when to monitor LVEF at set point intervals should be written. All patients should undergo a baseline MUGA scan and at least two subsequent MUGA scans; in the middle of chemotherapy treatment and after chemotherapy treatment. Patients follow up should also be long term in order to identify late cardiotoxic effects that may develop and treat them before they progress.

**INTRODUCTION**

The age standardised incidence rates of breast cancer according to the South African Cancer Registry is 32.6 in 100 000 women with a lifetime risk of 1 in 28 (National Cancer Registry, 2013). Breast cancer is more common in developed countries, before the age of 50, one in four women in developed countries is diagnosed with breast cancer (Brenner and Hakulinen, 2004).
Cardiotoxicity poses a serious health risk to Breast Cancer patients receiving cardiotoxic chemotherapy. Anthracyclines, monoclonal antibodies, taxanes and cyclophosphamide are the chemotherapy agents associated with cardiotoxicity. When cardiotoxicity is not identified at any early stage, cardiac damage may be irreversible (D’Amore, 2014).

Chemotherapy cardiotoxicity is seen from left ventricular dysfunction which is a manifestation of cardiac damage and may result in heart failure (D’Amore, 2014). Chemotherapy-induced cardiotoxicity according to Saidi and Alharethi (2011) is a, “Decline in LVEF of at least 5% to below 55% with accompanying signs or symptoms of HF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms”. A decreased LVEF definition which is accepted in oncology is a drop in LVEF by 10% from baseline or an LVEF which is less than 50% (Yoon et al., 2010). The former definition of cardiotoxicity was applied to this present study.

This study was designed to assess the cardiac function of patients receiving cardiotoxic chemotherapy by evaluating the Left Ventricular Ejection Fraction (LVEF) from the time they commence and during the course of their chemotherapy cycles using Multi-gated Acquisition (MUGA) scans. The majority of MUGA studies to monitor cardiotoxicity in breast cancer patients have been performed in developed countries (Reuvekamp et al., 2015; Ganz et al., 2008). In these studies there were incidences of chemotherapy-induced cardiotoxicity. There is a lack of literature on studies performed in developing countries such as South Africa. No such studies could be identified from literature searches.

MATERIALS AND METHODS

Study design

A descriptive study was performed. Patients acted as their own controls. This study was an exploratory study. Due to slow recruitment in the proposed prospective study, a retrospective component had to be via an approved protocol amendment (Appendix 2) in order to achieve an adequate sample size.

Study site

The study was performed at the Breast Oncology Clinic of the Department of Surgery and at the Nuclear Medicine Department at Dr George Mukhari Academic Hospital, Ga-Rankuwa, South Africa.
Study population

The prospective study population consisted of newly enrolled female breast cancer patients who were 18 years and older. The prospective study population consisted of breast cancer patients scheduled to be initiated on chemotherapy at the Breast Oncology Clinic at DGMAH.

The retrospective study population consisted of breast cancer patients who had completed chemotherapy treatment and have had at least two MUGA scans.

Data collection

The study ran from February, 2017 to October, 2017. The researcher obtained the names and hospital numbers of newly-diagnosed breast cancer patients at the Breast Oncology Clinic (BOC) and Nuclear Medicine (NM) departments to be recruited as prospective patients. The new patients who attended over a period of two months were approached for recruitment into the study.

Retrospective data from breast cancer patients who had completed their chemotherapy treatment was collected from the BOC files and Picture Achieving and Communication System (PACS). The retrospective data were collected from records starting from the 1st of January 2014 to 30th of September 2017. The researcher collected the following data from each patient; demographics and cardiovascular risk data, laboratory and breast cancer data and MUGA scan data.

Data entry and analysis

Demographic data, cardiovascular risk assessment and clinical data, as well as laboratory breast cancer data were entered into an Excel™ spreadsheet. The data were then expressed in terms of percentages, distribution mean values, and standard deviations. tables, graphs and figures were to present the results.

LVEF data from the MUGA scan were analysed quantitatively and compared with other patient parameters that may affect cardiotoxicity. The LVEF data from each of the three MUGA scans was compared.

Data were analysed statistically using the paired t-test with the Microsoft Excel 2016 data analysis tool.
Ethical considerations

Permission to perform the study was obtained from the Chief Executive Officer of DGMAH and the Head of Nuclear Medicine Department. Ethical clearance was obtained from the School of Health Sciences Research Committee and the Sefako Makgatho University Research and Ethics Committee before commencement of the study.

This study involved human subjects therefore informed consent was obtained from prospective participants prior to the study. Participants were made aware that they could withdraw at any time of the study. For the retrospective patients only file data were used, therefore no patient consent was needed. Confidentiality was also maintained, only the researcher and supervisors had access to any raw data.

RESULTS AND DISCUSSION

Data collection for prospective and retrospective patients

Patient enrollment for both prospective and retrospective breast cancer patients is illustrated in figure 4.1.
Figure 4.1: Retrospective and Prospective enrollment for breast cancer patients at DGMAH

The BOC at DGMAH did not have a systematic follow-up system for recently-diagnosed breast cancer patients, the filing system was manual and the BOC has been waiting for an electronic patient tracking system for more than 2 years. The files at BOC were not categorized according to patients that were recently diagnosed with breast cancer and patients already on chemotherapy. This made it difficult to follow up on prospective patients as they were not entered onto an electronic database which would make it easier to track patients. There was also no administrator to enter patient data.

Patient demographics

The age distribution and race of the enrolled patients is shown in Table 4.1.

Table 4.1: Age distribution and race for Breast Cancer female patients at DGMAH (n=40)

<table>
<thead>
<tr>
<th>Age range</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>40-49</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>50-59</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>60-69</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>70+</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

Black patients accounted for 95% of the study population and the Whites, 5%. DGMAH is a hospital which serves historically disadvantaged populations, so patients were mainly non-white. The age range of the breast cancer patients was 34 years to 79 years and the mean age for the patients with breast cancer in this study was 52.3(±11.6) years. The majority of the patients (60%) who presented with breast cancer were from ages 40 years to 59 years.
A study on breast cancer patients receiving chemotherapy conducted in Addington Hospital and Albert Luthuli Central hospital in Durban, South Africa showed comparable data. The mean age of breast cancer patients was 48.5 years (Ngidi et al., 2017).

According to Muss, breast cancer is a disease of the aging in the United States. The mean age of breast cancer patients in the United States was 63 years and the incidence of breast cancer increased more with age (Muss, 2010). In a study conducted in Brazil analyzing the risk factors of breast cancer in postmenopausal women, an age ≥40 was a risk factor for breast cancer (Borghesan et al., 2016).

Barrett-Lee et al. (2009) reported that ageing is one of the greatest risk factors for breast cancer, occurring in about 50% of women aged 61 years and older. Table 4.1 shows that 6 out of 40 (15%) patients were younger than 40 years in this study. Studies done in West Africa have shown that breast cancer develops in younger women, with a mean age ranging from 35 years to 45 years which is earlier by 10 to 15 years than high income areas (Fidler et al., 2017). Kruger and Apffelstaedt. (2009) reviewed the incidence of breast cancer in young women and stated that although breast cancer occurs mostly in older women who are both postmenopausal and premenopausal, it also presents in younger women. Kruger and Apffelstaedt. (2009) also stated that the burden of breast cancer is increasing in Africa and more younger women may be diagnosed with breast cancer as compared to developed countries.

The incidence of breast cancer according to menopausal status is shown in Figure 4.2.

Figure 4.2 shows the proportion of pre- and post-menopausal breast cancer patients at DGMAH.
Figure 4.2: Pre- and post-menopausal status of breast cancer patients at DGMAH (n=40)

Figure 4.2, indicates the proportion of post-menopausal patients (52.5%) is slightly more than that of pre-menopausal patients (47.5%). Results from a study of 100 breast cancer patients in the United States comparing the menopausal status, showed that 48 patients were premenopausal and 52 were post-menopausal patients which is similar to the results obtained in Figure 4.1 (Surakasula et al, 2014). According to a study conducted at the breast clinics of the Natal Academic hospitals, the pre- and post-menopausal percentages were similar whereas in the white population, post-menopausal percentages were larger (Pegoraro et al., 1995).

Ghiasvand et al. (2014) investigated the incidence of breast cancer in premenopausal women in less developed countries. In their findings the proportion of breast cancer in premenopausal in less developed countries was much higher as compared to more developed countries. Postmenopausal incidence rates were higher in more developed countries than less developed countries.

The Body Mass Index (BMI) proportions for obese and non-obese breast cancer patients are shown in Figure 4.3.
The mean BMI for the patients before commencement of chemotherapy was 30, these results are similar to the findings in another study done on breast cancer patients in South Africa where the mean BMI was 28.6 (Ngidi et al., 2017). Fifteen out of 40 breast cancer patients (37.5%) were classified as obese in this study. According to Borghesan et al., (2016) breast cancer cases were linked to an obese BMI $\geq 30$.

**Clinical Status**

The Retroviral Disease (RVD) status data for breast cancer patients was collected from BOC files. However, in some patient files the RVD status was not stated. Only four patients could be identified as being RVD positive. A number of studies have investigated the drug-drug interactions between Antiretrovirals (ARVs) and chemotherapy drugs. There is a concern of overlapping toxicities when ARVs and chemotherapy are given together (Rudek et al, 2011).

In this present study an observation seen was that the interactions between ARVs and chemotherapy drugs were not observed and hence the HIV status and regimens patients were on were not clearly stated in some of the patient files. Table 4.2 summarises the overlapping toxicities of ARVs and chemotherapy agents, as well as interactions.
Table 4.2: Drug-drug interactions and overlapping toxicities between ARVs and Chemotherapy drugs

<table>
<thead>
<tr>
<th>Condition</th>
<th>ARV drugs</th>
<th>Chemotherapy drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>Stavudine, Didanosine</td>
<td>Taxanes</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>Atazanavir, Lopinavir boosted with ritonavir</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Zidovudine</td>
<td>Most chemotherapy drugs</td>
</tr>
<tr>
<td>A high amount of cyclophosphamide active metabolite formed leading to toxicity</td>
<td>CYP2B6 inducers (ritonavir, efavirens, nevirapine)</td>
<td>Cyphoshamide</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>CYP3A4 inhibitors (Proton pump inhibitors)</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Risk of myelosupression and peripheral neuropathy is high</td>
<td>Ritonavir</td>
<td>Docetaxel</td>
</tr>
</tbody>
</table>

Source: (Rudek et al, 2011; Berretta et al., 2016)

Breast Cancer Data

Figure 4.4 shows the Breast Cancer staging of breast cancer patients at DGMAH.

Figure 4.4: Breast cancer initial staging of breast cancer patients at DGMAH (n=40)

Twenty-nine out of 40 (72.5%) of the patients initially presented with advanced breast cancer (Stage 3 and 4) as illustrated in Figure 4.4.

Table 4.3 shows the upstaging of breast cancers at DGMAH.
Chapter 4: Results and Discussion

Table 4.3: Breast cancer upstaging in breast cancer patients at DGMAH (n=40)

<table>
<thead>
<tr>
<th>Upstaging level</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Breast Cancer</td>
<td>2B</td>
<td>1</td>
</tr>
<tr>
<td>Advanced Breast Cancer</td>
<td>3B</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

Sixteen out of 40 (40%) patients had breast cancer upstaging; 2.5%, 12.5% and 25% of the patients upstaged to stages 2B, 3B and 4, respectively.

A study done in Africa and Europe reported that in Africa most of the women present with advanced breast cancer on initial diagnosis which is also seen from this present study. An early stage presentation was found in Europe (Abdulrahman and Rahman, 2012). The late stage presentation of breast cancer in Africa could be attributed to poverty and a poor healthcare coverage whereas in Europe healthcare is easily accessible and there is high public breast cancer awareness and screening programmes. (Abdulrahman and Rahman, 2012). In a review study by Sutter et al. (2017) the reason why most patients present with breast cancer at an advanced stage could be due to a delay from the patients’ side and/ or the hospital side. Patients might not have a clear understanding on how severe the condition is and some patients consult traditional healers, on the hospital side the delays might arise from patients not being treated on time, analysis of biopsy tests and also if the hospital cannot attend to some patients due to infrastructure inadequacy (Sutter et al., 2017), and this was the case for breast cancer patients at DGMAH. In a study done in the Central Republic of Africa, there was a delay in diagnosis of breast cancer, patients were diagnosed more than 48 months from the time of disease onset (Balekouzou et al., 2016). For most patients who initially present with advanced breast cancer, the survival rate is low (Jedy-Agba et al., 2016). In South Africa the incidence of patients presenting with advanced breast cancer was reported to be between 50 and 55% (Vanderpuye et al., 2017).

Table 4.4 shows the location of breast cancer at DGMAH
Table 4.4: Breast cancer location

<table>
<thead>
<tr>
<th></th>
<th>Number (n=40)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left breast Cancer</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Right breast Cancer</td>
<td>19</td>
<td>47.5</td>
</tr>
<tr>
<td>Left and Right breast cancer</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen from Table 4.4, the proportion of patients with left breast cancer was slightly higher than those with right breast cancer and only one patient had bilateral breast cancer. The left to right ratio of breast cancers in this study was 1.05. According to Sughrue and Brody. (2014) the ratio of left and right breast cancers is called the laterality ratio. In their study, laterality ratios according the country of birth were 1.14 for Japan, 2.6 for Ryukyu Islands, 1.62 for Laos, 2.1 for Algeria and 0.92 for Poland. In a study done in Egypt on 2531 breast cancer patients the ratio of left to right breast cancers was 1.16 (Zeeneldin et al., 2013).

Table 4.5 shows the chemotherapy regimens for the patients

Table 4.5: Chemotherapy regimens received by breast cancer patients at DGMAH (n=40)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAF</td>
<td>33</td>
<td>82.5</td>
</tr>
<tr>
<td>CAF-Docetaxel</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>CMF</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The majority (82.5%) of the patients were on Cyclophosphamide, Adriamycin and 5-Fluorouracil (CAF). The findings in this study are comparable with another study on breast cancer management in Africa which reported that the most commonly-prescribed neoadjuvant and adjuvant chemotherapy regimen in Sub-Sahara was the CAF combination (Vanderpuye et al., 2017). Vanderpuye et al. (2017) also stated that despite the discovery of Trastuzumab which targets HER2 positive breast cancers the high cost of these drugs makes them inaccessible, although they are easily available in high income African countries such as South Africa. Due to the fact that trastuzumab is expensive and not yet on code, no HER2 positive breast cancer patients received this drug at DGMAH.
In the United States, high-risk breast cancer patients are treated with anthracyclines followed by taxanes and low-risk patients are treated with four cycles of Cyclophosphamide and Docetaxel (Rampurwala et al., 2014). Cyclophosphamide, Adriamycin and 5-Fluorouracil (CMF) was reported to be the first adjuvant chemotherapy regimen to be tested for the treatment of breast cancer. In meta-analysis study the Early Breast Cancer Trialists’ Group (EBCTCG) breast cancer patients treated with CAF or Cyclophosphamide, Epirubicin or 5-Fluorouracil (CEF) for six cycles had reduced mortality rates compared to other combination regimens such as Adriamycin and Cyclophosphamide (AC) for four cycles or CMF for six cycles. In the EBCTCG meta-analysis, the treatment of AC for four cycles followed by Docetaxel for four cycles which extended the treatment duration was beneficial in reducing breast cancer mortality (Anampa et al., 2015).

The side effects experienced by breast cancer patients at DGMAH are shown in Table 4.6.

### Table 4.6: Side effects experienced by breast cancer patients receiving chemotherapy at DGMAH (n=34)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
</tr>
<tr>
<td>Hair loss</td>
<td>14</td>
</tr>
<tr>
<td>Pain</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>5</td>
</tr>
<tr>
<td>Mouth and throat sores</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
</tr>
</tbody>
</table>

The side effects mostly experienced during the course of chemotherapy were nausea and vomiting, hair loss, fatigue and pain, some patients experienced more than one side-effect.

Fatigue was experienced by approximately two thirds of women receiving adjuvant chemotherapy. In early studies on breast cancer chemotherapy, nausea and vomiting was experienced in approximately 70% of women. In anthracycline and taxane based chemotherapy alopecia is very common (Rampurwala et al., 2014).

The histology of breast cancers is shown in Table 4.7
Table 4.7: Breast cancer Biopsy results (n=40)

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal carcinoma</td>
<td>38</td>
<td>95</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Carcinoma (other)</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

A study on the epidemiology of breast cancer in Europe and Africa stated that ductal carcinoma is the most common type of breast cancer found in both Europe and Africa (Abdulrahman and Rahman, 2012). Table 4.7 shows that the majority of the patients in this study presented with invasive ductal carcinoma.

Invasive lobular carcinoma, which accounts for about 10% of breast cancers is the second most common type of histologic breast cancers (Barroso-Sousa and Metzger-Filho, 2016). In a study on the epidemiology of breast cancer in the Central African Republic, the most prevalent histological breast cancer carcinomas were invasive ductal carcinomas which accounted for 64.9% and 9.8% for invasive lobular carcinomas (Balekouzou et al., 2016). In another study on breast cancer patients conducted in Soweto, South Africa, invasive ductal carcinomas accounted for 93.9% and invasive lobular breast cancer accounted for 4% (Cubasch et al., 2017). The study done in Soweto is comparable with the findings in this present study where 95% of the patients presented with invasive ductal carcinoma and 2.5% with invasive lobular carcinoma.

Table 4.8 shows hormonal receptor positivity detection in breast cancer patients at DGMAH.

Table 4.8: Hormonal receptor positivity detection in breast cancer patients (n=34)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER +</td>
<td>20</td>
<td>58.8</td>
</tr>
<tr>
<td>PR +</td>
<td>16</td>
<td>47.1</td>
</tr>
<tr>
<td>HER2 +</td>
<td>5</td>
<td>14.7</td>
</tr>
</tbody>
</table>

In this study the incidence of HER2 positive breast was low (14.7%), ER positivity was 58% and PR positivity was 47.1%. Some patients were positive for more than one marker. These results are shown in Table 4.8. Approximately 60-75 % of oestrogen and progesterone positive breast cancers are diagnosed. HER2 positive breast cancers account for 20-25% of diagnosed breast cancers (Miller et al., 2014). In a study on receptor-defined breast cancer
in Southern African women according to racial status, the ER positive breast cancers were more prevalent in all Southern African races which is comparable with the findings in this study. Ten percent of the patients in the former study had HER2 positive breast cancers, this is also comparable with the 14.7% of HER2 positive breast cancers in this present study (Dickens et al., 2014)

The LVEF values after each chemotherapy cycle for the breast cancer patients are shown in Table 4.11.
MUGA scan data

Table 4.9: LVEF % change between 1st and last MUGA scans per patient (n=40)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cycle 0</th>
<th>Post 1</th>
<th>Post 2</th>
<th>Post 3</th>
<th>Post 4</th>
<th>Post 5</th>
<th>Post 6</th>
<th>Δ 1st scan and last scan</th>
<th>Δ%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>54,4</td>
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<td></td>
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<td>-12</td>
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<td>18</td>
<td>6</td>
<td>16</td>
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<td>61,6</td>
<td>59,9</td>
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<td>62,4</td>
<td></td>
<td>-3,7</td>
<td>-4,9</td>
</tr>
<tr>
<td>SD</td>
<td>8,1</td>
<td>4,2</td>
<td>6,7</td>
<td>7,7</td>
<td>8,5</td>
<td>10,7</td>
<td>9,1</td>
<td>14,1</td>
<td></td>
</tr>
</tbody>
</table>
### t-Test (assuming unequal variances) on the % change in LVEF between the first and last MUGA scan

<table>
<thead>
<tr>
<th></th>
<th>Muga scan (1st)</th>
<th>Muga scan (last)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>64.3</td>
<td>60.6</td>
</tr>
<tr>
<td>Observations</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Hypothesized Mean Difference</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>1.99</td>
<td></td>
</tr>
</tbody>
</table>
All patients had routine MUGA scans. The first six patients were prospective patients and the rest of the patients (34) were retrospective. The difference in LVEF values between first and last MUGA scans are shown, as well as the percentage change of the LVEF. The mean LVEF percentage drop was -4.9. Seven out of 40 (17.5%) patients had no baseline (i.e. pre-chemotherapy. MUGA scans and 16 out of 36 (44%) retrospective patients had a follow up MUGA scan after completion of chemotherapy.

The results from a paired t-Test assuming unequal variances for both the first and last MUGA scans using the Microsoft Excel 2016 data analysis tool are shown in Table 4.9. The p value 0.04 is < 0.05, therefore a statistically significant difference between the first and last MUGA scan.

The majority of the patients in this present study only had two MUGA scans to evaluate left ventricular dysfunction and the second scans were at different time intervals. In other studies monitoring of LVEF was done at specific set time intervals. In a study on early detection of anthracycline-induced cardiotoxicity conducted in Italy, LVEF was measured at baseline, following that at 3 months intervals after commencement of chemotherapy till the end of chemotherapy, following that at 3 months intervals within the first year after completion of chemotherapy, thereafter, follow up was done biannually for 4 years then annually (Cardinale et al., 2015). In another study where patients were treated with 4 cycles of Adriamycin and cyclophosphamide (AC) followed by 4 cycles of Paclitaxel, a baseline MUGA scan was done, 2nd MUGA scan was done after four cycles of AC and the 3rd MUGA scan was done 8 months after completion of chemotherapy (Sheela et al, 2016).

The cardiovascular risk factors for breast cancer patients as well as the number of cases of chemotherapy-induced cardiotoxicity are shown in Table 4.10.
Table 4.10: Cardiac Risk Factors for breast cancer patients receiving cardiotoxic chemotherapy at DGMAH (n=40)

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>%</th>
<th>Number of chemotherapy-cardiotoxicity cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>45</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>8</td>
<td>20</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Diabetes Mellitus and Hypertension</td>
<td>8</td>
<td>20</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Mediastinal radiation</td>
<td>40</td>
<td>100</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Obese patients</td>
<td>15</td>
<td>37.5</td>
<td>5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

In this study data on the relevant drugs and social drug use were not indicated due to missing information in patient files. Forty-five percent of the breast cancer patients presented with hypertension, 20% of the patients had diabetes mellitus, 20% of the patients presented with both hypertension and diabetes mellitus. All the patients underwent mediastinal radiation and 37.5% of the patients were obese.

Very young and old age, mediastinal radiation before chemotherapy treatment, female gender, hypertension, diabetes and concomitant administration of anthracyclines with cyclophosphamide and taxanes are risk factors for anthracycline induced cardiotoxicity (Volkova and Russell, 2012). In this present study, obesity and mediastinal radiation were significantly associated with anthracycline-induced cardiotoxicity. Hypertension and Diabetes Mellitus were not significantly associated with anthracycline-induced cardiotoxicity.

In a retrospective study on anthracycline and trastuzumab-induced cardiotoxicity, the most significant cardiac risk factor which correlated with a decline in LVEF was Hypertension (Hamirani et al., 2016). Diabetes was found to be significantly associated with cardiotoxicity induced by anthracycline in a study by Reinbolt et al., (2016).

In a review study assessing the cardiac risk factors in breast cancer patients with an obese BMI of ≥ 27 receiving anthracyclines, there was a significant association with left ventricular dysfunction. The other factor that may have attributed to this correlation is that obese patients receive higher doses of anthracyclines as compared to patients with an average weight (Barrett-Lee et al., 2009). However, the cardiac risk factors may be inter-linked. According to Artham et al. (2009) obesity is associated with a number of cardiac disease risk factors such as, hypertension, dyslipidaemia and diabetes mellitus.
Figure 4.5 summarises the LVEF % change data in Table 4.9

![Graph showing LVEF change](image)

**Figure 4.5: LVEF % change for breast cancer patients at DGMAH as measured by MUGA scans (n=40)**

Figure 4.5 summarises the LVEF data, the figure shows that there was a drop in LVEF in 25 out of 40 (62.5%) of the patients.

Table 4.11 shows the LVEF % drop of >10% in breast cancer patients as well as the number of patients that met the criteria for chemotherapy-induced cardiotoxicity

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10% drop in LVEF</td>
<td>15</td>
<td>37.5</td>
</tr>
<tr>
<td>&gt;10% drop in LVEF and LVEF &lt;55%</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

Fifteen out of 40 (37.5%) retrospective and prospective patients had a drop in LVEF of more than 10% from the first MUGA scan to the last MUGA scan. Six out of 40 (15%) of the patients met the criteria of chemotherapy-induced cardiotoxicity (10% drop in LVEF and a LVEF <55%). The proportion of cardiotoxicity cases was 1/6 and 5/6 for prospective and retrospective patients, retrospectively. It would be advisable for clinicians to make a detailed record for any cardiac abnormalities such as sinus bradycardia, as this was not noted on the patient files.

Anthracycline-induced cardiotoxicity experienced by patients in this present study was within a period of one year, this is comparable with a study by Cardinale et al. (2015) which investigated the early detection of anthracycline induced cardiotoxicity. In the latter study, the incidence cardiotoxicity was 9% in a study population of 2625 patients, and most cases
of cardiotoxicity in this study occurred also within a year. Due insufficient retrospective information from patient files in this present study and time constraints in follow-up of prospective patients, the recovery from cardiotoxicity was not studied. Cardinale et al. (2015) stated that patients who experienced cardiotoxicity in their study were treated with heart failure treatment and 11% of the patients experienced anthracycline-induced cardiotoxicity had a full recovery and 71% of the patients had a partial recovery. Therefore early detection of chemotherapy-induced cardiotoxicity is important in order to treat cardiotoxic effects to allow for recovery of the cardiac function (Cardinale et al., 2015). In a prospective study on the long term cardiac effects of anthracyclines, approximately 59% of the patients had 25% decrease in LVEF and 20% developed congestive heart failure 3 years after completion of chemotherapy treatment. Monitoring of these late cardiac effects that may occur is very crucial (Jensen, 2002).

Table 4.12 indicates the anthracycline cumulative dose ranges received by breast cancer patients at DGMAH and the cardiotoxicity cases according to cumulative doses.

**Table 4.12: Anthracycline cumulative doses and case of cardiotoxicity in breast cancer patients at DGMAH (n=40)**

<table>
<thead>
<tr>
<th>Cumulative dose (mg/m²)</th>
<th>Number</th>
<th>%</th>
<th>Number of cardiotoxicity cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>200</td>
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<td>15</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>250</td>
<td>3</td>
<td>7.5</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>300</td>
<td>27</td>
<td>67.5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>350</td>
<td>1</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

As seen from Table 4.12, most of the patients that met the criteria for chemotherapy induced cardiotoxicity received a cumulative dose of 300 mg/m². None of the patients in this study received cumulative doses of anthracyclines exceeding 500 mg/m², therefore the cumulative doses were within the recommended limits.

Other studies reported incidence rates of 18.3% (Giordano et al., 2002) and 11% (Sheela et al, 2016) for anthracycline-induced chemotherapy which are comparable with the incidence rate of 15% in this present study.

An increase in cumulative dose is associated with a risk factor for clinical cardiotoxic effects of anthracyclines. The acceptable lifetime cumulative dose of doxorubicin should range from
400 to 550mg / m^2. The incidence rates of doxorubicin-induced cardiotoxicity according to the cumulative doses which were found by different studies range from 3-5%, 7-26% and 18-48% at cumulative doses 400 mg/m^2, 550 mg/m^2 and 700 mg/m^2, respectively (Curigliano et al., 2012). Three trials consisting of 630 cancer patients receiving doxorubicin were retrospective analysed, with the majority of the adverse cardiac events occurring at cumulative doses ranging from 500-850 mg/m^2 (Swain et al, 2003). In another study done in South India on chemotherapy-induced cardiotoxicity, 6 out 12 (50%) patients who experienced anthracycline-induced cardiotoxicity received cumulative doses which ranged from 201-300 mg/m^2 (Nandennavar et al, 2016) this is comparable with the results in Table 4.14 where the majority (4/6) of cases of anthracycline-induced cardiotoxicity in this study received a cumulative dose 300 mg/m^2.

Figure 4.6 illustrates the percentage drop in LVEF according to different age categories.

![Figure 4.6: LVEF % drop by Age in breast cancer patients at DGMAH (n=39)](image)

A higher LVEF drop (15%) is seen in patients aged from 40 to 49 years and the lowest percentage drop (9) is seen in patients aged from 30 to 39 years.
A box and whisker diagram (Figure 4.7) categorises the % change in LVEF by CAF, CAF-D and CMF chemotherapy regimens.

![Box and whisker diagram](image)

**Figure 4.7:** % change in LVEF by regimen in breast cancer patients at DGMAH

The horizontal line represents the median, the shaded area is the interquartile range and the 5% and 95% percentiles are indicated by the whiskers. In the CAF arm, the median percentage change in LVEF is 6 (range -33 to 15; interquartile range -14 –2). Two data points in the CAF arm are out of the 95% distribution as shown by the blue circles. In the CAF-D arm, the median percentage change in LVEF is 1 (range -14 to 37; interquartile range -10 –14)

**CONCLUSION**

The age standardised incidence rate of breast cancer according to the South African Cancer Registry is 32.6 in 100 000 women with a lifetime risk of 1 in 28 (National Cancer Registry, 2013). Breast cancer is more common in developed countries. Before the age of 50, one in four women in developed countries is diagnosed with breast cancer (Brenner and Hakulinen, 2004). This study consisted mostly of Black patients (95%) from disadvantaged backgrounds. Approximately 73% of the patients presented with advanced breast cancer on initial diagnosis, which is a major cause for concern. The high ratio of advanced breast cancer indicates that there is not adequate breast cancer awareness education in the
communities and there is a lack of screening programmes to detect breast cancer at an early stage.

Another alarming finding in this study was the upstaging of 40% of the patients. Treatment with chemotherapy was delayed due to structural inadequacy and a delay in biopsy lab results. The hospital needs to address these issue as this compromises the health of breast cancer patients. Breast cancer in its advanced stage may be difficult to treat and this has an impact on the patients’ quality of life and they are at an increased risk of mortality and morbidity. Delays in healthcare treatment leading to increased mortality and morbidity are not being dealt with. In the researcher’s view, there is a lack of action in improving existing healthcare practices and infrastructure in order to adequately meet the healthcare needs of the patients.

The healthcare received by individuals in South Africa is determined by their economic class. The gap in provision of healthcare between the high income and low income populations needs to be narrowed through re-evaluation of the current healthcare systems. The Minister of Health, Dr Aaron Motsoaledi stated that one major challenge affecting the healthcare system is the deteriorating quality of healthcare in the public sector. He believes that the National Health Insurance (NHI) will be a step in the right direction in improving healthcare services. The implementation of the NHI is aimed to ensure that every individual will receive quality healthcare regardless of their socioeconomic status (Moyakhe, 2014). The latter view is disputed by many economists.

At DGMAH, during the study, HER2 receptor positive breast cancer patients were treated with CAF (Cyclophosphamide, Adriamycin and 5-Fluorouracil) combination, due to the fact that Trastuzumab was not available at the DGMAH. A study on adjuvant Trastuzumab treatment in HER2 positive breast cancer patients showed that patients receiving Trastuzumab had an improved survival (Slamon et al, 2011). The lack of availability of Trastuzumab at DGMAH must be addressed.
4.3 REFERENCES FOR CHAPTER 4


Chapter 5: Limitations, Recommendations and Conclusions

5.1 INTRODUCTION

This chapter discusses the limitations which arose from this study, the recommendations and conclusions drawn.

5.2 LIMITATIONS OF THE STUDY

The limitations of the study are as follows;

5.2.1 Time constraints

Due to time constraints, a low number of 40 patients was included in the study. The time frame to conduct this study was one year. Initially only prospective patients were enrolled but due to long waiting times (± 6 months) for recently diagnosed breast cancer patients to be initiated on chemotherapy, retrospective patients were also enrolled via an approved protocol amendment (See Appendix 2).

In this present study there were also delays from diagnostic procedures such as bone scans and biopsy results.

5.2.2 Problems in patient follow up

In this study prospective patients were followed up by phoning the patients on their cellular phone to track if patients had been initiated on chemotherapy but some patients could not be reached on their cellular phones. The Breast Oncology Clinic (BOC) at Dr George Mukhari Academic Hospital (DGMAH) had no systematic way or method of following up on recently diagnosed breast cancer patients to be initiated on chemotherapy. The files at the BOC were also not arranged in such a way as to easily identify patients to be initiated on chemotherapy.

5.2.3 Missing relevant data on patient files

The retroviral disease (RVD) status in the BOC clinic files was not indicated for most patients in this study. For patients with comorbid conditions, the relevant drugs they were taking were
not indicated in the patient files. Information on social drug use was also not written in most of the BOC patient files.

5.2.4 MUGA scans timing and frequency

Not all patients had a baseline MUGA scan, and the subsequent MUGA scans were not at consistent set points. There was no protocol on the timing of monitoring left ventricular ejection fraction (LVEF) using Multi-gated Acquisition (MUGA) scans. Most breast cancer patients had two MUGA scans, from the study early cardiac effects could be identified. However due to lack of LVEF monitoring on a long term basis the late cardiac effect of anthracycline-induced cardiotoxicity could not be evaluated.

5.2.5 Single institution study

This study was done in a single institution therefore the results in this study could not be generalized for the entire population in South Africa. The cardiotoxic effects of other chemotherapy agents such as Trastuzumab known to induce cardiotoxicity were not studied.

5.3 RECOMMENDATIONS

5.3.1.1. Time constraints

Prospective studies should be allocated a longer time frame ≥ 2 years is recommended to allow for adequate patient follow up. A prospective study on 30 breast cancer patients receiving chemotherapy by Sheela et al. (2016) was conducted from September 2009 to September 2011.

5.3.1.2. Problems in patient follow up

The BOC at DGMAH should implement an electronic database and employ an administrator who oversees all patient administration details. The status of each patient should be clearly indicated on the database; patients awaiting laboratory investigation results, patients to be initiated on chemotherapy and patients currently receiving chemotherapy and which cycle they are on. This will simplify the tracking of patients and causes for delay in initiation of chemotherapy will be identified earlier and fewer patients will be lost.
5.3.1.3. **Missing relevant data on patient files**

Doctors at the BOC should be advised to fill in all the relevant patient data on patient files. They need to be advised on the importance of monitoring drug-drug interactions between Antiretrovirals (ARVs) and chemotherapy, and any other drugs that may interfere with chemotherapy. Information for all patients such as social drug use should also be recorded in order to identify risk factors contributing to breast cancer and chemotherapy-induced cardiotoxicity.

5.3.1.4. **MUGA scan timing and frequency**

Protocols on when to monitor LVEF at set point intervals should be written. All patients should undergo a baseline MUGA scan and at least two subsequent MUGA scans; in the middle of chemotherapy treatment and after chemotherapy treatment. Patients follow up should also be long term in order to identify late cardiotoxic effects that may develop and treat them before they progress.

5.3.1.5. **Single institution study**

More large-scale studies in more than one healthcare institution should be done to identify different trends and pattern of chemotherapy-induced cardiotoxicity in patients of different races and socioeconomic status. Other chemotherapy agents known to induce cardiotoxicity should also be studied.

5.4 **CONCLUSIONS**

Although the main focus of this study was to assess chemotherapy-induced cardiotoxicity, the following outcomes were identified;

- Delay from diagnosis resulting in a delay in chemotherapy initiated
- Difficulty locating patient files and patient tracking
- Patients coming too late at DGMAH, as a result patients present with advanced breast cancer
- HER2 positive breast cancer patients not receiving Trastuzumab

From the above-mentioned outcomes, one key aspect that can be singled out is poor health care services at DGMAH. In an article by the Healthy Times. (2017), it stated that the people
that can afford best-healthcare services of good quality are the rich, and the poor population does not afford such services. The National Health Insurance (NHI) that was proposed would address the problem of poor patients receiving poor-quality health-care services. The Minister of Health, Dr Aaron Motswaledi released the recent white paper on NHI on the 29th of June 2017. However, the implementation of the NHI is still far-fetched as there are still questions on how it will be funded (Guedes, 2017).

According to an article by the Times Live the government proposed to renovate and refurbish DGMAH for the past 17 years, however that has not been implemented. This puts a strain on the hospital as it has not been expanded (Naidoo et al, 2012). The Breast Oncology Clinic at DGMAH can only book a maximum of ±15 patients every week for chemotherapy and this results in a delay to initiate chemotherapy for some patients.

According to an article on the challenges of managing breast cancer in developing countries, there is an absence of breast cancer prevention, no control policies and programmes in place in South Africa and other Sub-Saharan countries. The article also stated that breast cancer screening tests like mammography are very expensive and the low income populations cannot afford them (Edge et al, 2014). Most breast cancer patients in this present study presented with advanced breast cancer initially, more breast cancer screening tests and targeted awareness campaigns are needed. This will help detect early stage breast cancer and improve the prognosis.

Based on studied literature chemotherapy agents such as anthracyclines have adverse cardiotoxic effects. In this study the incidence rate of chemotherapy-induced cardiotoxicity was 15% and cardiotoxic effects manifested early (within 1 year after initiation of chemotherapy). Cardiotoxicity in this study was dose-dependent as most chemotherapy-induced cardiotoxic cases occurred at 300 mg/ m².

As part of the objectives in this study the LVEF percentage change values between the first and last MUGA scan were compared using a paired t-test. Cases of chemotherapy-induced cardiotoxicity were identified according to protocol defined cardiotoxicity. The LVEF percentage change was also compared to other parameters such as age and chemotherapy regimen.

As recommended in this study a protocol on when to assess LVEF using MUGA scans is of uttermost importance.
REFERENCES


References


Kang, S. (n.d.). *Anti-neoplastic Drugs and Cardiovascular Complications*.


# APPENDICES

## Appendix 1: Breast cancer staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ: Tumors that have not grown beyond their site of origin and invaded the neighboring tissue. They include: ductal carcinoma in situ, lobular carcinoma in situ.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Tumor size &lt;2 cm, metastases to other organs and tissues not available</td>
</tr>
<tr>
<td>Stage 2a</td>
<td>Tumor &lt;2 cm in cross-section with involvement of the lymph node or tumor from 2 to 5 cm without involvement of the axillary lymph nodes</td>
</tr>
<tr>
<td>Stage 2b</td>
<td>Tumor more than 5 cm in cross-section (the result of axillary lymph node research is negative for cancer cells) or tumor from 2 to 5 cm in diameter with the involvement of axillary lymph nodes</td>
</tr>
<tr>
<td>Stage 3a</td>
<td>Also called local spread of breast cancer: tumor more than 5 cm with spread to axillary lymph nodes or tumor of any size with metastases in axillary lymph nodes, which are knitted to each other or with the surrounding tissues</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>Tumor of any size with metastases into the skin, chest wall or internal lymph nodes of the mammary gland (located below the breast inside of the chest)</td>
</tr>
<tr>
<td>Stage 3c</td>
<td>Tumor of any size with a more widespread metastases and involvement of more lymph nodes</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Defined as the presence of tumors (regardless of the sizes), spread to parts of the body that are located far removed from the chest (bones, lungs, liver, brain or distant lymph nodes)</td>
</tr>
</tbody>
</table>

Appendices

Appendix 2: SMUREC Clearance certificate

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

No 4501, St. Constantine, Pretoria
Tel: (012) 521 6017/3609 fax: (012) 521 3749
Email: kimah.miller@amu.ac.za
P.O. Box 163 Medunsa 0204

uml shihanda

department of pharmacy
p.o box 219
medunsa 0204

dear dr muru

re: smurec/h176/2016: pg - amendment to protocol request

researcher: uml shihanda
supervisor: prof e summers

smurec approved title: determination of cardiotoxic effect of chemotherapy drugs used in breast cancer patients at dr george mukhari academic hospital using multi-organ compartmental analysis

smurec noted a letter dated 16 october 2016 requesting to include patients already on treatment and make use of files for retrospective data collection.

motivation:

the prospective nature of the original study has resulted in low patient numbers. in order to achieve the target sample size within the two year time line for the completion of the academic internship and mphm degree the amendment is requested.

smurec noted and approved a request to include patients already on treatment and make use of files for retrospective data collection as mentioned above.

yours sincerely,

prof ga ogunde
chairperson smurec

02 november 2017

c: prof e summers

international certificate (hcm) number: 2015-00366 expiry date: 06 june 2018, federal hvh assurance
(fmu419028839) expiry date: 03 march 2021 etc nh recc acc: acc 2142-2-393
Appendix 3a: Preferred regimens for HER2-positive Breast cancer

(NCCN guidelines, 2014)
Appendix 3b: Other regimens for HER2-positive Breast Cancer

(NCCN guidelines, 2014)
Appendix 4a: Patient Information Leaflet (English)

**Study Title:** Determination of cardiotoxic effects of chemotherapy drugs used in breast cancer patients at Dr George Mukhari Academic Hospital using Multigated Acquisition scans.

**Researcher:** Unami Sibanda, BPharm  
**Supervisor:** Professor Beverley Summers

You are invited to participate in a research study which will be carried out at the Nuclear Medicine department in co-operation with the Breast Oncology Clinic at DGHAM. Taking part in this study is voluntary.

**Why is this study being done?** Some breast cancer chemotherapy drugs may cause damage to the heart, which may be irreversible if not identified at an early stage. To monitor any changes in your heart at an early stage, caused by chemotherapy, a scan will be performed before you receive your treatment, and two other scans will be performed during the course of your treatment.

**Why am I being asked to take part in this study and how is this beneficial to me?** You are being asked to take part in this study to help us understand the effects of certain medication on the heart. Therefore this will be beneficial to you as your heart function will be monitored during the course of your treatment and prevent any heart related problems that may occur as a result of being treated with chemotherapy.

**Is this study confidential?** All information obtained in this study will be handled confidentially, your identity or any other personal information will not be revealed.

**Has this study been approved?** This study has been approved by the Sefako Makgatho University Research Ethics Committee (SMUREC) of SMU and Dr George Mukhari Academic Hospital.

Your participation in this study will be highly appreciated. For more information with regards to the study contact the researcher (Unami Sibanda) on her cell (076 236 2918)
Appendices

Appendix 4b: Patient Information Leaflet (Setswana)

Setlhogo sa Patlisiso: Patlisiso ka ditlamorago tse di senyang pelo, tse di tlang ka meriana ya kalafo e e diriswang mo balwetsing ba kankere ya letswele, kwa Dr George Mukhari Academic Hospital (DGMAH), mme go diriswa scan sa MUGA.

Mmatlisisi: Unami Sibanda  
Supervisor: Beverley Summers

O lalediwa go tsaya karolo mo thutopatlisisong eo e tileng go diragatswa kwa lefapheng la Nuclear Medicine ka tirisano le Kliniki ya Breast Oncology Clinic kwa DGMAH. Go tsaya karolo mo patlisisong e, ke ka go ithaopa.

Goreng patlisiso eno e diragadiwa? Meriana mengwe ya kalafo ya kankere ya letswele e ka thola go senyega ga pelo, mo e leng gore ga go ne go dirololwa fa go senyega goo go sa bonwa go sa le gale. Go sekaseka diphetogo mo pelong ya gago go sa le gale, tse di thholwang ke kalafi eo, go tla dirwa scan pele o amogela kalafo ya gago, mme go dirwe gape di-scan di le pedi fa o ntse o le mo pakeng ya kalafo ya gago.

Goreng ke kopiwa go tsaya karolo le gore e tiile go nthusa ka eng? O kopiwa go tsaya karolo mo patlisisong e, go re thusa go thalaganya ditlamorago tsa meriana mengwe e e rieng mo pelong. Ka moo o tiile go thusega ka fa e le gore pelo ya gago e tiile go nna e beilwe leitlho gore e dira jang mo pakeng yotthe ya kalafo ya gago, mme e bile go tla thibelelwa mathata mangwe le mangwe a a ka tswelelang e le ka nthla ya meriana eo ya kalafo.

A patlisiso e tla nna mo sephiring? Tshedimosetso yotthe e e tla bonwang mo patlisisong e, e tiile go tshwarwa jaaka ya khupamarama, mme boitshupo kgotsa tshedimosetso nngwe le nngwe e e mabapi le bowena ga e ne e ribololwa.

A patlisiso e edumeletswe? Patlisiso e e dumeletswe ke komiti ya Sefako Makgatho University Research Ethics Committee (SMUREC) ya SMU le DGMAH.

Go tsaya karolo ga gago go ka itumellwa thata. Go bona tshedimosetso e nngwe gape mabapi le patlisiso e, o ka letsetsa mmatlisisi (Unami Sibanda) mo mogaleng wa gagwe (0762362918)
Appendix 5a: Patient consent form (English)

Statement concerning participation in a Research Project.

Determination of cardiotoxic effects of chemotherapy drugs used in breast cancer patients at Dr George Mukhari Academic Hospital using Multigated Acquisition scans

I have read the information and the aims and objectives of the proposed study and was provided the opportunity to ask questions and given adequate time to consider the matter. The aim and objectives of the study are sufficiently clear to me and are to

- Obtain relevant patient information for patients about to receive chemotherapy at the Breast Oncology Clinic DGMAH.
- Measure heart function (via special scans) in breast cancer patients at DGMAH prior to commencement of chemotherapy treatment and at set points during the chemotherapy treatment cycle

I have not been pressurized to participate in any way. I consent to this provide that my name and hospital number are not revealed.

I understand that participation in this study is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition neither will it influence the care that I receive from my regular doctor.

I know that this study has been approved by the Sefako Makgatho University Research Ethics Committee (SMUREC), Sefako Makgatho Health Sciences University and Dr George Mukhari Hospital. I am fully aware that the results of this study will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this study.

.............................................................................. ............................................................
Name of patient/volunteer Signature of patient or guardian.

.............................................................................. ............................................................
Place. Date. Witness

Statement by the Researcher

I provided verbal and written information regarding this study
I agree to answer any future questions concerning the study as best as I am able.
I will adhere to the approved protocol.

.............................................................................. ............................................................
Name of Researcher Signature Date Place
Appendices

Appendix 5b: Patient Consent Form (Setswana)

Seteitemente se se ka ga go tsaya karolo mo Tekopatlisisong / Porojeke ya Patlisiso.
Leina la Porojeke

_Determination of cardiotoxic effects of chemotherapy drugs used in breast cancer patients at Dr George Mukhari Academic Hospital using Multigated Acquisition scans._

Ke buisite tshedimosetso mo patlisiso e e tshitshintsweng mme ke filwe tšhono ya go botsa dipotso le go fiwa nako e e lekaneng ya go akanya gape ka nthia e. Maitlhomo le maikemisetso a patlisiso e a thaloganyega sentle. Ga ke a patelediwa ke ope ka tsela epe go tsaya karolo.

Ke thaloganya gore go tsaya karolo mo Porojeke ke boithaopo le gore nka ikgogela morago mo go yona ka nako nngwe le nngwe kwa ntle ga go neela mabaka. Se ga se kita se nna le seabe sepe mo kalafong ya me ya go le gale ya bolwetsi jo ke nang le jona e bile ga se kita se nna le thotheletso epe mo thokomelong e ke e amogelang mo ngakeng ya me ya go le gale.

Ke a itse gore Porojeke e e rebotswe ke Patlisiso le Molao wa Maitsholo tsa Khampase ya Sefako Makgatho University Research Ethics Committee (SMUREC), Yunibesithi ya Sefako Makgatho Health Sciences / Bookelo jwa Ngaka George Mukhari. Ke itse ka botlalo gore dipholo tsa Porojeke di tla dirisetswa mabaka a saentifikasi e bile di ka nna tsa phasaladiwa. Ke dumelana le seno, fa fela go netefadiwa gore se e tla nna khupamarama. Fano ke neela tumelelo ya go tsaya karolo mo Porojeke e.

.........................................................................................................................
Leina ka molwetse/moithaopi .........................................................................................

.........................................................................................................................
Tshaeno ya molwetse kgotsa motlamedi.

.........................................................................................................................
Lefelo. ..................................................................................................................... Letha.
......................................................................................................................... Paki

_Seteitemente ka Mmatlisisi_

Ke tiamese tshedimosetso ka molomo le/kgotsa e kwadi lweng malebana le Porojeke e.
Ke dumela go araba dipotso dingwe le dingwe mo nakong e tlang tsed emanang le Porojeke ka moo nka kgonang ka teng.
Ke tla-tshegetsa porotokolo e rebotswe.

.........................................................................................................................
Unami Sibanda ........................................................................................................ Lefelo

.........................................................................................................................
Tshaeno ................................................................................................................... Lefelo

.........................................................................................................................
Letha.
Appendix 6: Patient Demographics and cardiovascular assessment

<table>
<thead>
<tr>
<th>Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient study number: __________________</td>
</tr>
<tr>
<td>Date of Birth/Age: ____________ Sex: M / F Race: ________________</td>
</tr>
<tr>
<td>Height (cm): ____________</td>
</tr>
<tr>
<td>*Weight(kg): Baseline________ 2&lt;sup&gt;nd&lt;/sup&gt; scan__________ 3&lt;sup&gt;rd&lt;/sup&gt; scan__________</td>
</tr>
</tbody>
</table>

**Social Drug Use**

Do you use or consume the following?

- Alcohol: Y / N
- Caffeine: Y / N
- Tobacco: Y / N

Other (state) :__________________

**Lifestyle**

Diet: (description of daily diet)

________________________________________________________

Exercise: Do you engage in physical exercise? Y / N, if yes state

________________________________________________________

**Family and Social History**

________________________________________________________

**Medical History**

<table>
<thead>
<tr>
<th></th>
<th>Baseline scan</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; scan</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Blood transfusion</td>
<td>Y / N, if yes when:</td>
<td>Y / N, if yes when:</td>
<td>Y / N, if yes when:</td>
</tr>
<tr>
<td>*Past chest x-ray</td>
<td>Y / N, if yes when:</td>
<td>Y / N, if yes when:</td>
<td>Y / N, if yes when:</td>
</tr>
<tr>
<td>*Acute / chronic</td>
<td>Y / N, if yes state:</td>
<td>Y / N, if yes state:</td>
<td>Y / N, if yes state:</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RVD Positive: Y / N  Past surgery: Y / N, if yes state when:

Comorbid condition(s): Y / N  If Yes, state condition(s)______________________________

________________________________________________________

________________________________________________________

*Information to be acquired at each scan
Appendix 7: Laboratory and Breast Cancer Data Form

Patient Study number: ________________

Breast cancer data

History of present illness:

Breast cancer stage:

Breast cancer chemotherapy regimen and dose

<table>
<thead>
<tr>
<th>Regimen (tick)</th>
<th>CMF</th>
<th>CAF</th>
<th>CAF-Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>F</td>
<td>D</td>
</tr>
</tbody>
</table>

Side Effects or Adverse Drug Reactions experienced

<table>
<thead>
<tr>
<th>Side effects (tick appropriate)</th>
<th>Baseline</th>
<th>2nd scan</th>
<th>3rd scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Fatigue</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hair loss</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Appetite loss</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Mouth and throat sores</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Constipation</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Other side effects (state)

Laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Reference Range</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10-15 g/ dL</td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>3.9-5.3 x 10^12/L</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>3.0-5.2 mmol/L</td>
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</tr>
<tr>
<td>LDL</td>
<td>&lt;3.3 mmol/L</td>
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</tr>
<tr>
<td>HDL</td>
<td>0.5-1.8 mmol/L</td>
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<tr>
<td>Triglycerides</td>
<td>0.35-1.70 mmol/L</td>
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</tbody>
</table>
Appendices

Appendix 8: Patient MUGA scan form

Patient Study number: ___________________

<table>
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<th>SCAN</th>
<th>DATE</th>
<th>RP INJECTED</th>
<th>ACTIVITY ADMIN</th>
<th>TIME</th>
<th>ESV</th>
<th>EDV</th>
<th>LVEF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE SCAN</td>
<td></td>
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<td>2ND SCAN</td>
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<tr>
<td>3RD SCAN</td>
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</tr>
</tbody>
</table>

Notes re MUGA Image:

________________________________________________________________________
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