PATTERN OF ADVERSE DRUG REACTIONS TO ANTICANCER DRUGS IN ONCOLOGY DEPARTMENT OF LAGOS UNIVERSITY TEACHING HOSPITAL, NIGERIA

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SPS/13/MPC/00011

A DISSERTATION SUBMITTED TO THE DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS, BAYERO UNIVERSITY KANO, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF SCIENCE DEGREE IN PHARMACOLOGY.

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DECLARATION

I hereby declare that this work is the product of my own research efforts undertaken under the supervision of Dr. Musa Aliyu and has not been presented anywhere for the award of a degree or certificate. All sources have been duly acknowledged.

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CERTIFICATION

This is to certify that the research work for this dissertation and the subsequent write-up "Pattern of Adverse Drug Reactions to Anticancer drugs In Oncology Department of Lagos University Teaching Hospital, Nigeria" (Abubakar Sule Danbatta, SPS/13/MPC/00011) were carried out under my supervision.

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APPROVAL

This dissertation has been examined and approved for the award of Master of Science in Pharmacology.

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DEDICATION

I dedicate this work to my late father Alhaji Sule Ibrahim Danbatta and my mother Hajiya Binta Sule Danbatta.

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ABSTRACT

Studies have shown high prevalence of adverse drug reactions (ADRs) with chemotherapeutic agents. The research was aimed at studying the pattern of ADRs due to cancer chemotherapeutic agents with specific objectives of assessing the causality, severity and management of these reactions in Lagos University Teaching Hospital (LUTH), Lagos Nigeria from October 2015 to January 2016. The study was a single centred retrospective study. Medical records of patients were studied, with patient details, ADRs and medications used to manage the reactions recorded using the designed ADR collection form. The ADRs were assessed for causality and severity using the Naranjo and Hartwig assessment scales respectively. A total of 433 ADRs were recorded from 170 patients of which 96 (56.47%) were females and 74 (43.53%) were males. Most common cancers encountered were breast (25.30%), colorectal (21.20%), cervical (10.00%) and prostate (10.00%). Nausea/vomiting (21.50%) accounted for most ADRs followed by alopecia (17.10%). Antimetabolites (28.00%) and platinum compounds (24.00%) were the most implicated drug classes causing ADRs. Naranjo causality scale showed (66.48%) of the reactions to be "possible" and (33.52%) to be "probable" while the Hartwig severity scale revealed majority of the reactions to be "moderate" (63.50%), followed by "mild" (35.11%) and "severe" (1.39%). Medications commonly prescribed for the management of the reactions were ondansetron, proton pump inhibitors, dexamethasone, chlorpheniramine and metoclopramide. The prevalence of ADRs was considerably high in spite of the use of medications for management. Most of the ADRs were not reported using the pharmacovigilance system, leading to under reporting. Therefore, health care givers should be educated to look out for such, with emphasis to employ strategies to prevent, minimize and manage ADRs of cytotoxic agent. The knowledge will serve to prevent similar reactions in the future by rational and judicious use of preventive measures.

CHAPTER ONE
INTRODUCTION

1.1 Background of the study

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease or for the modification of physiological function (WHO, 2002; Abubakar *et al.* 2014; Kiran *et al.* 2014). Majority of ADRs arise due to wrong use of drugs by patients and medication errors by health practitioners which may lead to patient hospitalization or prolong hospital stay and augmented health expenses to individuals and nations (Awodele *et al.* 2011). ADRs are considered as the fourth to sixth leading cause of death among hospitalized patients (Prasad *et al.* 2013). A study from Northern Nigeria reported the death of 47 children in the year 1990 due to treatment with contaminated paracetamol syrup (Oshikoya and Sanbajo, 2010; Iwokwagh, 2013). About 2.9 – 5.6% of all hospital admissions are caused by adverse related events, and approximately 35% of hospitalized patients experience an ADR (Lau *et al.* 2004). Unfortunately, studies conducted have shown that about 95% cases of ADRs have not been documented and reported globally. In addition, awareness of ADRs and its surveillance are inadequate with few reports available in developing countries like Nigeria (Sanghavi *et al.* 2013; Showande and Oyelola, 2013; Adedeji *et al.* 2013). Patients who are on polypharmacy, those with multiple chronic medical conditions, those with a history of ADRs and those with dementia are at a greater risk of developing ADR (Adedeji *et al.* 2013). Drugs with narrow therapeutic index or those that require outpatient therapy monitoring account for about 41.5% of all drug-induced hospitalizations (Budnitz *et al.* 2006). Nearly two thirds of adverse drug reactions that required hospitalizations were considered to be potentially preventable (McDonnell and Jacobs, 2002).

Evaluation of ADRs may be complex based on clinical diagnosis because some ADRs tend to mimic natural disease occurring process (Adedeji *et al.* 2013). Although some ADRs are peculiar to few classes of drugs, it is crucial to ascertain the time relation linking the use of drug and emergence of the ADRs. Other parameters to be looked out for includes, the differential diagnosis, choosing suspected drug based on the nature of the reaction, exclusion, de-challenge or re-challenge (Farcas and Bojita, 2009). It is imperative to note that manifestation of ADRs, while taking several medications does not confirm that one of these medications is the cause. Also lack of time relationship between the drug administration and emergence of ADRs does not rule out the drug as a likely cause (Oreagba *et al.* 2011). It is risky to treat unrecognized drug related ADRs with another drug as it may predispose the patient to injury and poly pharmacy (Oshikoya and Awobusuyi, 2009). The main purpose of causality assessment is to find out the level of probability or how certain one can be, that the suspected ADR is actually due to the drug (Naranjo *et al.* 1992). Several scales were used to assess causality e.g. WHO scale, European ABO system and Naranjo Scale. Naranjo algorithm is the most simple and widely used method of ADRs assessment. It categorizes ADRs into: Certain, Probable, Possible, Unlikely, and Doubtful (Naranjo *et al.* 1992; Farcas and Bojita, 2009). The Hart wig assessment scale is widely used to determine the severity of encountered reactions and is used to classify severity of ADR into mild, moderate and severe (Hartwig *et al.* 1992).

Management of ADRs requires a multidimensional approach. Some ADRs are severe in nature, e.g. anaphylactic shock therefore, speedy measures should be taken. The results of diagnosis determine which drug should be suspected. If the patient is treated with many essential medicines, the less important one should be removed first (Edward and Aronson, 2000). However, if all the medications were withdrawn at once, the most vital drug should be reintroduced first. But once the suspected medicine is identified, alternatives that may not generate the

same ADR should be prescribed. When the first drug was withdrawn and the effect persists the next most likely culprit drug should be removed (Classen *et al.* 1997). However, if the patient suffers the withdrawal of these drugs, the same drug can be given at lower doses. In a rare situation whereby the drug causing ADR is considered necessary the treatment can continue while the patient is managed symptomatically (Edward and Aronson, 2000).

Pharmacovigilance (PV) is described by the WHO as a process of detection, assessment, understanding and prevention of adverse effects or any other drug-related problem in its entire ramifications (WHO, 2002). The first endeavor made to resolve the problem of drug safety was announced in 1961 promptly after the disaster caused by thalidomide treatment in pregnant women (WHO, 2002; Iffat *et al.* 2014). So far, many countries from various continents have commenced PV programs to identify ADRs, reasons for their occurrence, and their incidence. The Nigerian National Pharmacovigilance Centre (NPC) was established in 2004 and affiliated with the WHO universal drug monitoring center, Uppsala which was established in 1978. Pharmacovigilance program in Nigeria involves ADRs surveillance and reporting by the health care team and traditional medicine practitioners. However, up to this period few cases were documented and few studies were carried out by the relevant authorities (Showande and Oyelola, 2013). The method usually applied in PV is a spontaneous reporting system (SPR) and it is used to collate information and signals from different locations (Nwokike *et al.* 2008; Palaian *et al.* 2011; Iffat *et al.* 2014). The spontaneous reporting system on many occasions was applied to facilitate early detection and prevention of new drugs tragedy. The primary focus of SPR is to report all the prevalence of ADRs even if not much data is available and the causal relationship is yet to be established. However, apart from the advantages of SPR, the major hitch is underreporting. In many hospitals, only 10% of ADR incidents were reported to the relevant authorities (Kamtane and Jayawardhani, 2012; Hanafi *et al.* 2012).

Cancer is a potentially fatal disease caused mainly by environmental factors that mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behavior leads to expansive masses of abnormal cells that destroy surrounding normal tissue and can spread to vital organs resulting in disseminated disease (Oudard, 2013). The global burden of cancer continues to increase largely because of aging and growth of the world population coupled with an increasing adoption of cancer-causing behaviors particularly smoking (Jemal *et al.* 2011). According to the World Health Organization (WHO), about 7.4 million cancer related deaths (13% of all deaths) occurred in 2013 and the figure is projected to continue rising, with an estimation of 11.5 million deaths by 2030 (Jemal *et al.* 2011).

The practice of cancer medicine has changed dramatically in the past four decades, as curative treatments have been identified for a number of previously fatal malignancies such as testicular cancer, lymphomas, and leukaemia (Guo *et al.* 2012). Different modalities for treatment of cancer include radiation, surgery, chemotherapy, hormonal therapy, immunotherapy, biologic therapy and cryosurgery (Kirthi *et al.* 2014).

Cancer chemotherapy is employed as part of a multimodal approach to the treatment of many tumors. Anticancer drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells (Jinichi *et al.* 2014). It is well recognized that cancer chemotherapeutic agents are associated with severe adverse effects leading to economic burden and decreased quality of life (Aslam *et al.* 2014). The normal tissues adversely affected by these drugs are those which are rapidly dividing such as the bone marrow, gastrointestinal tract and hair follicles (Marilia *et al.* 2014). The most common side effect of cancer chemotherapy is nausea, with or without vomiting (Trueb, 2009). Other common adverse drug reactions are diarrhea, alopecia, myelosuppression, mucositis, gonadal

dysfunction, hyperuricemia, neuropathy, cardiomyopathy, hemorrhagic cystitis, impaired renal function and electrolyte imbalance (Trueb, 2009).

Major groups of anticancer drugs includes the Nitrogen mustards/alkylating agents, Antimetabolites, Antitumor antibiotics, Platinum coordination compounds, Microtubule inhibitors and Chromatin function inhibitors (Amartya, 2010).

1.2 Statement of research problem

Investigations have shown that ADRs remain a substantial cause of morbidity and mortality among patients and further studies have shown that ADRs are the 4th leading cause of death in the USA (Abubakar *et al.* 2014; Iffat *et al.* 2014; Aithal *et al.* 2014). Various researchers reported that ADRs are one of the fundamental causes of hospital admissions, extended hospital stays, and increased health care cost (Kamtane and Jayawardhani, 2012; Hanafi *et al.* 2012). The Institute of Medicine (IOM) reported that more than one million avoidable adverse events occur each year and out of this figure 44,000 to 98,000 were devastating (Institute of Medicine, 2000). Many cases of ADRs go unreported. A study carried out in Nigeria reported a high prevalence of ADRs across the country. Unfortunately, only 6-10% cases were reported (Okezie and Olufunmilayo, 2008; Fadare *et al.* 2011). Regulatory authorities consider only the information and outcome of the premarketing clinical trial in controlled settings to approve and register a drug for human use. However, not much is known about the drug beyond the data obtained from clinical trials in controlled setting (Adedeji *et al.* 2013). The outcome of pre-marketing studies for safety, efficacy, and quality of new medicines will not signify the whole population of patients that will use the drugs when they are approved. As such, suitable and constant post-marketing surveillance (PMS) is indispensable (Sanghavi *et al.* 2013). It is well recognized that cancer chemotherapeutic agents are associated with severe adverse effects due to high toxicity and narrow therapeutic window leading to economic burden, patient hospitalization, prolonged hospital stay and

decreased quality of life (Aslam *et al.* 2014). Extensive literature search showed no published data regarding the adverse effects of anticancer agents in Nigerian population.

1.3 Significance of the study

Established in 1962, Lagos University Teaching Hospital is one of only few existing and functional oncology centers in the country. The number of cancer patients estimated from the registry is around 6000 with the oncology clinic fully equipped with a functional Linear Accelerator Machine since year 2007. The vast majority of these patients undergo cancer chemotherapy. Cytotoxic agents have been shown to be highly toxic mostly due to narrow therapeutic index (Mallik *et al*. 2007). Under-reporting of ADRs is a worldwide phenomenon which has been established from previous studies (Lopez *et al.* 2009). It is a known fact that information regarding ADRs changes on a daily basis and hence the need for constant updating of the knowledge of health care professionals.

1.4 Research objectives

1.4.1 Aim

To determine the pattern of adverse drug reactions of cancer chemotherapeutic drugs in Lagos University Teaching Hospital (LUTH) Lagos, Nigeria.

1.4.2 Specific objectives

The specific objectives in the study includes the following:

- To determine the demography of the cancers in LUTH
- To study the occurrence of suspected ADRs with anticancer agents in LUTH.

- To assess the causality of the ADRs using the Naranjo ADR causality assessment scale
- To assess severity using the Hart wig severity scale respectively.
- To determine the medications used in management of the ADRs.

1.4.3 Research questions

- What are the demographic presentations of cancers in LUTH?
- What are the types of suspected ADRs experienced by patients on cancer chemotherapy?
- What are the common drugs responsible for the ADRs?
- How likely are the drugs responsible for the ADRs?
- How severe are the encountered ADRS?
- What are the medications used to manage the various ADRs?

1.4.4 Research hypothesis

The null hypothesis (H_o) states that there is no statistically significant existence of ADRs in patients treated with anti-cancer agents in Lagos University Teaching Hospital while the alternate hypothesis (H_a) states that there is statistically significant existence of ADRs in patients treated with anti-cancer agents in LUTH.

1.5 Scope and limitations

1.5.1 Scope

The research focused on the retrospective study of adverse drug reactions in patients on anticancer agents at the oncology clinic of Lagos University Teaching Hospital from October 2015 to January 2016. Health records of cancer patients will be sampled and analyzed for adverse drug reactions. The result of the study will hopefully show the prevalence of various cancers in LUTH, the range of anticancer drugs in use and the existence of different ADRs associated with cancer chemotherapeutic agents.

1.5.2 Limitations

- The study lacked the ability to monitor suspected ADRs continuously because it was retrospective.
- There was no provision for recalling back a patient.
- Information on therapeutic drug monitoring is not usually available which made causality determination cumbersome.
- The short duration of the study also made it difficult to study chronic or delayed ADRs.

1.6 Potential risks

The study was retrospective and dealt with health records hence posed no direct or indirect harm to patients.

1.7 Inclusion/exclusion criteria

All patients who developed at least one ADR with any cancer chemotherapeutic agent were included in the study. Patients who developed ADRs due to concomitant drugs, blood products, infusions, accidental poisoning, history of drug abuse and pregnant were excluded.

CHAPTER TWO

LITERATURE REVIEW

2.1 Adverse drug reactions

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as a response to a drug which is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function (WHO, 2002; Kiran *et al.* 2014). Adverse drug reaction can also be explained as a harmful outcome elicited by a drug at doses primarily administered for therapeutic effect, diagnoses or prophylaxis which compels decrease in dose or removal of the drug or foretells the likelihood of ADR when the drug is used again. (Eluwa *et al.* 2014). Adverse drug reaction unlike adverse drug event, include the causal relationship

between the drug and its manifestation, it is also distinguished from side effects that may be favorable (Edward and Aronson, 2000).

2.1.1 Classification of adverse drug reaction

Generally, ADRs are classified as type A (dose-related or augmented), type B (non-dose related or bizarre), type C (dose-related and time-related or chronic), type D (time-related or delayed), type E (withdrawal or end of use), type F (unexpected or failure of therapy) (Classen *et al.* 1997).

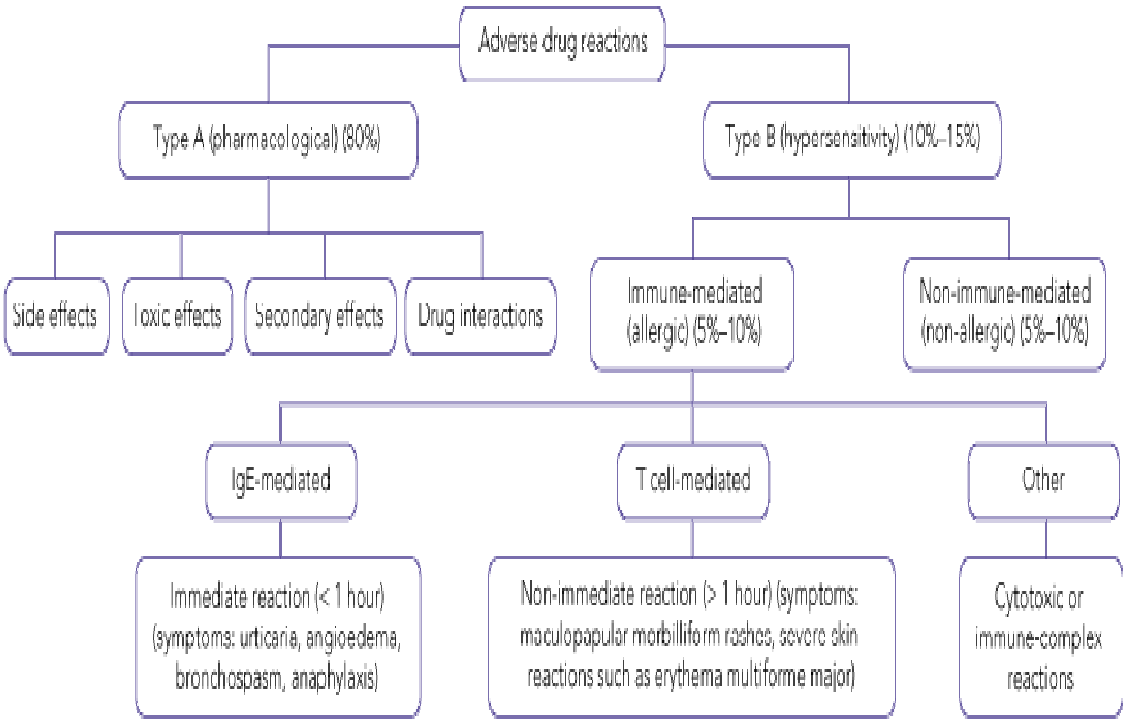

Figure 2.1 Major types of ADRs (Type A and Type B ADRs)
https://www.mja.com.au/journal/2006/185/6/3-drug-hypersensitivity

To advance ADR management, a new system of classification based on drug dose, time course and patient predisposition to ADRs was introduced. This system grouped ADRs into dose related, time-related and susceptibility related as follows:

(a) Dose related

Conventionally, immunological and other ADRs have not been regarded as dose related. Although there was an impression that, some of the immunological

reactions are clearly dose dependent e.g. hay fever in response to high pollen counts, immune response to hepatitis B vaccine and type IV hypersensitivity skin reactions (Aronson and Ferner, 2003; Alomar, 2014).

(b) Time-related

The pharmacological action of the drug is based on its concentration at the receptor site and the time course to reach the receptor site. Based on the time course, ADRs can be grouped into time-dependent and time-independent reactions (Aronson and Ferner, 2003).

(b1) **Time-dependent reactions:** Time-dependent reactions are divided into six sub-groups:

(i) **Rapid reaction:** It is caused by rapid administration of drug parenterally (e.g. the red man syndrome) with vancomycin (Aronson and Ferner, 2003).

(ii) **First dose reaction:** This type of reaction happens when the first dose is given and not after a prolonged duration e.g. hypotension after the first dose of angiotensin converting enzyme inhibitor or type1 hypersensitivity reaction such as anaphylaxis to penicillin at first exposure (Aronson and Ferner, 2003).

(iii) **Early reaction:** These are reactions that occur at the beginning of the treatment e.g. Nitrate induced headache (Aronson and Ferner, 2003).

(iv) **Intermediate reaction:** The intermediate reaction does not occur immediately, it takes some time before it happens. Examples includes type II hypersensitivity reactions e.g. Thrombocytopenia to quinine, type III reactions e.g Interstitial nephritis to penicillin and type IV reactions e.g cutaneous hypersensitivity to antihistamines (Aronson and Ferner, 2003).

(v) **Late reaction:** Usually, late reaction appears after repeated administration of the drug. Common examples include tardive dyskinesia with dopamine receptor antagonists. Late reaction also includes reactions that occur after withdrawal or dose reduction e.g. myocardial infarction after withdrawal of β-blocker and hypotension after withdrawal of methyldopa (Aronson and Ferner, 2003).

(vi) **Delayed reaction:** This type of reaction takes place long-time after the completion of treatment. This includes Phocomelia due to thalidomide and vaginal adenocarcinoma in women treated with diethylstilboestrol (Aronson and Ferner, 2003).

(b2) **Time-independent reactions:** Time-independent reactions occur at any time during the exposure and does not depend on the time course e.g. digoxin toxicity in association with potassium depletion or poor renal function (Aronson and Ferner, 2003).

(c) Susceptibility related

Under this section, ADRs are categorized based on patient susceptibility in a given population. The risk of developing ADRs differs from one patient to another. Several factors predispose patient to the development of ADRs. The type and nature of ADRs depend on patient factors that made him vulnerable (Aronson and Ferner, 2003).

2.2 Diagnosis of adverse drug reaction

It is indispensable in every hospital for a physician to carry out a broader diagnosis of patients. This encompasses not only diagnosing the patient based on the disease he presented, but also the chance of ADRs being the chief complaint or its occurrence in a near future (Brahma *et al.* 2013). Sometimes it may become essential to ascertain baseline parameters at the beginning of treatment in anticipation of ADRs. This can be done through laboratory investigations such as plasma concentration, allergy test, biopsy as well as baseline organ function test (Macedo *et al.* 2005; Farcas and Bojita, 2009). Evaluation of ADRs may be complex based on clinical diagnosis because some ADRs tend to mimic natural disease occurring process (Brahma *et al.* 2013). Although some ADRs are peculiar to few classes of drugs, it is crucial to ascertain the following: time relation linking the use of drug and emergence of ADRs, differential diagnosis to assess other potential sources, choosing suspected drug based on the nature of the reaction, exclusion, de-challenge or

re-challenge (Edward and Aronson, 2000; Farcas and Bojita, 2009). It is imperative to note that manifestation of ADRs, while taking several medications does not confirm that one of these medications is the cause. Furthermore, lack of time relationship between the drug administration and emergence of ADRs does not rule out the drug as a likely cause (Farcas and Bojita, 2009). It is risky to treat unrecognized drug related ADRs with another drug as it may predispose the patient to injury and poly pharmacy (Macedo *et al.* 2005).

2.3 Causality classification of adverse drug reactions

Adverse drug reaction can also be classified according to its nature, the condition at which it occurs, and other possible clinical investigations. ADRs are commonly classified into the following:

(i) **Certain:** Adverse drug reaction can be considered as certain if it happens within the period of drug treatment, proved by laboratory findings. To be labeled certain, a reaction should not arise due to drug-drug interaction, drug-disease interaction or other chemicals. Similarly, removing the drug (de-challenge) relieved the symptom clinically while on replacing drug (re-challenge) the ADR reappears (Edward and Aronson, 2000; Pichler *et al.* 2010).

(ii) **Probable/likely:** Adverse drug reaction can be regarded as probable if it occurs during treatment with the drug and justified by laboratory assessment. It must not be associated with the patient's disease condition, other drugs or chemicals. Similarly, when the drug is removed (de-challenge) the symptoms are diminished. The ADRs are probable if devoid of re-challenge information (Edward and Aronson, 2000).

(iii) **Possible:** Adverse drug reaction is classified as possible if it occurs during the treatment with the drug, established by laboratory result and not associated with drug-drug interaction, drug-disease interaction, other disease or chemicals. The ADRs are possible if devoid of de-challenge and re-challenge information (Edward and Aronson, 2000).

(iv) **Unlikely:** Adverse drug reaction is considered as unlikely even if it happens when the drug was administered and assessed in the laboratory. It is classified as unlikely if it can be explained by the existence of other drugs, chemicals, or underlying disease condition (Edward and Aronson, 2000).

(v) **Conditional/unclassified:** This type of ADR is assessed in a laboratory as an abnormality that has been testified to be an adverse reaction but which more data are crucial for an appropriate judgment or additional information (Edward and Aronson, 2000; Pichler *et al.* 2010).

(vi) **Un-assessable /unclassifiable:** This is a class of ADRs that cannot be justified due to insufficient information, sometimes the information may be available, but is confusing or contradicting (Edward and Aronson, 2000)**.**

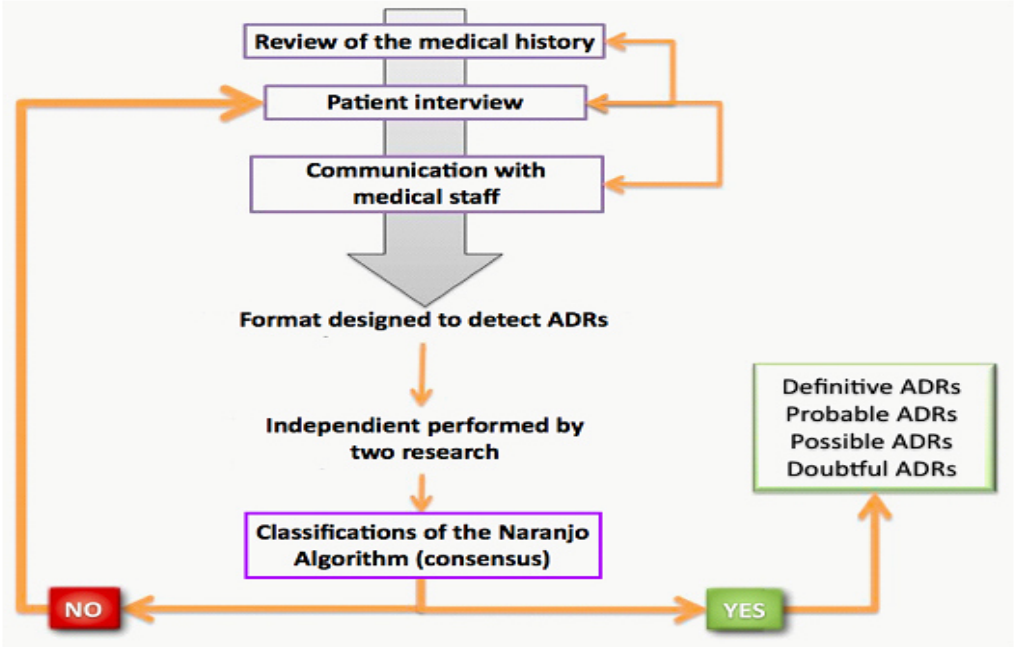

Figure 2.2 Causality classifications of ADRs.
http://www.scielo.org.co/scielo.php?pid=S1657-95342010000100006&script=sci_arttext

2.4 Assessment of causality and severity of ADR

The main purpose of causality assessment is to find out the level of probability or how certain one can be that the suspected ADRs is actually due to the drug. The establishment of a causal relationship between specific drug and a clinical event is a fundamental problem in pharmacovigilance. Firstly, ADRs frequently mimic other disease and secondly many of the symptoms attributed to ADRs occur commonly in healthy individuals who are not taking any medication (Smith *et al.* 2007; Amartya, 2010). Several scales were used to assess causality e.g. WHO scale, European ABO system and Naranjo Scale. Naranjo algorithm is the most simple and widely used method of ADRs assessment. It categorizes ADRs into: Certain, Probable, Possible, Unlikely, and Doubtful (Edward and Aronson, 2000; Farcas and Bojita, 2009).

Table 2.1 Naranjo causality assessment scale (Farcas and Bojita, 2009)

S/N	Assessment	Yes	No	Don't Know
1	Was there any conclusive report on this reaction before?	+1	0	0
2	Did the reaction occur after the ingestion of the suspected drug?	+2	-1	0
3	Was there any relief after withdrawal of the suspected drug or when the antagonist was administered?	+1	0	0
4	Did the reaction reoccur after re-challenge with same drug?	+2	-1	0
5	Was there any possible cause of this reaction apart from the suspected drug?	-1	+2	0
6	Did the reaction reoccur when the placebo was administered?	-1	+1	0
7	Did the suspected drug accumulated in toxic concentration in any of the body fluids?	+1	0	0

8	Does the reaction increase when the dose of the drug was raised, or decreased when the dose reduced?	+1	0	0
9	Based on history, did the patient react to the same or similar drug before?	+1	0	0
10	Was the suspected ADR confirmed by any established facts before?	+1	0	0

SCORE 9 = definite; 5-8 = probable; 1-4 = possible; 0 = doubtful.

Severity is often used to describe the intensity of a medical event. The United States Food and Drug Administration (USFDA) classifies an ADR as 'serious' when it results in death, life- threatening, causes or prolongs hospitalization, causes a significant persistent disability, results in a congenital anomaly, or requires intervention to prevent permanent damage (Amartya, 2010).

Karch and Lasagna classified severity into the following:

- Minor: no antidote, therapy or prolongation of hospitalization required.
- Moderate: requires a change in drug therapy, specific treatment or an increase in hospitalization by at least 1 day.
- Severe: potentially life threatening, causing permanent damage or requiring intensive medical care.
- Lethal: directly or indirectly contributes to the death of the patient. (Karch and Lasagna, 1977)

The most commonly used severity assessment scale is the Hart wig severity scale which categorizes ADRs into seven levels based on their severity as follows:

(a) Mild:

Level 1: The ADR requires no change in treatment with the suspected drug.

Level 2: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.

(b) Moderate:

Level 3: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required. There is no increase in length of stay.

Level 4 (a): Any level 3 ADR that increases length of stay by at least one day.

Level 4 (b): The ADR is the reason for admission.

(c) Severe:

Level 5: Any level 4 ADR that requires intensive medical care.

Level 6: The ADR causes permanent harm to the patient.

Level 7: The ADR either directly or indirectly leads to the death of the patient (Hartwig *et al.* 1992; Amartya, 2010).

2.5 Pharmacovigilance

Pharmacovigilance (PV) is defined by W.H.O as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem (WHO, 2002). Pharmacovigilance program was initiated in 1961 after the case report by Australian doctor on serious ADR by the drug thalidomide used as an antiemetic and sedative in pregnant women. Subsequently, in 1968 WHO strengthened the program on international drug monitoring with the aim of collecting worldwide ADRs data at a central point. Adverse drug reaction signals detected from all parts of the world are received and documented as individual case safety report (ICSR) (NPC, 2004; Mazzitello *et al.* 2013). Hospitalized patients who were treated with different medications have 40% chance of developing adverse drug events (ADEs). Similarly, patients that have experienced ADRs 2-3 times before are more likely to develop ADRs again (Wood and Martinez, 2004; Isah *et al.* 2012). It was established that 57% of drugs banned in India were due to cardiovascular adverse effects, and 14% were as a result of liver damage (Hashmi, 2013; Ahmad *et al.* 2014). A study carried out in the USA by institute of medicine accounted that, ADRs increase the cost of health care between 17 to 29 billion US dollars annually (Abideen, 2013). The majority of these ADRs are

considered preventable, as such careful documentation and examination of patient history will help to avoid such threat (Abideen, 2013; Abubakar *et al.* 2014). Information on PV is usually reported using a designed form referred to as yellow form. The yellow forms serve as an early warning and have been used to detect ADRs as soon as they occur. It provides valuable information on the type of ADRs detected, the nature of the patients experiencing ADRs as well as possible causal relationship (WeMeReC, 2013). Recently, there has been a significant decrease in ADRs reports using yellow cards which raise the alarm on the need for urgent awareness on the ADRs report among health care professionals (Osakwe *et al.* 2013).

2.5.1 Aim and objectives of pharmacovigilance

The primary aim of PV is to detect early signals and try to establish causal relationship between the detected signals and the suspected drug by collecting similar information from different sources which involves observational and experimental studies. It also involves monitoring the use of herbal products, traditional and complementary medicines, blood products, biological and medical devices as well as vaccines (WHO, 2000; NPC, 2004; Isah *et al.* 2012). The objective of PV study is to improve patient safety, contribute to the assessment of benefit, harm, effectiveness, risk, rational and cost effective use of medicines (Hauben and Aronson, 2009).

2.5.2 Detection and monitoring of adverse drug reactions

By the time a drug is marketed it will usually have been given to an average of 2500 people and it is likely that clinical trials will have picked up the most common ADRs. It is also unlikely that Type B reactions with an incidence of 1 in 500 or less will have been identified by the time a drug becomes available for widespread use. It is only after much wider use that rare reactions, or those which occur predominantly in certain subgroups within the populations, such as the elderly, are detected, and it is therefore essential to monitor safety once a

drug has been marketed (Van Grootheest *et al.* 2005; Gupta, 2011). Various strategies of pharmacovigilance include:

- Case reports and case series: The publication of single case reports or case series of ADRs in the medical literature is an important means of detecting new and serious reactions, particularly Type B reactions. Case reports have, in the past, been vital in alerting the medical profession to several serious adverse reactions. Examples include oculomucocutaneous syndrome associated with practolol and halothane induced hepatitis (Amartya, 2010; Ohaju-Obodo and Iribhogbe, 2010).
- Case-control studies: Case control studies compare drug usage in a group of patients with a particular disease with use amongst a matched control group who are similar in potentially confounding factors, but who do not have the disease. Examples of associations that have been established by case control studies are Reye's syndrome and aspirin, and the relationship between maternal diethylstilbestrol ingestion and vaginal adenocarcinoma in female offspring. The case control method is an effective means for confirming whether or not a drug causes a given reaction once a suspicion has been raised (Amartya, 2010; Ohaju-Obodo and Iribhogbe, 2010).
- Cohort studies: Cohort studies are prospective studies which study the fate of a large group of patients taking a particular drug. Cohort studies include ad hoc investigations set up to investigate specific problems (often sponsored by pharmaceutical companies), prescription event monitoring and a variety of record linkage schemes (Zancan *et al.* 2009; Amartya, 2010).
- Spontaneous reporting schemes: The thalidomide tragedy led to the institution in many countries of national schemes for voluntary collection of adverse drug reaction reports. Spontaneous reporting schemes cannot provide estimates of risk because the true number of cases is invariably under estimated and the denominator is not known. To be successful,

reports should be made despite uncertainty about a causal relationship, irrespective of whether or not the reaction is well recognized and regardless of other drugs having been given concurrently (Zancan *et al.* 2009; Amartya, 2010; Gupta, 2011).

2.6 Overview of cancer

Cancer is a potentially fatal disease caused mainly by environmental factors that mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behavior leads to expansive masses of abnormal cells that destroy surrounding normal tissue and can spread to vital organs resulting in disseminated disease, commonly a harbinger of imminent patient death (Akarolo-Anthony *et al.* 2010). The global burden of cancer continues to increase largely because of aging and growth of the world population coupled with an increasing adoption of cancer-causing behaviors particularly smoking (Fatimah, 2009). According to the World Health Organization (WHO), about 7.4 million cancer related deaths (13% of all deaths) occurred in 2013 and the figure is projected to continue rising, with an estimation of 11.5 million deaths by 2030. WHO also estimated the annual mortality rate of some cancers to be: Lung (1.3 million deaths/year), Stomach (803,000 deaths/year), Colorectal (639,000 deaths/year), Liver (610,000 deaths/year) and Breast (519,000 deaths/year) (Jemal *et al.* 2011). The burden of cancer in Nigeria is unknown, mainly because of lack of statistics or under reporting (Fatimah, 2009). In a study of cancer registry literature updated from all over the world, only 1% of the literature emanated from Africa compared to 34% and 42% from Europe and Asia respectively (Yawe *et al.* 2007). The six most common cancers in Nigeria in descending order of frequency are breast, cervix, prostate, colorectal, liver cancer and Non Hodgkins Lymphoma (Fatimah, 2009). Presently, there are 11 cancer registries in Nigeria most of which are poorly funded that includes:

- University of Benin Teaching Hospital, Benin Cancer Registry

- University of Maiduguri Teaching Hospital, Maiduguri
- The Cancer Registry, University of Ilorin Teaching Hospital, Ilorin
- Cancer Registry, Nnamdi Azikwe University Teaching Hospital, Nnewi
- Cancer Registry, University of Nigeria Teaching Hospital, Enugu
- Cancer Registry, Obafemi Awolowo Teaching Hospital Complex, Ile-Ife
- Cancer Registry, Ahmadu Bello University Teaching Hospital, Zaria
- Cancer Registry, Jos University Teaching Hospital, Jos
- Cancer Registry, Lagos University Teaching Hospital, Lagos
- The Ibadan Cancer Registry, University College Hospital, Ibadan
- Cancer Registry, Aminu Kano University Teaching Hospital, Kano

(Fatimah, 2009; Alabi *et al.,* 2010)

An individual's risk of developing cancer depends on many factors, including age, lifestyle and genetic makeup (Farmer *et al.* 2010). Carcinogens interact with the individual's constitution both inherited and acquired which determines vulnerability to cancer. The science of classical epidemiology has identified populations at high cancer risk (e.g. users of tobacco products). However, many lifelong smokers do not get cancer, perhaps because of the way they handle potential carcinogens metabolically (Thun and Jemal, 2006). Many issues concerning diet and cancer are also controversial (e.g. fat intake and breast cancer). This may be because only certain polyunsaturated fatty acids generate damaging free radicals (Parkin *et al.* 2010). Reducing infection, particularly in the poorer countries, will lead to reductions in cancer incidence. Infectious agents associated with increased cancer risk include hepatitis B virus (liver), certain subtypes of human papillomavirus (cervix), Helicobacter pylori (stomach) and human immunodeficiency virus (many sites) (Samaras *et al.* 2010).

Different modalities for treatment of cancer include radiation, surgery, chemotherapy, hormonal therapy, immunotherapy, biologic therapy and

cryosurgery (Camphausen *et al.* 2008). The management of a patient with cancer is dependent upon a number of pieces of information that can be gathered about the tumour such as the tissue of origin, benign or malignant, tumour grade and tumour stage (Beumer *et al.* 2012). Benign tumours can normally be removed by surgery. Malignant solid tumours will, if possible, be surgically resected, probably followed and even preceded by other treatment modalities. More diffuse tumours such as leukaemias with circulating tumour cells require systemic chemotherapy (Steinberg *et al.* 2003).

2.7 Cancer chemotherapy

Chemotherapy is the use of any drug (such as aspirin or penicillin) to treat any disease including cancer (Sausville *et al.* 2012). Chemotherapy is employed as part of a multimodal approach to the treatment of many tumours. Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells (Jemal *et al.* 2011). It is well recognized that chemotherapeutic agents are associated with severe adverse effects leading to economic burden and decreased quality of life (Patrick, 2008; Aslam *et al.* 2014). The normal tissues adversely affected by these drugs are those which are rapidly dividing: the bone marrow, gastrointestinal tract and hair follicles (Balmer *et al.* 2005). More than 100 chemotherapy drugs are currently in use today either alone or in combination with other drugs or treatments. These drugs vary widely in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects (Conklin, 2004; Chabner and Roberts, 2005). To properly understand the principle of cancer chemotherapy, there is the need to know the cell cycle. This is because many chemotherapeutic drugs exert their mechanism by acting on specific phases of the cell cycle (Mahmoudi, 2011). All living tissues are made up of cells which grow and reproduce to replace other cells lost through injury or normal "wear and tear. The cell cycle is the normal life cycle of a cell. It's a series of steps

that both normal cells and cancer cells go through in order to form new cells (Wang and Levin, 2009). The cell cycle has 5 phases and all the phases lead back to the resting phase (G_0), which is the starting point. When a cell goes through the cell cycle, it reproduces 2 new identical cells. Each of the 2 cells made from the first cell can go through this cell cycle again when new cells are needed (Lilly and Duronio, 2005).

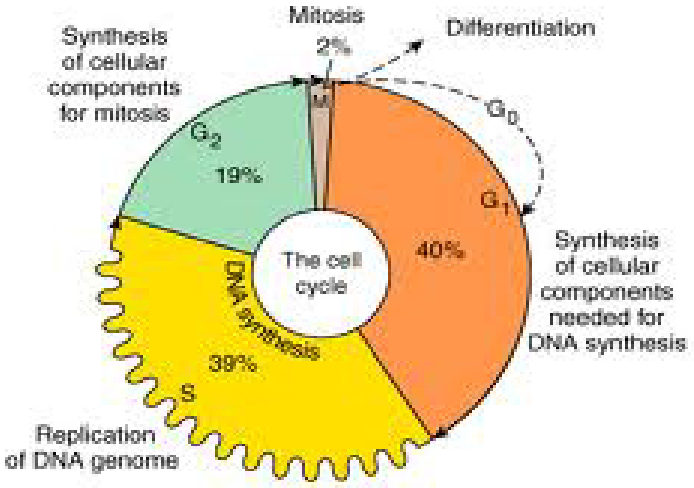

Figure 2.3 Cell cycle

The clinical Importance of cell cycle in chemotherapy emanates from the fact that all cells normal or neoplastic must traverse the cycle before and during cell division. Malignant cells spend time in each phase with longest time at G_1, but may vary (Caponigro *et al.,* 2005). Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are referred to as "**Cell Cycle Specific (CCS) drugs".** The "**Cell cycle nonspecific (CCNS) drugs** sterilize tumor cells whether they are cycling or resting in the G_0 compartment (Chabner and Roberts, 2005). CCS are effective against hematologic malignancies and in solid tumors with large growth fraction while CCNS drugs are effective in solid tumors with low growth fraction (Cohen and Geva-Zatorski, 2008). Example of CCNS includes nitrogen mustards, cyclphosphamide, chlorambucil, carmustine, dacarbazine, busulfan, L-asparginase, cisplatin, procarbazine and actinomycine D. CCS drugs are made up of vincristine (G_1), methotrexate, cytarabine, 6-

thioguanine, 6-MP, 5-FU, daunorubicin, doxorubicin etc (S phase). Other CCS agents include daunorubicin and bleomycin (G_2), Vincristine, vinblastine, paclitaxel (M phase) (Patrick, 2008).

2.8 Major groups of anticancer drugs

2.8.1 Nitrogen mustards and other alkylating agents

All of the alkylating agents form strong electrophiles through the formation of carbonium ion intermediates. This results in the formation of covalent linkages by alkylation of various nucleophile moieties. The chemotherapeutic and cytotoxic effects are directly related to the alkylation of DNA mainly through the 7 nitrogen atom of guanine although other moieties are also alkylated. The ultimate cause of cell death related to DNA damage is not known. Some of the cellular responses produced include cell-cycle arrest, DNA repair and apoptosis or programmed cell death (Huang and Retain, 2009). The alkylating agents are generally considered to be cell cycle phase nonspecific agents. They are also known to be most cytotoxic to rapidly proliferating cells. Thus, although DNA alkylation can occur anytime in the cell cycle, the biological consequences are most severe when this occurs during DNA synthesis. This is because cells exposed to the alkylating agents earlier, such as in G1 phase, would have enough time to repair some of the DNA damage before the next DNA synthesis phase. Non-proliferating cells would have an even greater period for DNA repair to occur before irreversible damage occurs. Thus the alkylating agents are proliferation dependent but cell-cycle phase nonspecific. Example include: chlorambucil, cyclophosphamide, mechlorethamine, iphosphamide etc (Yamamoto and Iwase, 2012).

Cyclophosphamide was originally designed so that it would be preferentially activated in tumor tissue which is believed to contain high levels of enzymes that would convert it to an active form. Although selectivity is now known not to be achieved, the drug undergoes metabolic activation in the liver catalyzed by the cytochrome P450 microsomal enzymes. One of the metabolites formed is

believed to be active as a cytotoxic agent while another metabolite, acrolein, is believed to be responsible for the cystitis produced by cyclophosphamide (Balmer *et al.* 2005). Therapeutic uses: The nitrogen mustards can be used for treatment of a variety of tumors ranging from leukemia's to solid tumors. Mechlorethamine is used mainly to treat Hodgkin's disease (MOPP regimen). Chlorambucil is used almost exclusively in the treatment of chronic lymphocytic leukaemia (CLL). Occasionally it has been used to treat certain lymphomas. Melphalan has been used principally to treat multiple myeloma (Chabner, 2011). The most commonly used alkylating agent is cyclophosphamide. It is an extremely versatile agent used in Hodgkin's disease and other lymphomas. In addition it is useful to treat Acute Lymphocytic Leukaemia (ALL) and a variety of solid tumours (Chen *et al.* 2007). Toxicity: The dose limiting toxicity of all the nitrogen mustards is bone marrow depression which is usually of a delayed nature. It is important to monitor leukocyte and platelet counts carefully during therapy with these drugs (Shephard, 2003). All of the nitrogen mustards produce acute nausea and vomiting, and with some, such as mechlorethamine the effect is quite severe (Lee *et al.* 2012). Cyclophosphamide frequently causes alopecia and a haemorrhagic cystitis. The cystitis is attributed to formation of acrolein during the metabolism of cyclophosphamide. Its incidence can be reduced by ensuring good fluid intake/frequent voiding and can be prevented by coadministration of sulfhydryl scavenging compounds such as Nacetylcysteine or mesna (Warr, 2008).

2.8.2 Antimetabolites

Antimetabolites are structural analogs of naturally occurring compounds. They interfere with the production of nucleic acids. The three categories of antimetabolites includes antifolates, purine analogs and pyrimidine antimetabolites (Gunaseelan *et al.* 2014).

Antifolates: Folic acid must be reduced in two successive steps by the enzyme dihydrofolate reductase (DHFR) before it can function as a coenzyme. DHFR is the primary target of action of most folate analogs such as methotrexate. Inhibition of this enzyme leads to toxicity through partial depletion of cofactors required for the synthesis of purines and thymidylate (Agarwal *et al.* 2013; Lau *et al.* 2004). Methotrexate is the drug of choice for gestational choriocarcinoma and related trophoblastic tumors of women where cures are obtained in a substantial number of cases. In this cancer, it is usually used in combination with dactinomycin. In the treatment of ALL in children, it is used for the maintenance of remissions. Finally, high dose methotrexate along with leucovorin rescue is used for the treatment of osteogenic sarcomas, leukemias and lymphomas (Agarwal *et al.* 2013; Huang and Ratain, 2009). The primary toxic effects are against the rapidly dividing cells of the bone marrow and gastrointestinal epithelium. All of the stem-cell type of the marrow can be affected to produce leukopenia, thrombocytopenia and with long-term administration, anemia. Mucositis is one of the earliest signs of toxicity and its appearance indicates that the dose must be reduced or other serious toxicities will occur. If diarrhea and ulcerative stomatitis occur, therapy with the drug must be stopped. Methotrexate causes kidney damage which is a frequent complication of high dose therapy. Crystalline deposits of methotrexate and methotrexate derived materials have been found in the renal tubules which seem to account for most of the nephrotoxicity. Both low and high dose therapy can cause hepatotoxicity. Methotrexate can cause a reversible pulmonary syndrome which has been observed primarily in children undergoing maintenance therapy. Nausea and anorexia frequently occur as acute side effects of methotrexate therapy (Maleki *et al.* 2012; Agarwal *et al.* 2013).

High dose methotrexate-rescue therapy: This involves administration of methotrexate at high doses along with leucovorin to rescue host tissues from the effects of the intense methotrexate therapy. The leucovorin provides the normal

tissues with the reduced folate leucovorin which circumvents the inhibition of DHFR. The protection seems to be selective in that it does not alter the antitumor effect of methotrexate. Apparently, only the host cells are able to utilize the leucovorin (Amartya, 2010; Agarwal *et al.* 2013).

Purine analog: The two major category are 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG). Both drugs are used primarily in the treatment of leukemias. Response rates are higher in children than adults. 6-MP is used in the maintenance therapy of ALL and 6-TG in the treatment of acute nonlymphocytic leukemia (Surendiran *et al.* 2010; Patricia *et al.* 2012).

Toxicity: Bone marrow depression is dose limiting with both drugs. Other major toxicities include nausea, vomiting and stomatitis. Hepatotoxicity is seen as jaundice in about 33% of patients treated with 6-MP (Surendiran *et al.* 2010; Sharma *et al.* 2015).

Pyrimidine antagonists: Principal members are the fluoropyrimidines and cytosine arabinoside. The most important fluoropyrimidine is 5-fluorouracil (5-FU). They are direct inhibitors of thymidylate synthetase, the key enzyme in thymidylate synthesis (Patrick, 2008). 5-FU is used to treat several common solid tumors (Chen *et al.* 2007).

Toxicity: Anorexia and nausea are among the earliest toxicities seen. These are followed by stomatitis and diarrhea which are indicative of a sufficient dose being given. Stomatitis and diarrhea are the most common dose-limiting toxicities when continuous infusions are used. The major toxicity resulting from a bolus dose is bone marrow depression. This is manifested by leukopenia and somewhat less often by thrombocytopenia and anaemia. Skin toxicity manifested by alopecia, thinning of the skin, nail changes, dermatitis and photosensitivity can also occur (Rahman, 2006; Aslam *et al.* 2014).

Another analog of pyrimidine is cytosine arabinoside (cytarabine or ara-C). Ara-C is used primarily for the treatment of acute myeloid leukemia (AML) due to its potent myelosuppressive action. It is the single most effective agent for

induction of remission in this disease and it is used primarily in combination with daunorubicin (Mrugank and Hareesha, 2013).

Toxicity: The principal toxicity is bone marrow depression manifested as granulocytopenia and thrombocytopenia. Other toxicities include oral ulceration, nausea, vomiting and diarrhea, and peripheral neurotoxicity with high doses (Mrugank and Hareesha, 2013; Aslam *et al.* 2014).

2.8.3 Antitumor antibiotics (non-covalent DNA-binding drugs)

These drugs interact with DNA in a variety of different ways including intercalation, DNA strand breakage and inhibition of the enzyme topoisomerase II. Most of these compounds have been isolated from natural sources and are antibiotics. However, they lack the specificity of clinically used antimicrobial antibiotics and thus produce significant toxicity (Amartya, 2010; Mrugank and Hareesha, 2013). **Actinomycin D** (Dactinomycin) is the only actinomycin used clinically. At low concentrations dactinomycin inhibits DNA directed RNA synthesis and at higher concentrations DNA synthesis is also inhibited. Dactinomycin is cytotoxic to cells in any phase of the cell cycle and it is probably equally toxic to exponentially growing cells and stationary cells (Maleki *et al.* 2012).

Dactinomycin is used mainly in the treatment of pediatric solid tumors (e.g. Wilm's tumor, rhabdomyosarcoma). It is also an alternative drug for choriocarcinoma when methotrexate can't be used because of resistance. The treatment of several solid tumors utilizes combination therapy with dactinomycin and radiotherapy. There seems to be an improved antitumor effect when the two are used in combination (Maleki *et al.* 2012).

Toxicity: The primary and dose limiting toxicity of dactinomycin is bone marrow depression. Also nausea, vomiting, malaise, ulceration of the oral mucosa and gastrointestinal tract and acneiform eruptions of the skin occur. If given to a patient who has had radiation treatment, a ‘recall’ effect may be observed i.e. when the drug is administered, the patient may develop a reaction

in normal appearing tissue that was included in the field of radiation (Lee *et al.* 2012; Maleki *et al.* 2012).

The **Anthracycline** antibiotics, like Doxorubicin, Daunorubicin, Idarubicin and Epirubicin, are among the most important antitumor drugs available. Daunorubicin has limited use in treatment of ALL and AML while doxorubicin has a much broader range of use against solid tumors, particularly breast cancer. Other solid tumors against which doxorubicin have good activity are ovary, bladder and lung carcinomas. It is also active in the treatment of Non-Hodgkin's lymphoma and Hodgkin's disease. Idarubicin appears to be as effective as daunorubicin in combination treatment of AML with perhaps more efficacy in patients less than 60 years old (Shephard, 2003; Patricia *et al.* 2012).

Toxicity: The toxic effects of the anthracyclines are similar. They frequently cause nausea and vomiting and patients may experience anorexia and diarrhea. The drugs and their metabolites may color the urine red for one or two days after administration. Bone marrow depression is dose-limiting and occurs in 60%-80% of patients. This is seen primarily as leukopenia which reaches a low point at approximately one to two weeks. Thrombocytopenia and anemia may also occur but is not as severe. Stomatitis is dose related and may be severe. Alopecia also occurs in most patients but reverses when therapy is stopped. The anthracyclines potentiate the effects of radiation. Additionally, enhancement of radiation reactions and radiation recall effects on normal tissues have been seen. Cardiac toxicity is a peculiar adverse effect observed in both adults and children (Shephard, 2003; Patricia *et al.* 2012).

The **Bleomycins** are a group of antitumor agents isolated from *Streptomyces verticillus*. The drug employed clinically is a mixture of compounds of complex structure containing about 70% bleomycin A2. Bleomycins have attracted interest because of their significant anticancer activity against certain solid tumors as well as the fact that they are minimally toxic to the bone marrow unlike most other anticancer agents. Bleomycin has been found to profoundly

inhibit DNA synthesis while RNA and protein synthesis are much less affected. Bleomycin is highly active against squamous cell tumors of the head, neck and lungs. It is also highly effective against germ cell tumors of the testis and ovary. It is often used to treat testicular carcinomas along with cisplatin and vinblastine. It is also active against Hodgkin's disease and other lymphomas where it is often included in the ABVD regimen (Amartya, 2010; Chabner, 2011).

Toxicity: Bleomycin is marrow sparing and is not immunosuppressive but the most common toxicity involves the skin and mucous membranes. Oral mucositis is dose related and common in the more aggressive regimens. Alopecia occurs in about 10 - 20% of patients. Toxic reactions of the skin include hyperpigmentation, sclerotic changes with collagen infiltration, edema and erythema of the hands and feet. Pulmonary toxicity is dose-limiting and the most severe toxicity associated with use of bleomycin. Symptoms include dyspnea, tachypnea, and a nonproductive cough. Other toxicities of bleomycin include nausea, vomiting, anorexia, drug-induced fever and chills. These effects are usually seen within the first few hours of bleomycin therapy. About 1% of lymphoma patients develop allergic reactions similar to anaphylaxis. For this reason, lymphoma patients are given 2 units or less for the first 2 doses. If no acute reactions occur, the regular dosage schedule may be followed (Amartya, 2010; Chabner, 2011).

2.8.4 Platinum coordination compounds

Cisplatin and carboplatin are among a number of platinum coordination complexes with antitumor activity. Recently oxaliplatin was put on the market. The platinum compounds are DNA cross-linking agents similar to but not identical to the alkylating agents (Miller *et al.* 2010; Maleki *et al.* 2012). These drugs are used in the treatment of testicular cancer (with bleomycin and vinblastine), bladder cancer, head and neck cancer (with bleomycin and 5-FU), ovarian cancer (with cyclophosphamide or doxorubicin) and lung cancer (with

etoposide). Cisplatin has been found to be the most active single agent against most of these tumors (Miller *et al.* 2010; Haddad *et al.* 2013).

Toxicity: The dose limiting toxicity of cisplatin is nephrotoxicity. This effect is dose related and is manifested by a decrease in creatinine clearance and electrolyte imbalances particularly hypomagnesemia. Several approaches can reduce the nephrotoxicity which includes the use of diuretics and hydration. Thiol containing compounds such as thiosulfate have also been shown to prevent the nephrotoxicity and may allow increased dosage of the cisplatin. Other toxic effects associated with this drug include bone marrow depression, severe nausea and vomiting, anaphylactic reactions and peripheral neuropathy (Miller *et al.* 2010; Haddad *et al.* 2013).

Nausea and vomiting occur in virtually all patients receiving cisplatin and this usually occurs within a short period of time. Cisplatin also causes a neurotoxicity that is most commonly seen as a peripheral neuropathy with sensations of numbness in the hands, feet, arms, and legs. In most cases stoppage of the drug allows the symptoms to disappear (Miller *et al.* 2010; Maleki *et al.* 2012).

2.8.5 Microtubule inhibitors

Microtubules are protein polymers that are responsible for various aspects of cellular shape and movement. The major component of microtubules is the polymer tubulin, a protein containing two non-identical subunits (alpha and beta). These drugs act by affecting the equilibrium between free tubulin dimers and assembled polymers (Poddar *et al*. 2009; Amartya, 2010)

Vinca alkaloids: This includes vincristine, vinblastine and vindesine. They are large complex molecules produced by the leaves of the periwinkle plant but vindesine is a semisynthetic vinca alkaloid (Yamamoto and Iwase, 2012). They are cell cycle phase specific agents and block cells in mitosis. Their biological activity is explained by specific binding to tubulin. Upon binding to vinca alkaloids, tubulin dimers are unable to aggregate to form microtubules. This

effectively decreases the pool of free tubulin dimers available for microtubule assembly, resulting in a shift of the equilibrium toward disassembly (Chen *et al.* 2007, Amartya, 2010). Despite close similarity in structure the different vinca alkaloids have quite different therapeutic uses. Vincristine is used mainly in combination therapy for the induction of remission in childhood acute leukemias. Vincristine together with prednisolone is the main therapy for induction of ALL (Chen *et al.* 2007). Complete remissions are obtained in 80 to 90% of patients. It is also used for the treatment of Hodgkin's and non-Hodgkin's lymphoma where it is part of several complex protocols (Yamamoto and Iwase, 2012). On the other hand the most important clinical use of vinblastine is for metastatic testicular tumors where it is combined with bleomycin and cisplatin. Beneficial responses have also been obtained in the treatment of Hodgkin's and non-Hodgkin's lymphoma. In Hodgkin's disease it has been used in place of vincristine, providing similar antitumor activity with less neurotoxicity. Vindesine, the newest of the vinca alkaloids, has significant activity in the treatment of acute leukemia, blast crisis of CML, Hodgkin's and non-Hodgkin's lymphomas (Chen *et al.* 2007; Poddar *et al.* 2009; Amartya, 2010; Yamamoto and Iwase, 2012).

Toxicity: The dose limiting toxicity of vincristine is mainly peripheral neuropathy and other neurological toxicities. Autonomic neuropathy often occurs early in the course of therapy resulting in abdominal pain, constipation, paralytic ileus, urinary retention and orthostatic hypotension. Unlike most antineoplastic agents, vincristine usually does not cause significant bone marrow suppression. Therefore it is often found in combination therapies with other drugs that are myelosuppressive. Gastrointestinal symptoms are also common with this vinca alkaloid. Unlike vincristine, the other vinca alkaloids produce mainly bone marrow depression. Myelosuppression (primarily neutropenia) is the major toxicity of vinblastine while lymphopenia is the dose

limiting toxicity of vindesine, but neurotoxicity also occurs frequently (Chen *et al.* 2007; Amartya, 2010; Yamamoto and Iwase, 2012).

Taxanes: Paclitaxel was first isolated from the bark of the Pacific yew tree (*Taxus brevifolia*). Docetaxel is a more potent analog that is produced semisynthetically. In contrast to other microtubule antagonists, the taxanes disrupt the equilibrium between free tubulin and microtubules by shifting it in the direction of assembly, rather than disassembly. As a result, taxol treatment causes both the stabilization of microtubules and the formation of abnormal bundles of microtubules. Taxanes have significant activity against ovarian cancer, breast cancer, carcinoma of the lung and head and neck carcinoma (Lee *et al.* 2012).

Toxicity: The major toxicity of these drugs is bone marrow depression with neutropenia the common dose limiting toxicity. Hypersensitivity reactions are also common. They are characterized by dyspnea, urticaria and hypotension. Mucositis is also common and is manifested as ulcers of the mouth and throat. Taxol also causes some reversible neurotoxicity, most often numbness and paresthesias in the hands and feet (Raffaghello *et al.* 2008; Lee *et al.* 2012).

2.8.6 Chromatin function inhibitors

These constitute a class of drugs that owe their antitumor effects to disruption of chromosomal dynamics. Chromosomes are complex structures which undergo many changes in conformation and intracellular position during the cell cycle. Drugs that interfere with the proteins responsible for these changes are selectively toxic to proliferating cells (Halkidou *et al.* 2004). The topoisomerase inhibitor epipodophyllotoxins, **Etoposide** (VP-16) and **Teniposide** (VM-26), are semisynthetic glycosidic derivatives of podophyllotoxin. These drugs form complexes with the topoisomerase II enzyme. This complex produces inhibition of the enzyme along with production of double stranded breaks in the DNA. (Song *et al.* 2005). Etoposide has shown activity against a variety of tumor types. Its greatest effectiveness is in the treatment of testicular tumors where it

is effective against tumors resistant to treatment with other drugs. It is most effective when combined with bleomycin and cisplatin. Etoposide also has an important role in the treatment of small cell lung carcinomas where it is often combined with cisplatin while teniposide appears to be effective for the treatment of ALL and childhood neuroblastomas as well as brain tumors in adults (Halkidou *et al.* 2004; Song *et al.* 2005).

Toxicity: The principal dose-limiting toxicity of these drugs is bone marrow depression, primarily leukopenia and thrombocytopenia. Nausea and diarrhea are common but not severe while mucositis can be severe at higher doses. Other toxic effects seen include fever, chills, erythema. Allergic reactions have been noted in some patients (Sakuma *et al.* 2006).

2.8.7 Camptothecin

The camptothecins are a new class of chemotherapeutic agents with a novel mechanism of action targeting the nuclear enzyme topoisomerase I. One derivative with a lot of promise is Irinotecan. It is one of the most active compounds available for the treatment of non-small cell lung cancer. Leukopenia and diarrhea are the most severe toxicities seen. Nausea and vomiting are common but manageable (Ackermann *et al.* 2007).

2.8.8 Other class of anticancer drugs

There are other drugs and biological treatments that are used to treat cancer, but aren't usually considered chemotherapy. While chemotherapy drugs take advantage of the fact that cancer cells divide quickly, these drugs target other properties that make cancer cells different from normal cells. They often have less serious side effects than those commonly caused by chemotherapy drugs because they are targeted to affect cancer cells, not normal healthy cells. Many are used along with chemotherapy. (Oudard, 2013). Examples of targeted therapies include:

Signal transduction inhibitor (Imatinib): In 2001 the Food and Drug Administration announced the approval of Imatinib mesylate, also known as a

promising new oral treatment for patients with Chronic Myeloid Leukemia (Droogendijk *et al.* 2006).

Tamoxifen: is a competitive inhibitor of estradiol binding to the estrogen receptor. By binding to the receptor it competes with the binding of endogenous estradiol and its major therapeutic effect reflects this antiestrogenic mechanism (Vehmanen *et al.* 2006). Tamoxifen is used in the treatment of metastatic breast cancer. It is used alone for palliation of advanced breast cancer in women with estrogen receptor positive tumors, and it is used for adjuvant therapy in certain types of early stage disease (Criscitiello *et al.* 2011). Tamoxifen is very well tolerated. The most frequent side effect is acute nausea and vomiting. This usually disappears after a few weeks and it can be reduced by taking the drug with meals. More chronic effects include hot flushes, transient/mild thrombocytopenia and leukopenia, vaginal bleeding, skin rashes, hypercalcemia, retinopathy and corneal opacities with high dose long-term therapy (Vehmanen *et al.* 2006; Criscitiello *et al.* 2011).

Anastrozole: This is a selective non-steroidal aromatase inhibitor (aromatase is a P450 enzyme that catalyzes various steps in the conversion of androgen to estrogen). It is used for the treatment of postmenopausal women with advanced breast cancer that has progressed during treatment with tamoxifen (Howell *et al.* 2005).

Immunotherapy: Some drugs are given to people with cancer to help their immune systems recognize and attack cancer cells (Weiner *et al*. 2010). There are different types of immunotherapy that include: Active immunotherapies which stimulate the body's own immune system to fight the disease. Passive immunotherapies such which do not rely on the body to attack the disease but employ immune system components such as antibodies created outside the body to destroy cancer cells. Example of passive immunotherapies include: Alemtuzumab, Bevacizumab, Cetuximab, Rituximab, Trastuzumab (Weiner *et al*. 2010; Palucka and Banchereau, 2013).

Examples of active immunotherapies include: Rituximab, Alemtuzumab, BCG, interleukin-2 (IL-2) and interferon alfa (Palucka and Banchereau, 2013).

CHAPTER THREE
MATERIALS AND METHODS

3.1 Study site

The study site was Lagos University Teaching Hospital (LUTH) Lagos, Nigeria which was established in 1962 and has grown from a 300 bed hospital to about 761 beds presently. The Oncology Department of LUTH is a designated center of excellence in cancer care. The department is equipped with functional Linear Accelerator Machine since year 2007 with about 6,000 registered patients that undergo both chemotherapy and radiotherapy.

3.2 Study design

A retrospective, descriptive design was adopted for the study which was conducted on patients undergoing cancer chemotherapy at the Oncology clinic of Lagos University Teaching Hospital.

3.3 Sampling method and sample size

A convenient sampling method known as the Slovins statistical formula for sample size with finite population was used. A total sample number of 6500 which was the estimated number of cancer patients obtained from the registry was used as "N"

$n = N / (1 + Ne^2)$: where:

n = Number of samples

N = Total population

e = Error tolerance

CI= Confidence interval

e= 1-CI (95%) or 0.95 =0.05

A total of 250 files were sampled out where 170 files satisfied the inclusion criteria of the study.

3.4 Health records retrieval

Comprehensive health records were collected from October 2015 to January, 2016 and subsequently studied for adverse drug reactions. The diagnosis and demographic details of the patients were recorded. Details of the medications given, nature of ADR, suspected drug(s), and medications used in management of ADR were carefully recorded.

3.5 Data collection instrument

For capturing of data, a modified Nigeria National Pharmacovigilance Centre (NPC) form for reporting of suspected ADRs was used. The form allowed data to be organized into:

A. Demography

B. Diagnosis

C. Suspected ADRs

D. Suspected Medications

E. Causality class

F. Severity class

G. Management of ADR

3.6 Inclusion and exclusion criteria

Patients of both sexes and all ages diagnosed with cancer and treated with chemotherapy at the same time developing at least one ADR during or after the treatment period were included in the study. Patients who developed ADR due to blood products, concomitant drugs, intentional or accidental poisoning or history of drug abuse/intoxication were excluded.

3.7 Data analysis

The recorded ADRs were assessed for causality using the Naranjo's algorithm which has 10 objective questions with three options for answers “yes”, “no” or “do not know”. Scores were given accordingly and the causality of the drug was classified as “definite,” “probable,” “possible,” and “unlikely.” The severity of

the reported reactions was assessed using modified Hartwig scale. The scale classifies severity of ADR as “mild,” “moderate,” or “severe” with various levels, depending on a number of factors like the requirement for change in treatment, duration of hospital stay and the disability produced by the ADR. The data collected were coded using Microsoft excel and analyzed using SPSS (Statistical Package for the Social Sciences), IBM Corporation, version 20. The results were subjected to descriptive statistical analysis to study the characteristics of ADRs using frequencies, percentages, tables, pie chat and bar chats.

3.8 Ethical approval

Ethical approval for the study was obtained from LUTH Research and Ethics committee dated 12th October, 2015 with LUTH Health Research Ethics committee (LUTHHREC) reference number ADM/DCST/HREC/APP/546 prior to conducting this research.

CHAPTER 4

RESULTS AND DISCUSSIONS

4.1 Results

4.1.1 Demographic information

Of the 250 case notes of patients sampled out, 170 records were found worthy to be included in the study, the rest were rejected for failing to meet up with the inclusion criteria. A total of 96(56.47%) patients who developed ADRs due to cancer chemotherapy were females while 74(43.53%) were males. Further analysis revealed that married patients recorded higher incidence of cancer (65.80%) compared to patients that were single (34.13%). The prevalence of cancers was found to be most common in the age groups 51 – 60 years (29.40%) and 61 – above (24.70%). The least was seen in the age group of 11 – 20 years (2.35%).

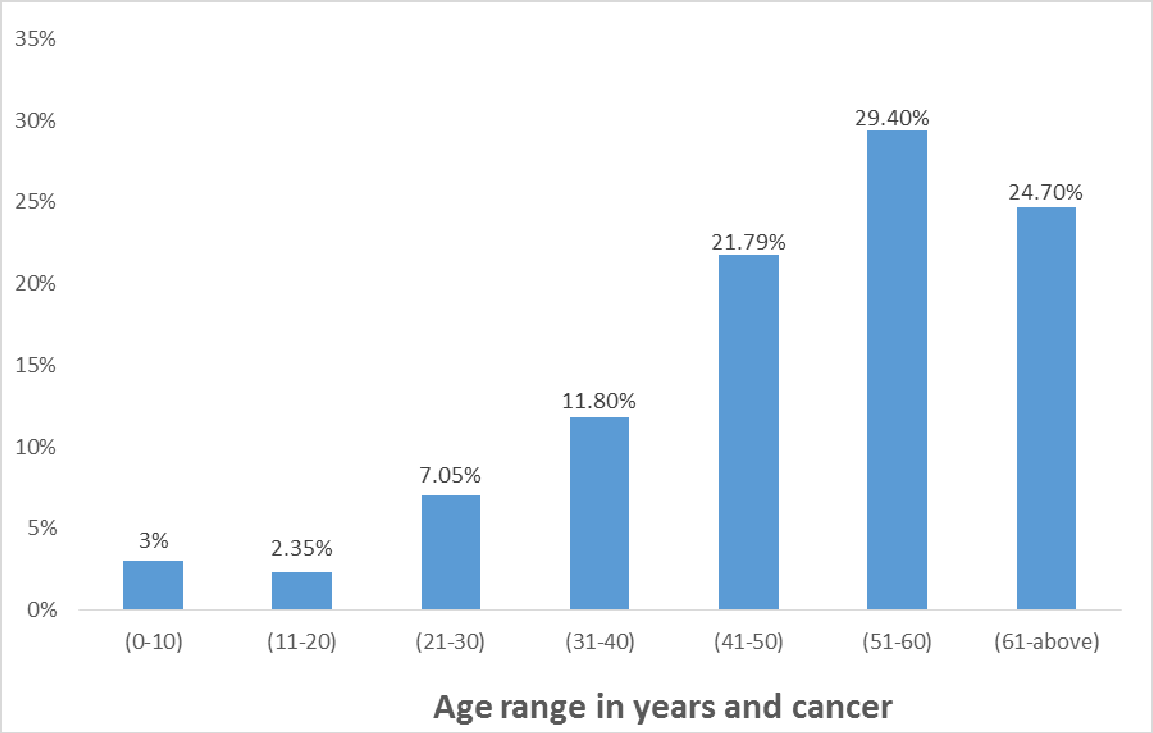

Figure 4.1 Age range distribution of cancers in LUTH

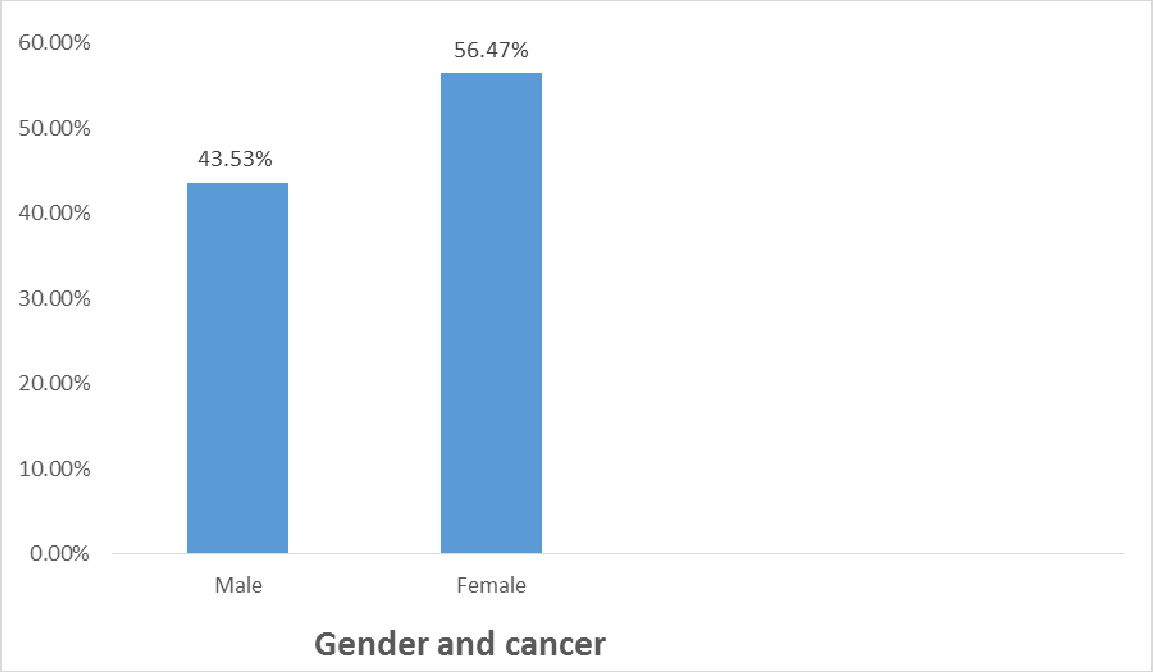

Figure 4.2 Gender distribution of cancer patients in LUTH

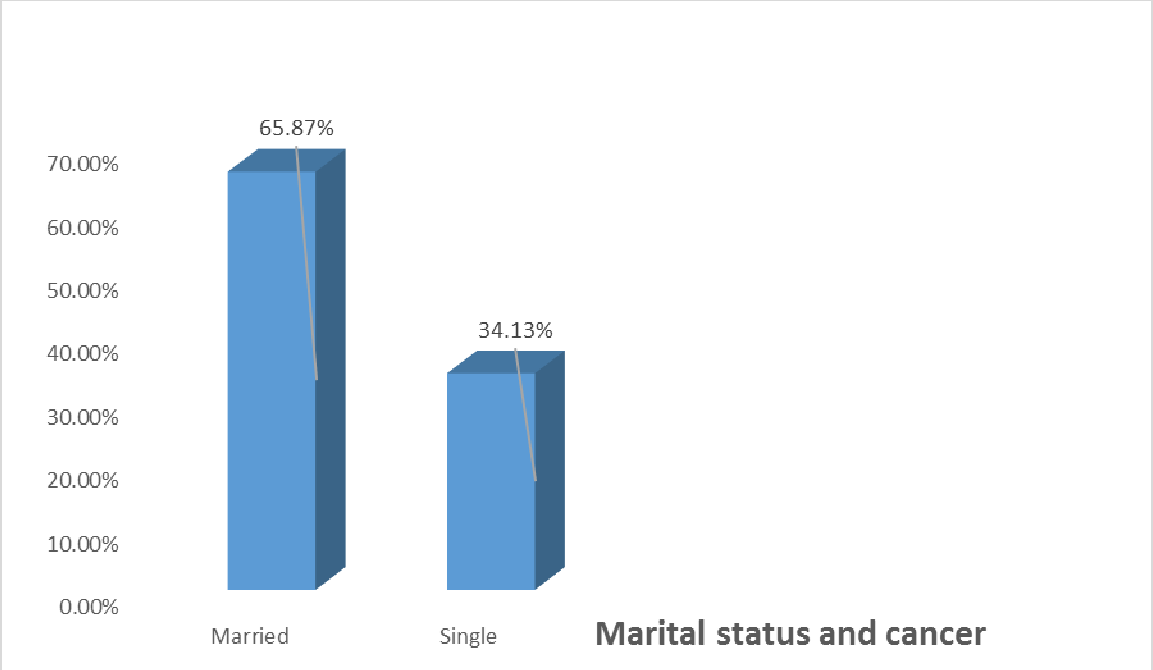

Figure 4.3 Marital status and cancer frequency in LUTH

Breakdown of occupational category of patients showed 41.80% of the studied population to be business men/women. Civil servants and other earners of regular salary made up 24.70%, while those that were unemployed comprised

18.20%. Students' population also stood at 10.60%, whereas other categories of patients such as farmers and clerics made up 4.70%.

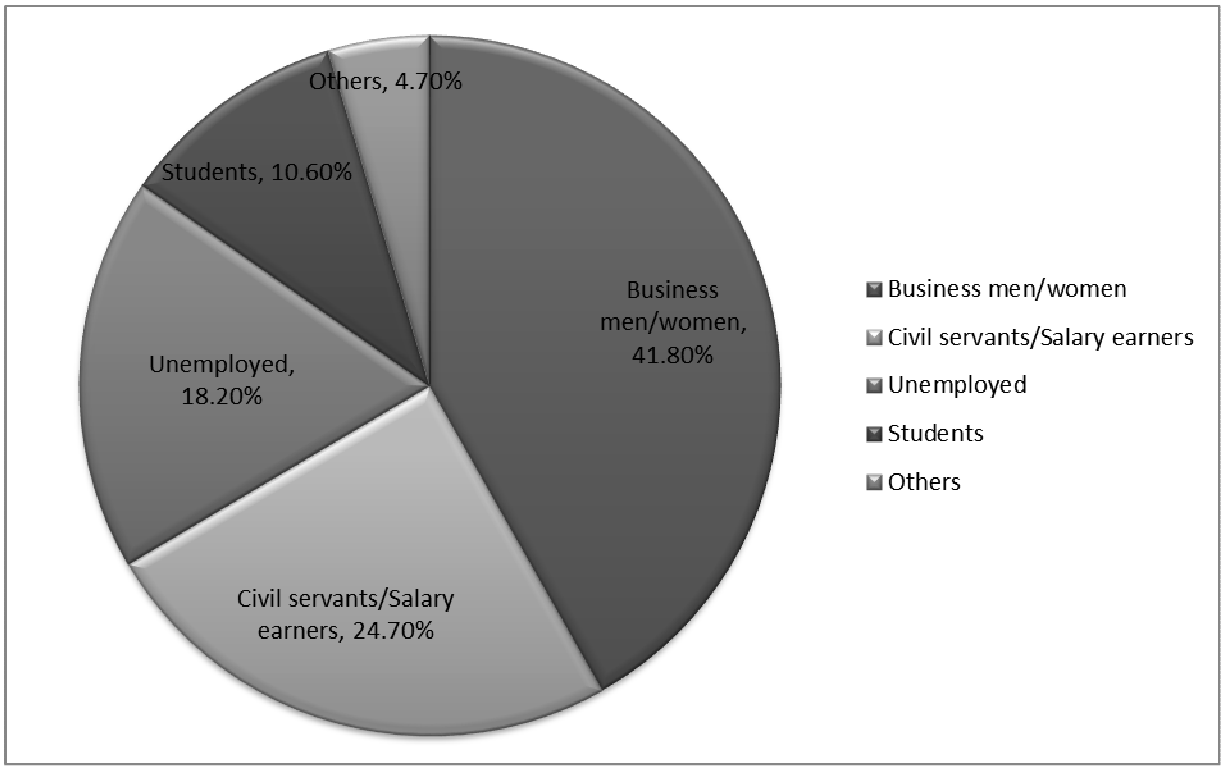

Figure 4.4 Occupational category of cancer patients in LUTH

4.1.2 Clinical diagnosis

Analysis of the clinical diagnosis data showed that patients were mostly affected by breast cancer (25.30%) followed by colorectal cancer (21.20%). Cervical and prostate cancer both occurred in similar frequencies of 10.00% each, while lung, ovarian, liver and nasopharyngeal cancers were encountered at frequencies of 7.05%, 5.30%, 4.12% and 3.51% respectively. The least malignancies seen were Acute Myeloid Leukaemia (AML) and Non-Hodgkin's Lymphoma (NHL) with each occurring at a frequency of 0.59%.

Table 4.1 Disease profile of 170 patients with cancer in LUTH

Type of malignancy		Frequency	Percentage (%)
1.	Breast Cancer	43	25.30
2.	Colorectal Cancer	36	21.20
3.	Cervical Cancer	17	10.00

4.	Prostate Cancer	17	10.00
5.	Lungs Cancer	12	7.05
6.	Ovarian Cancer	09	5.30
7.	Liver Cancer	07	4.12
8.	Nasopharyngeal Cancer	06	3.51
9.	Burkitt Lymphoma	03	1.76
10.	Gastric Cancer	03	1.76
11.	Bladder Cancer	03	1.76
12.	Head and Neck Cancer	03	1.76
13.	Acute Lymphoblastc Leukemia	03	1.76
14.	Retinoblastoma	02	1.18
15.	Bone Cancer	02	1.18
16.	Kaposi Sarcoma	02	1.18
17.	Acute Myeloid Leukemia	01	0.59
18.	Non-Hodgkin's Lymphoma	01	0.59
	TOTAL	**170**	**100%**

Further analysis based on gender revealed the cancer with the highest prevalence in female to be breast cancer (44.80%), followed by cervical and ovarian cancers with 17.70% and 9.38% respectively. In males, colorectal cancer (41.90%) was found to be most common, followed by prostate (23.00%) and lungs (10.80%).

Table 4.2 Distribution of cancers according to gender in LUTH

Type of cancer		**Females (%)**	**Males (%)**
1.	Breast Cancer	43(44.80)	--
2.	Colorectal Cancer	05(5.20)	31(41.90)
3.	Cervical Cancer	17(17.70)	--

4.	Prostate Cancer	--	17(23.00)
5.	Lungs Cancer	04(4.17)	08(10.80)
6.	Ovarian Cancer	09(9.38)	--
7.	Liver Cancer	02(2.08)	05(6.76)
8.	Nasopharyngeal Cancer	02(2.08)	04(5.41)
9.	Burkitt Lymphoma	01(1.04)	02(2.70)
10.	Gastric Cancer	02(2.08)	01(1.35)
11.	Bladder Cancer	01(1.04)	02(2.70)
12.	Head and Neck Cancer	01(1.04)	02(2.70)
13.	Acute Lymphoblastic Leukemia	02(2.08)	01(1.35)
14.	Retinoblastoma	02(2.08)	--
15.	Bone Cancer	02(2.08)	--
16.	Karposi Sarcoma	02(2.08)	--
17.	Acute Myeloid Leukemia	01(1.04)	--
18.	Non-Hodgkin's Lymphoma	--	01(1.35)
	TOTAL	**96(100)**	**74(100)**

4.1.3 Frequency and number of associated ADRs for each drug

Breakdown of the frequency and number of associated ADRs to individual chemotherapeutic agent showed that 5-Fluorouracil accounted for most number of prescriptions and ADRs at 16.80% and 18.90% respectively. Cisplatin recorded 12.20% prescriptions and ADRs of 15.90%. Doxorubicin with a higher prescription rate of 11.40% recorded fewer ADRs of 9.00% compared to cyclophosphamide that had a prescription frequency of 10.20% and ADRs of 11.30%. Estramustine and Idarubicin with 0.28% prescription each recorded no ADR.

Table 4.3 Frequency of prescription and recorded ADR for each drug

Drug Name		No. of Prescriptions (%)	No. of ADR (%)
1.	5-Fluorouracil	59(16.80)	82(18.90)

2.	Cisplatin	43(12.20)	69(15.90)
3.	Cyclophosphamide	36(10.20)	49(11.30)
4.	Doxorubicin	40(11.40)	39(9.00)
5.	Paclitaxel	32(9.10)	36(8.30)
6.	Oxaliplatin	33(9.40)	31(7.16)
7.	Docetaxel	21(5.97)	26(6.00)
8.	Gemcitabine	23(6.54)	24(5.64)
9.	Carboplatin	08(2.27)	15(3.46)
10.	Capecitabine	11(3.13)	14(3.23)
11.	Vincristine	11(3.13)	10(2.31)
12.	Goserelin	07(1.99)	09(2.08)
13.	Epirubicin	08(2.27)	08(1.85)
14.	Bicalutamide	05(1.42)	06(1.36)
15.	Methotrexate	06(1.72)	05(1.15)
16.	Etoposide	03(0.85)	03(0.69)
17.	Cytarabine	01(0.28)	03(0.69)
18.	Tamoxifen	02(0.57)	02(0.46)
19.	Anastrazole	01(0.28)	02(0.46)
20.	Estramustine	01(0.28)	--
21.	Idarubicin	01(0.28)	--
	TOTAL	**352(100)**	**433(100)**

4.1.4 Drug classes responsible for ADRs

Analysis of the chemotherapeutic classes associated with ADRs revealed that the antimetabolites were responsible for most ADRs with a frequency of 29.61%. This was followed by platinum compounds (26.52%), microtubules inhibitors (16.67%), alkylating agents (11.30%), antibiotics (10.85%), hormonal inhibitors (4.36%) and chromatin inhibitors (0.69%).

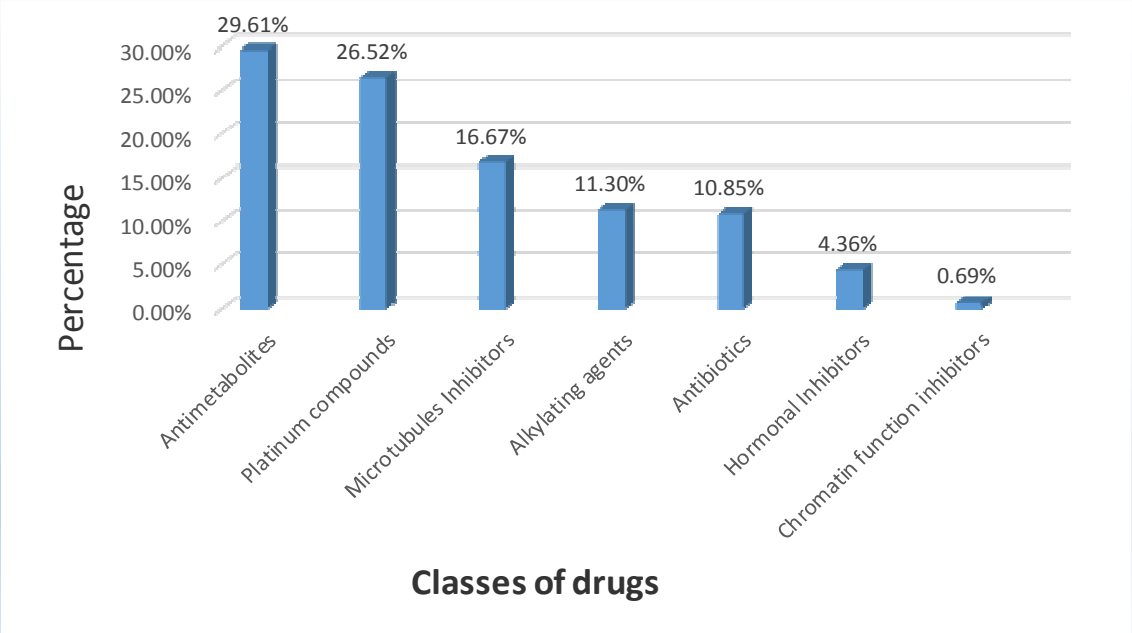

Figure 4.5 Chemotherapeutic classes and frequencies of ADRs

4.1.5 Frequency of prescriptions and ADRs for each regimen

The frequency of prescriptions and recorded ADRs for each regimen showed that the FLOX (5FU/Oxaliplatin) combination with 14.70% prescriptions recorded ADRs of 15.00%. The FAC regimen (5FU/Doxo/Cyclopho) followed with 8.82% prescriptions and 10.20% ADRs, while cisplatin/5FU has prescriptions of 6.50% and ADRs of 8.08%.

Table 4.4 Frequency of prescriptions and recorded ADRs per regimen type

	Type of Regimen	No. of Prescriptions (%)	No. of ADR (%)
1.	5-Fluorouracil/Oxaliplatin	25 (14.70)	65 (15.00)
2.	Cylophospham/Doxorubucn/5FU	15 (8.82)	44 (10.20)
3.	Cisplatin/5FU	11 (6.50)	35 (8.08)
4.	Gemcitabine/Cisplatin	10 (5.88)	27 (6.23)
5.	Cisplatin/Paclitaxel	10 (5.88)	23 (5.31)
6.	Doxorubicin/Paclitaxel	09 (5.29)	21 (4.85)
7.	Oxaliplatin/Capecitabine	08 (4.81)	20 (4.62)
8.	Vincristin/Cyclophosp/Doxorubicn	06 (3.53)	20 (4.62)
9.	Docetaxel/Prednisolone	09 (5.29)	18 (4.16)
10.	Gemcitabine/Paclitaxel	08 (4.71)	18 (4.16)
11.	Doxorubicin/Cisplatin	05 (2.94)	12 (2.73)
12.	BicalutamideGoserelin	05 (2.94)	11 (2.54)
13.	Cyclophosphamid/Epirubicin/5FU	04 (2.35)	11 (2.54)
14.	Cyclophosphamid/Vincristine/5FU	03 (1.77)	10 (2.30)
15.	Carboplatin/Docetaxel	04 (2.35)	09 (2.08)
16.	Docetaxel/Cisplatin	04 (2.35)	08 (1.85)
17.	Cyclophosphamide/MTX/5FU	03 (1.77)	08 (1.85)
18.	Cyclophosphamide	03 (1.77)	08 (1.85)
19.	Carboplatin/Gemcitabine	03 (1.77)	07 (1.62)
20.	Epirubicin/Cisplatin	02 (1.18)	07 (1.62)
21.	Capecitabine	03 (1.77)	05 (1.16)
22.	Tamoxifen/Epirubicin	02 (1.18)	05 (1.16)
23.	Etoposide/Vincristine	02 (1.18)	05 (1.16)
24.	Doxorubicin/Cyclophosphamide	02 (1.18)	05 (1.16)
25.	Doxorubicin	02 (1.18)	04 (0.92)

26.	Goserelin	02 (1.18)	04 (0.92)
27.	Gemcitabine/Docetaxel	02 (1.18)	04 (0.92)
28.	Paclitaxel	02 (1.18)	03 (0.69)
29.	Carboplatin/Paclitaxel	01 (0.59)	03 (0.69)
30.	Cytarabine/Idarubicin/Etoposide	01 (0.59)	03 (0.69)
31.	Carboplatin/5FU	01 (0.59)	03 (0.69)
32.	Doxorubicin/Cisplatin/Paclitaxel	01 (0.59)	03 (0.69)
33.	Anastrazole	01 (0.59)	02 (0.46)
34.	Estramustine/Docetaxel	01 (0.59)	02 (0.46)
	TOTAL	**170 (100%)**	**433 (100%)**

4.1.6 Frequency of adverse drug reactions

Analysis of the ADRs revealed that a total of 433 types were encountered in the study with nausea and vomiting accounting for 21.50%. Alopecia, other GI symptoms, skin rash/pruritus, oral mucositis, constipation and diarrhoea were observed to have a prevalence rate of 17.10%, 15.80%, 8.45%, 7.16%, 6.00% and 4.16% respectively. The lowest ADRs observed from the study were gynaecomastia, thrombocytopenia, ototoxicity, erythema and peripheral neuropathy with each accounting for 0.23% of the ADRs.

Table 4.5 Types and frequency of ADRs in oncology clinic of LUTH

Type of ADR		Count	Percentage (%)
1.	Nausea and Vomiting	93	21.50
2.	Alopecia	74	17.10
3.	Other GI symptoms	69	15.90
4.	Skin rash/Pruritus	33	7.62
5.	Oral mucositis	31	7.16
6.	Constipation	26	6.00
7.	Diarrhoea	18	4.16
8.	Nausea	11	2.54

9.	Leukopenia	10	2.31
10.	Anaemia	09	2.08
11.	Anorexia	08	1.85
12.	Nail discolouration	07	1.62
13.	Fever	06	1.39
14.	Neutropenia	04	0.92
15.	Headache	04	0.92
16.	Tinnitus	04	0.92
17.	Hypotension	04	0.92
18.	Insomnia	03	0.69
19.	Dyspnoea	03	0.69
20.	Hiccups	02	0.46
21.	Eye irritation	02	0.46
22.	Myalgia	02	0.46
23.	Dermatitis	02	0.46
24.	Numbness on nails	02	0.46
25.	Gyanaecomastia	01	0.23
26.	Thrombocytopenia	01	0.23
27.	Ototoxicity	01	0.23
28.	Erythema	01	0.23
29.	Peripheral neuropathy	01	0.23
30.	Maculopapular rash	01	0.23
	TOTAL	**433**	**100**

4.1.7 Causality and severity rating of reported ADRs

Causality breakdown of the ADRs showed 66.48% to be “Possible” based on the Naranjo ADR probability scale, while 33.52% fell within the “Probable” classification. There were no cases of “Doubtful” or “Definite” ADRs. The Hartwig severity scale showed 63.50% of the 433 ADRs documented to be

"Moderate" while 35.11% were "Mild". About 1.39% of the total ADRs that include thrombocytopenia, ototoxicity and tinnitus were found to be "Severe".

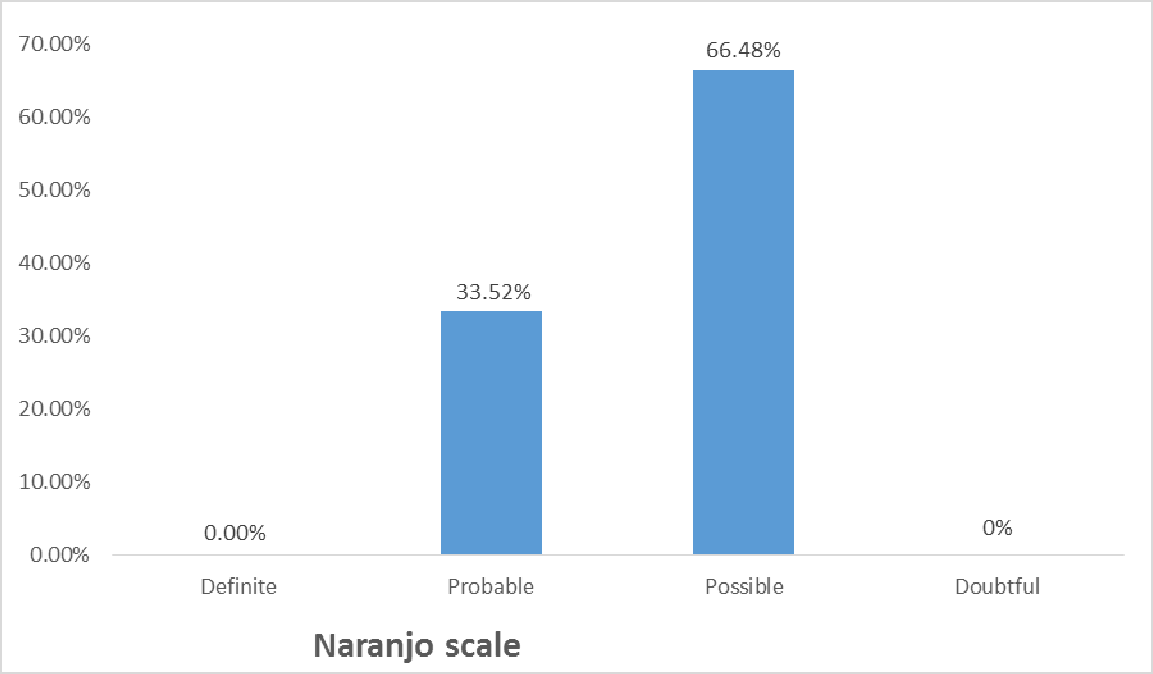

Figure 4.6 Naranjo causality distribution of recorded ADRs

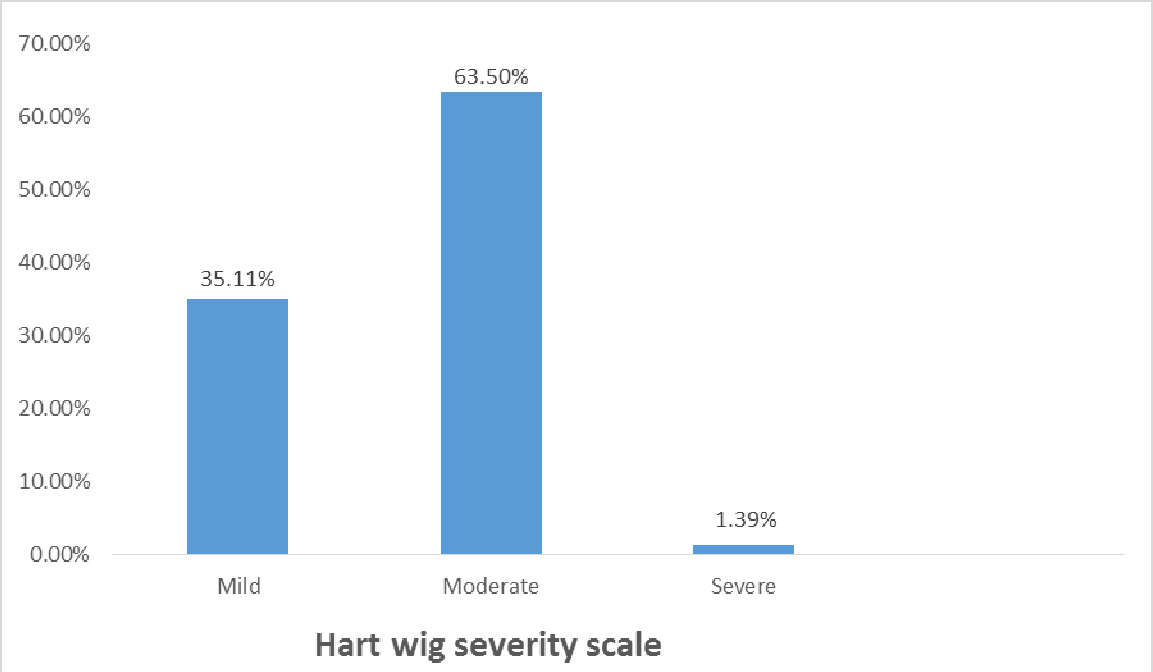

Figure 4.7 Hart wig severity distribution of recorded ADRs

4.1.8 Chi-square Tests

From the chi square analysis carried out using the SPSS (Statistical Package for the Social Sciences), IBM Corporation, version 20, the following deductions

were made on the Naranjo causality result:

- The association (pearson chi square) between the drugs suspected to cause the ADRs and the frequency of occurrence of the ADRs in the presenting patients was significant when the reactions were scored as probable on the Naranjo scale ($p<0.001$, dF 104).
- The association (pearson chi square) between the drugs suspected to cause the ADRs and the frequency of occurrence of the ADRs in the presenting patients was also significant when the reactions were scored as possible on the Naranjo scale ($p<0.001$, dF 360).

Table 4.6: Chi-Square Tests

NARANJO		Value	df	Asymp. Sig. (2-sided)
Probable	Pearson Chi-Square	289.414[b]	104	.000
	Likelihood Ratio	109.769	104	.330
	Linear-by-Linear Association	4.220	1	.040
	N of Valid Cases	57		
Possible	Pearson Chi-Square	1011.987[c]	360	.000
	Likelihood Ratio	398.246	360	.080
	Linear-by-Linear Association	3.246	1	.072
	N of Valid Cases	363		
Total	Pearson Chi-Square	1152.738[a]	450	.000
	Likelihood Ratio	540.070	450	.002
	Linear-by-Linear Association	9.519	1	.002
	N of Valid Cases	420		

From the chi square analysis carried out using the SPSS (Statistical Package for the Social Sciences), IBM Corporation, version 20, the following deductions were made on the Hartwig severity result:

- The association (pearson chi square) between the drugs suspected to

cause the ADR and the occurrence of the ADR in the presenting patients was significant when the reactions were scored as mildly severe (p<0.001, dF 156).

- The association (pearson chi square) between the drugs suspected to cause the ADR and the frequency of occurrence of the ADR in the presenting patients was significant when the reactions were scored as moderately severe (p<0.001, dF 340).
- The association (pearson chi square) between the drugs suspected to cause the ADRs and the frequency of occurrence of the ADRs in the presenting patients was not significant when the reactions were scored as Severe (p=0.05, dF 12).
- The association (pearson chi square) between the drugs suspected to cause the ADRs and the frequency of occurrence of the ADRs in the presenting patients was significant when the reactions were considered in totality- without considering the Hartwig ranking of ADRs severity (p<0.001).

Table 4.7: Chi-Square Tests

HARTWIG		Value	Df	Asymp. Sig. (2-sided)
Mild	Pearson Chi-Square	367.219[b]	156	.000
	Likelihood Ratio	172.409	156	.175
	Linear-by-Linear Association	.211	1	.646
	N of Valid Cases	129		
Moderate	Pearson Chi-Square	910.768[c]	340	.000
	Likelihood Ratio	368.650	340	.137
	Linear-by-Linear Association	10.682	1	.001
	N of Valid Cases	284		
Severe	Pearson Chi-Square	21.000[d]	12	.050
	Likelihood Ratio	16.152	12	.184
	Linear-by-Linear Association	.064	1	.800
	N of Valid Cases	7		

Total	Pearson Chi-Square	1152.738[a]	450	.000
	Likelihood Ratio	540.070	450	.002
	Linear-by-Linear Association	9.519	1	.002
	N of Valid Cases	420		

4.1.9 Prevalence of adverse drug reactions in age groups and gender

The data obtained showed that ADRs were more prevalent in the age group of 51 – 60 years (31.20%) followed by age group 61 – above (22.90%). The age group 41 – 50 years also recorded significant ADRs of 19.60%, while the least ADRs were observed in the age group 11 – 20 years (2.77%). Further analysis based on gender revealed the highest prevalence of ADRs in females (65.50%) compared to males (39.50%) (Figure 4.5).

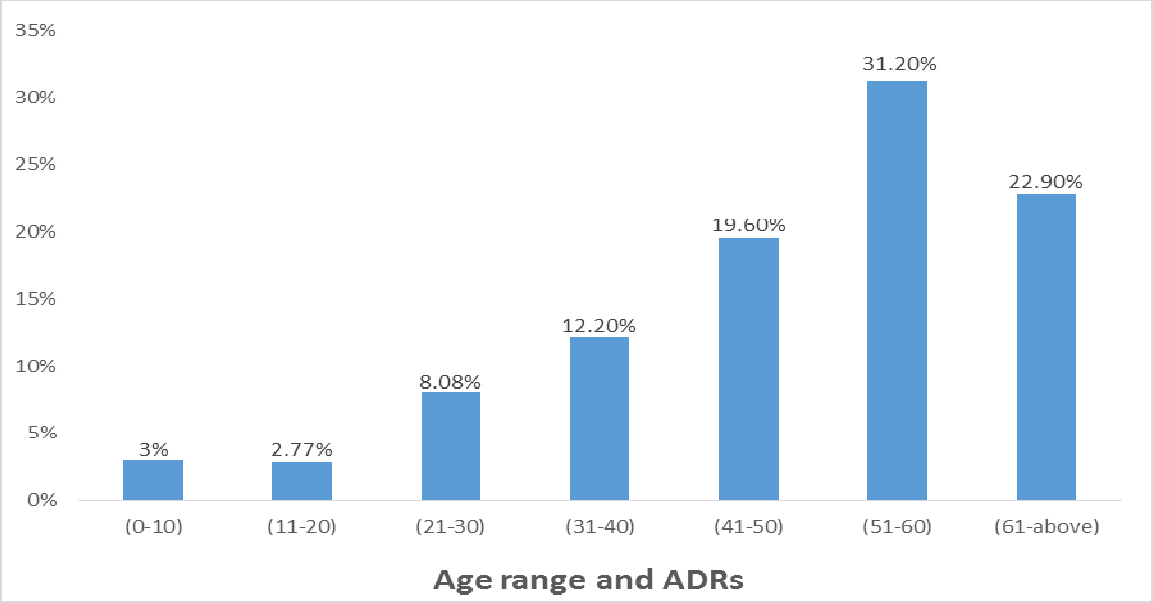

Figure 4.8 Prevalence of ADRs in age groups

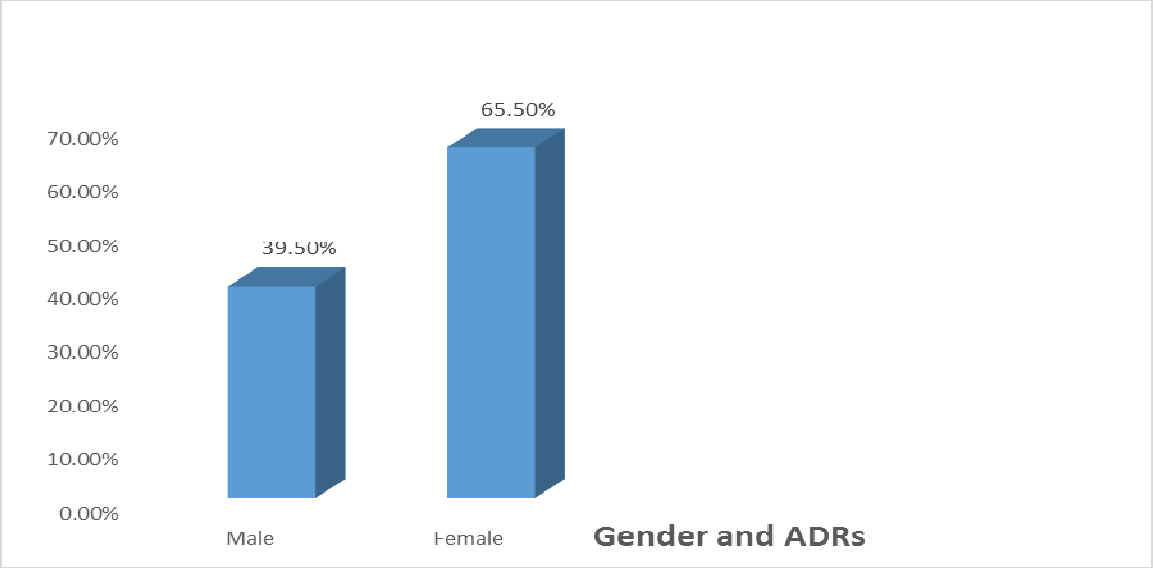

Figure 4.5 Prevalence of ADRs in genders

4.2 Medications used in the management of the ADRs in LUTH

A total of 249 medications were prescribed to manage the recorded adverse drug reactions. The serotonin $5HT_3$ receptor antagonist ondansetron accounted for 24.90% of the prescriptions followed by proton pump inhibitors with 14.50% prescriptions. Dexamethasone and chlorpheniramine followed with 13.70% and 12.50% prescriptions respectively. However, promethazine (1.21%) accounted for the lowest number of prescriptions.

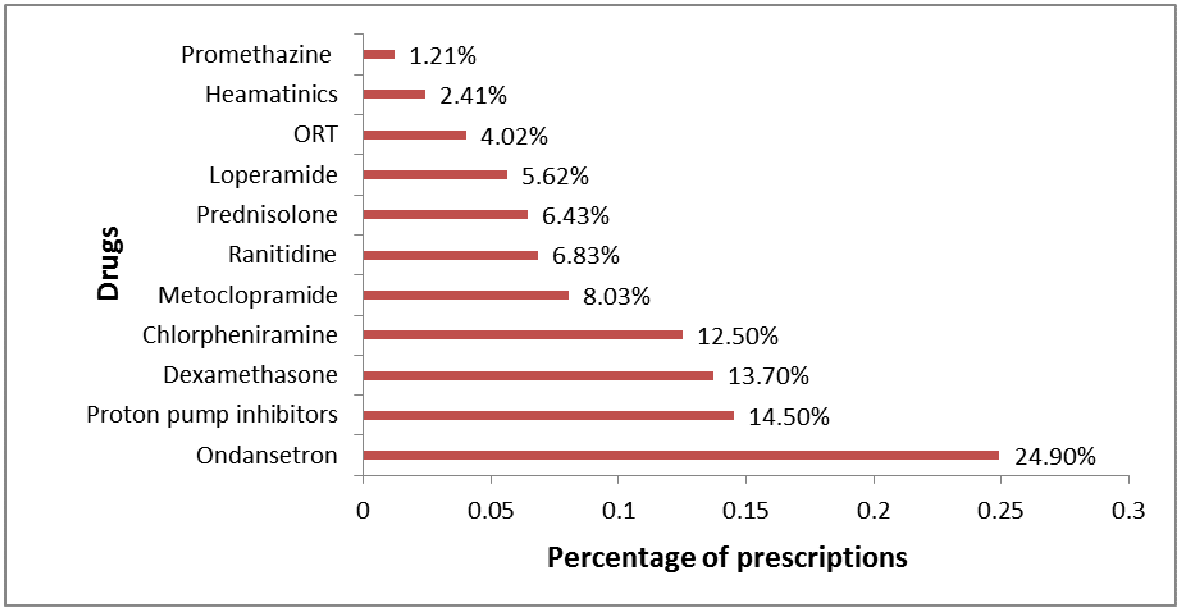

Figure 4.10 Medications used in the management of the ADRs in LUTH

4.2.1 Discussions

A study by Jinichi *et al.* (2014) at the Institute of Medical Science, University of Tokyo showed high prevalence of adverse drug reactions in cytotoxic drugs. Extensive literature search showed no previous studies on ADRs in cytotoxic agents in Nigeria.

In the present study, of the 170 patients studied 56.47% were females while 43.53% were males. These findings are similar to a study carried out in an oncology unit of a cancer research institute in Meldova, Italy by Tenti *et al.* 2014 who reported 57.40% females and 42.60% males. In contrast, Yash *et al*. (2014) in a Teaching Hospital in Gujarat India observed higher incidences in males (54.29%) compared to females (45.71%). Some reasons for these differences can be hormonally related e.g. meningioma which is more common in females because the tumor has estrogen and progestin receptors (Arnold, 2000). Many more differences are due to behavioral pattern of the sexes as more women are historically more overweight, while males have higher incidence of smoking (more lung cancer) and higher alcohol consumption (more liver cancer) (McCann, 2010).

A study by Sharma *et al.* (2015) from the Department of Pharmacology Pondicherry Institute of Medical Sciences India, reported the age group 51 – 60 years (26.20%) to be more prone to cancers. This is in consonance with the present study where age group 51 – 60 years has the highest prevalence of 29.40%. This observation can be explained by remarkable association of some studied cancers (breast, cervical, prostate etc.) with age (Battikhi *et al.* 2006).

Additionally, 65.80% of the patients were married while (34.13%) were singles. This corresponds to similar study by Poddar *et al.* (2009), in a Tertiary Care Hospital in Bangladesh who reported married (82.00%) and unmarried (12.00%). This view could be partly explained by the established association of some cancers to child bearing (Treth *et al.* 2013) and sexual intercourse (Akinwande *et al.* 2009). Business men/women constituted 41.80% of the present study group. Poddar *et al.* (2009) also revealed highest prevalence in the same category (30.00%) compared to other groups. Further breakdown of the present study showed civil servants/other salary earners to accumulate 24.70%, patients that are unemployed made up 18.20%, students' population with 10.60% and other class of patients comprising of groups such as clerics and farmers made up 4.70%.

The prevalence of different cancers revealed that patients were mostly affected by breast cancer (25.30%). This finding is similar to the study by Amartya, (2010) from the Oncology Unit of an Urban Multispecialty Hospital in India. Amartya also reported the 2^{nd}, 3^{rd}, 4^{th} and 5^{th} most frequent cancers to be lung, ovary, cervical and rectal cancers respectively. This is slightly different from the present study that showed the prevalence rate to be colorectal (21.20%), cervical (10.00%), prostate (10.00%) and lung (7.05%) in similar categories above.

Sub classification based on gender revealed the three most common cancers in females to be breast (44.80%), cervical (17.70%) and ovarian (9.38%), while colorectal (41.90%), prostate (23.00%) and lung (10.80%) were most seen in males. This finding is closely related to the study by Kirthi *et al*. (2014) in a Tertiary Hospital in Hydrabad who reported frequency of cancers in females to be breast (40.00%), cervical (11.40%) and ovarian (8.60%) while the common cancers in males were lung (10.00%), bladder (8.30%) and NHL (8.30%). A study by Morgan *et al*. (2013) from the Research Institute in Harvalhoehe, Berlin Germany reported the most frequent cancers in males to be colorectal (23.00%) followed by lung cancer (19.00%), while females have breast cancer

(49.00%) and colorectal cancer (13.00%) predominantly**.** Another study conducted at the Institute of Biochemistry and Biotechnology in Lahore Pakistan by Aslam *et al*. (2014) observed the frequent cancers in females to be breast cancer (61.00%) and uterine cancer (14.00%) while the most frequent cancer in males was GIT related cancer (30.00%).

This study also revealed the frequency of prescriptions and suspected ADRs of individual cancer chemotherapeutic agents. 5-Fluorouracil accounted for most prescriptions (16.80%) and suspected ADRs (18.90%). This was followed by cisplatin with ADRs of 15.90% and 12.20% prescriptions. Cyclophosphamide had 10.20% prescriptions and of 11.30% ADRs, while doxorubicin had 11.40% prescriptions and ADRs of 9.00%. The study by Tenti *et al.* (2014) in an Oncology Pharmacy unit in Meldova, Italy showed the five most frequent ADRs causing anticancer agents to be paclitaxel (19.90%), oxaliplatin (16.10%), carboplatin (14.00%), fluorouracil (11.20%) and gemcitabine (10.00%).

Further analysis from the present study based on the type of therapeutic regimen employed showed the FLOX regimen (5FU/Oxaliplatin) accounting for the greater number of prescriptions (14.70%) and ADRs of 15.00%. This is similar to the findings by Marilia *et al*. 2014 from the State University of Campinas in Brazil who observed the FLOX regimen to be at 22.50%. Subsequent breakdown from our study gives out the next regimen with most ADRs to be the FAC regimen (5FU/Doxorubicin/Cyclophosphamide) with ADRs of 10.20% and 15.00% prescriptions.

Among the chemotherapeutic classes, the antimetabolites were suspected to cause the most ADRs (29.61%) followed by the platinum compounds (26.52%). Microtubules inhibitors were third with 16.67% while alkylating agents (11.30%) and antitumor antibiotics (10.85%) occupied the fourth and fifth spot respectively. Similar study by Yash *et al.* (2014) showed the platinum compounds and antimetabolites to produce ADRs at frequencies of 54.29% and

48.71% respectively. However, the percentage representations indicating involvement of individual drugs/classes/regimen in adverse events should be viewed with caution as it may simply be dependent on the frequency of usage of the drug or therapeutic category. This observation was seen in the case of 5-fluorouracil (16.80% prescription) and cisplatin (12.20% prescriptions) having frequency of ADRs to be 18.90% and 15.90% respectively. A deviating example from this perspective was seen in the case of cyclophosphamide with prescriptions of 10.20% having more ADRs (11.30%) than doxorubicin with 11.40% prescriptions and ADRs of 9.00%.

Analysis of the encountered reactions showed nausea and vomiting (21.50%) to be the most prevalent ADR followed by alopecia (17.10%). Lakshmi *et al*., 2015 from the Department of Pharmacy, Chalapati Institute of Pharmaceutical Sciences reported alopecia (95.00%) and nausea/vomiting (82.00%) to be the two most occurring ADRs. Nausea and vomiting are very common side effects of cancer chemotherapeutic drugs which may induce vomiting by both a central action on the chemoreceptor trigger zone (CTZ) and a peripheral action on the gastrointestinal tract (Jordan *et al.* 2007). The basic principle of chemotherapy is to impair the mitotic and metabolic process of cancer cells. Unfortunately, certain normal cells and tissues with rapid metabolic and mitotic rates such as the hair follicles are also affected by the chemotherapy (Batchelor, 2001). Up to 90% of hair follicles undergo anagen which is an active growing phase of the follicles at a given time. The rapid hair growth as well as the high blood flow rate around the hair bulb leading to the accumulation of drugs is a key predisposing factor for rapid and extensive alopecia (Batchelor, 2001). Initially, majority of patients undergoing chemotherapy were expected to develop alopecia. However, although alopecia was the second most commonly encountered ADR in the present study, its manifestation occurred in less than half of the patients (43.50%) which was lower than the stated value by Trueb, 2009 who estimated incidence of alopecia in chemotherapy to be at 65.00%.

The lower figure observed may be as a result of higher prescriptions of 5-fluorouracil and oxaliplatin which have been shown to induce lower proportions of alopecia (Trueb, 2009).

From the present study, other GI symptoms (15.80%), skin rash/pruritus (8.45%) and oral mucositis (7.16%) occurred as the 3rd, 4th and 5th most common ADRs respectively, whereas Lakshmi *et al.* 2015 reported myelosuppression (42.00%), skin pigmentation (15.30%) and Itching (11.40%) in similar fashion above. Constipation and diarrhoea also occurred at frequencies of 6.00% and 4.16% respectively. Most GI symptoms including mucositis are due to the effect of chemotherapy on rapidly proliferating cells. Diarrhoea occurs because the epithelial cells of the GIT are destroyed by certain antineoplastic agents that promote poor digestion and absorption of nutrients (Marilia *et al*. 2014). Adverse events such as gynaecomastia, thrombocytopenia, ototoxicity, erythema, peripheral neuropathy and maculopapular rash were all encountered but in lesser frequencies of 0.23% each.

Causality status was assessed using the Naranjo adverse drug reaction probability scale where 66.48% of the reported ADRs had causality rating of "Possible" while 33.52% were termed "Probable". No reaction was found to be doubtful or definite. This finding is closely related to the study by Sharma *et al.* (2015) who got "possible" 65.40% and "probable" 34.40%. An ADR is termed "probable" if it occurred with a clear temporal relationship to drug administration and improves on drug withdrawal or treatment while "possible" is when there are some temporal relationship to drug administration but the effects could have been due to the basic or inter current illness (Farcas and Bojita 2009). Proving causality beyond Probable is a challenging and multi-disciplinary task because several drugs which in most cases have similar tendencies to cause same reactions are used together. Furthermore, there is the need to determine plasma concentration of the drug (Brahma *et al.* 2013).

Unfortunately, Therapeutic Drug Monitoring (TDM) is not common in the studied centre.

Based on the Hart wig severity scale 63.50% of the ADRs were found to be "Moderate", 35.11% were "Mild" while 1.39% were "Severe". This pattern is closely related to what was reported by Gunaseelan *et al.* 2014 from the Department of Pharmacology Regional Institute of Tropical Science Manipul who observed severity to be "Moderate" (74.10%), "Mild" (17.90%) and "Severe" (8.00%). An ADR is classified "moderate" when the suspected drug is withheld or an antidote or other treatment administered. "Severe" is when an ADR is fatal or potentially life threatening while "mild" is the ADR that requires no treatment and no effect on length of stay in hospital (Hart wig *et al.* 1992).

The ADRs prevalence revealed that practically all the patients on cytotoxic drugs suffer one or more ADRs. Data analysis from the study showed ADRs to occur most commonly in the age group 51 – 60 years (31.20%). This is comparable to the study conducted in a Tertiary Care Hospital in Nepal by Mallik *et al*. (2007) and similar to what was also obtained by Prasad *et al.* (2013) who reported ADRs prevalence in age group 50 – 59 years to be 42.00%. The observed increase in ADRs in elderly apart from higher cancer prevalence maybe attributed to decreased metabolising capacity and reduced excretory functions leading to accumulation of drugs in the body (Brahma *et al*. 2013). Adverse effects were also observed to have occurred more in female gender (65.50%) compared to males (34.50%). Another study by Kirthi *et al.* (2014) reported ADRs in both genders to occur in similar frequencies. However, increase in female gender from our study group in addition to higher cancer prevalence may also be due to the established facts that female patients are known to have 1.5 to 1.7 fold greater risk of developing ADRs compared to male patients (Rodenburg *et al.* 2011). The reasons for the increased risk are attributed to gender-related differences in immunological, hormonal and

pharmacokinetic factors. Additionally, women are also affected by lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate (Schwartz, 2007).

Majority of the encountered adverse events were managed or pre managed using therapeutic interventions. Anticancer agents such as cisplatin and cyclophosphamide are highly emetogenic, but the use of antiemetics especially the newer classes have significantly decreased the morbidity associated with chemotherapy induced nausea and vomiting (Lihara *et al.* 2011). About 249 intervention prescriptions were recorded. The most commonly prescribed antiemetics from the study were ondansetron (24.90%), dexamethasone (13.70%) and metoclopromide (8.03%). This was different from what was obtained by Lakshmi *et al*. 2015, who reported metoclopramide (87.00%), followed by ondansetron (25.10%). Gastrointestinal symptoms such as heartburn, dyspepsia, abdominal pain, flatulence were managed mostly by proton pump inhibitors (14.50%) and ranitidine (6.83%). Anti-histamines such as chlorpheniramine (12.50%) were also significantly used to counter skin rash/pruritus and other allergic cases. Loperamide (5.62%) with or without Oral Rehydration Therapy (4.02%) were frequently prescribed for disturbing cases of diarrhoea while those with anaemia were given haematinics (2.41%) except in few cases were blood transfusion was administered.

Limitations discovered during the study were the inability to monitor suspected ADRs continuously because of the retrospective nature of the study and lack of scope for patients recall. Therapeutic drug monitoring is also not a common practice at the centre as such information on plasma drug concentration was not available. The short duration of the study also makes it difficult to detect chronic or delayed ADRs.

CHAPTER FIVE

SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Summary

Cancer is a disease that is spreading rapidly in Nigeria and the world. Several interventions are employed in the treatment of cancer to which chemotherapy is the most used for treatment of larger number of cancers. The anticancer agents employed in addition to attacking cancer cells are also highly toxic to normal rapidly dividing cells of the body due to narrow therapeutic index which leads to high incidence of adverse drug reactions. The aim and objectives of the study

was to study the pattern of adverse drug reactions due to cancer chemotherapeutic agents and to assess the causality, severity and management of these reactions in Lagos University Teaching Hospital, Nigeria. The study was a single centred retrospective study where health records of patients were studied and relevant information such as suspected ADRs, demography, diagnosis and treatments were extracted. The study revealed high prevalence of ADRs with cancer chemotherapeutic agents used in LUTH. A total of 433 ADRs were recorded from 170 patients of which 96 were females and 74 were males. Most common cancers encountered were breast cancer (25.30%), colorectal cancer (21.20%), cervical cancer (10.00%), prostate cancer (10.00%) and lung cancer (7.05%). Nausea/vomiting (21.50%) accounted for the most ADRs followed by alopecia (17.10%). Antimetabolites (28.00%), platinum compounds (24.00%), microtubules inhibitors (18.18%), antibiotics (13.93%) and alkylating agents (10.23%) were the most implicated drug classes causing ADRs. Naranjo causality assessment scale showed 66.48% of the reactions to be "possible" and 33.52% to be "probable" while the Hartwig severity assessment scale revealed majority of the reactions to be "moderate" (63.50%), followed by "mild" (35.11%) and "severe" (1.39%). Medications most commonly prescribed for the management of the reactions were ondansetron (24.90%), proton pump inhibitors (14.50%), dexamethasone (13.70%), chlorpheniramine (12.50%), metoclopramide (8.03%), ranitidine (6.83%), prednisolone (6.43%), loperamide (5.62%) and Oral Rehydration Salt (4.02%).

5.2 Conclusion

The study showed high prevalence of ADRs with the use of cancer chemotherapeutic agents. Females were slightly found to have more cancers (56.47%) compared to males (43.53%). 5FU and Cisplatin were found to be most drugs responsible ADRs. In terms of class of drugs, antimetabolites, platinum compounds and microtubules inhibitors were the class of drugs responsible for most ADRS. Nausea/vomiting, Alopecia and other GI symptoms

occurred as the most frequent ADRs. Naranjo method of classification showed the most ADRs to be possible (66.48%) followed by probable at 33.52%. Hart wig severity classification also showed majority of the ADRs to be moderate (63.50%) and mild (35.11%). Most of the medications for the management of the ADRs target emesis and gastrointestinal symptoms where ondansetron and proton pump inhibitors were most prescribed at 24.90% and 14.50% respectively. Majority of the ADRs were found not reported using the pharmacovigilance system, leading to under reporting. Medications mainly prescribed for ADRs tackle emesis and GIT symptoms. However, there is very low probability that other ADRs like hemorrhagic cystitis from cyclophosphamide, cardio and nephrotoxicity from antitumor antibiotics such as doxorubicin and cisplatin or tumor lysis syndrome due to cytotoxics did not occur in the subjects. Therefore, emphasis should be placed on strategies to prevent, minimize and manage ADRs of cytotoxics with peculiar side effects. The result of the study will serve as an insight into the various ADRs associated with the agents used in cancer chemotherapy in LUTH.

5.3 Recommendations

- Analysis of the study revealed that health care givers have not been fully active in reportage of ADRs which could be due to factors such as difficulty in causality assessment, low awareness or work burden. Emphasizes should be placed on the need to encourage the health service providers to report ADRs which may be considered common and not significant.
- Due to the increasing number of chemotherapeutic drugs available and their increasing use in the different patient population, it is important to track the potential adverse effects of these drugs. As such, health care givers should be constantly educated to look out for such, with emphasis to employ strategies to prevent, minimize and manage ADRs of cytotoxics with peculiar side effects.

- A multidisciplinary health team should be tasked with undertaking a long term prospective study covering larger number of patients with heamatological and other laboratory parameters.

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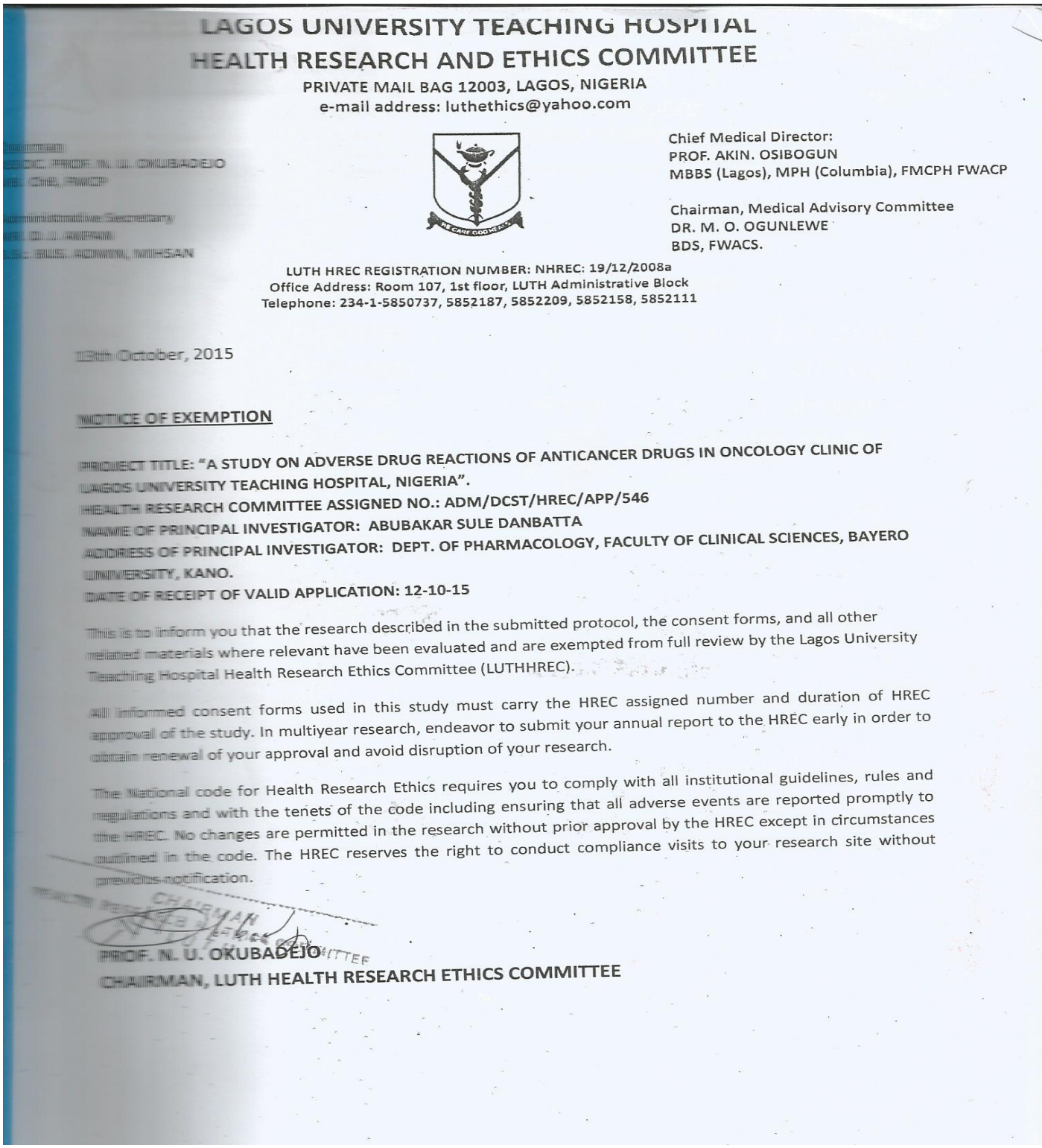
Appendix I: Adverse drug reaction reporting form

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

A	PATIENTS DETAILS
	CODE NAME..... AGE..... SEX : M ☐ F ☐ MARITAL STATUS: SINGLE ☐ MARRIED ☐ DIVORCED ☐ WIDOWED ☐ HOSPITAL/TREATMENT CENTRE..... WEIGHT ☐

B	ADVERSE DRUG REACTION			
DESCRIPTION	SUSPECTED DRUG NAME	CONCOMITANT DRUGS	CAUSALITY SCALE (Naranjo's scale)	PREMEDICATION/MANAGEMENT
I.				
II.				

Appendix II: Ethical committee approval



LAGOS UNIVERSITY TEACHING HOSPITAL
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BDS, FWACS.

LUTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st floor, LUTH Administrative Block
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13th October, 2015

NOTICE OF EXEMPTION

PROJECT TITLE: "A STUDY ON ADVERSE DRUG REACTIONS OF ANTICANCER DRUGS IN ONCOLOGY CLINIC OF LAGOS UNIVERSITY TEACHING HOSPITAL, NIGERIA".
HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/546
NAME OF PRINCIPAL INVESTIGATOR: ABUBAKAR SULE DANBATTA
ADDRESS OF PRINCIPAL INVESTIGATOR: DEPT. OF PHARMACOLOGY, FACULTY OF CLINICAL SCIENCES, BAYERO UNIVERSITY, KANO.
DATE OF RECEIPT OF VALID APPLICATION: 12-10-15

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been evaluated and are exempted from full review by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

CHAIRMAN

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE

Appendix III: Respondent informed consent form

Title of research: A study of the Adverse Drug Reaction of anticancer drugs in oncology clinic of Lagos University Teaching Hospital, Idi-Araba, Nigeria.

Name and affiliation of researcher: This study is being conducted by Pharm. Abubakar Sule Danbatta, postgraduate student of the Department of Pharmacology, Faculty of Clinical sciences, Bayero University, Kano.

Introduction: Adverse Drug Reactions (ADR) remain a substantial cause of morbidity and mortality among patients and further studies have shown that ADRs are the 4th leading cause of death in the USA (Showande and Oyelola, 2013). Anticancers are associated with severe adverse effects due to high toxicity and narrow therapeutic window. (Showande and Oyelola, 2013; Kirthi *et al.,* 2014).

Purpose(s) of the research: To study the incidence of adverse drug reactions of anticancer agents in oncology clinic at the Lagos University Teaching Hospital.

Procedure of the research: Data on demography, medication history, type of reactions, suspected drugs, social history, types of intervention and outcome of intervention will be obtained. The ADRs will be assessed for causality and severity using the Naranjo and Hartwig scales respectively modified.

Potential benefit(s): The results of the study will be presented to the administration of LUTH and Aminu Kano Teaching Hospital (AKTH) to influence decisions, evidence-based prescribing, documentation, collaboration and overall care of cancer patient.

Potential risks: The study is a retrospective study and deals with medical and pharmacy records hence pose no direct or indirect harm to patients and respondents.

Confidentiality: All information obtained in this study will be given code numbers and no name will be used. The confidentiality of the data will be ensured.

Willingness to participate: Your participation in this research is entirely voluntary and if you chose not to participate no punishment will be attached to your decision. You will not be paid any fees for taking part in this research. You may choose to withdraw from the research at any time.

What happens to research participants and communities when the research is over? The researcher will inform you of the outcome of the research through the health research ethics committee. There is no conflict of interest whatsoever.

Statement of person obtaining informed consent: I have fully explained this research to the respondent and given sufficient information, including the risks and benefits, to make an informed decision.

Date_____
Signature_____

Statement of person giving consent

I have read the description of the research. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form to keep for myself.

Date _____

Signature _____

For further enquiry, please contact:

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