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NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

Drug Related Problems in Cervical Cancer Patients on Chemotherapy in Ahmadu Bello University Teaching Hospital, Nigeria

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES

NEAR EAST UNIVERSITY

BY

SAGIR MUSTAPHA

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmacology

NICOSIA 2016

TURKISH REPUBLIC OF NORTHERN CYPRUS

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SAGIR MUSTAPHA

Master of Science in Pharmacology

Advisor

Assoc. Prof. Dr. Bilgen BASGUT

NICOSIA 2016

Dedication

I dedicate this work to Almighty Allah for giving me the knowledge, wisdom and strength. So also to my Dad, Mom, Siblings and my entire family for giving me the well-deserved encouragements and supports. To my mentors in Ahmadu Bello University for their unlimited encouragements. And finally to Kaduna State Government, for making it a reality to study overseas.

Special thanks to my one and only hocam, Assoc. Prof. Dr. Bilgen Basgut.

Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirements for the degree of **Master of Science in Pharmacology.**

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SAGIR Mustapha

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List of Abbreviations

S/No.	Abbreviations	Meaning
1.	5FU	5-Fluorouracil
2.	ABUTH	Ahmadu Bello University Teaching Hospital
3.	ADR	Adverse Drug Reaction
4.	ASHP	American Society of Hospital Pharmacist
5.	CCT	Cervical Cancer Treatment
6.	CIN	Cervical Intraepithelial Neoplasia
7.	CCSG	Cervical Cancer Screening Guideline
8.	CCP	Cervical Cancer Prevention
9.	DDI	Drug-Drug Interaction
10.	DRP	Drug Related Problem
11.	FDA	Food and Drug Administration Administration
12.	HPV	Human Papilloma Virus
13.	NCI	National Cancer Institute
14.	NCCN	Nation Comprehensive Cancer Network
15.	NSAID	Non-steroidal Anti-inflammatory Drugs
16.	PCNE	Pharmaceutical Care Network Europe
17.	WHO	World Health Organisation
18.	WCR	World Cancer Report

Abstract

Drug-related problem(s) (DRP) is defined as an event or circumstance involving medication therapy that actually or potentially interferes with an optimum outcome for specific patients. The increase in number of available drugs and drug users as well as more complex drug regimens (cervical cancer) lead to more side effects and drug interactions, and complicate follow-up. The aim of this study is to investigate DRPs in cervical cancer patients receiving chemotherapy.

It was a retrospective cross sectional study on patients receiving cervical cancer chemotherapy at Ahmadu Bello University Teaching Hospital, Kaduna-Nigeria. Patients' medication charts were reviewed for a period of twelve months (July, 2015 to June, 2016). Data were collected using the Pharmaceutical Care Network Europe Classification V 6.2. (PCNE). Then the data was analyzed using frequency and percentages.

The result of our study shows that 224 DRPs were detected from 65 patients out of 76 that where screen for the study. The most prevalence DRPs were treatment effectiveness, adverse drug reaction, treatment cost, drug selection and dose selection with the following percentages (28.13%, 29.02%, 26.79%, 28.13% and 29.02% respectively). The risk factors for DRPs were comorbidities and number of medications (polypharmacy).

In conclusion, drug related problems were significantly common among cervical cancer patients receiving chemotherapy in our set up which indicate the need for intervention like involvement of a pharmacist for better therapeutic results.

Keys: Drug related problem, cervical cancer, chemotherapy, polypharmacy

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1.0 Introduction

1.1 Overview

Cancer of the cervical is a cancer that arises from the cervix (CCT,2014). It is due to irregular growth of cells that have the capacity to invade or feast to other parts of the body (NCI,2014). Initially , no symptoms are seen. Later symptoms may comprise abnormal vaginal bleeding, pelvic pain or pain during sexual intercourse (CCT,2014). Human papillomavirus (HPV) are virus that appears to be involved in the development of more than 90% of cases ;(Kumar et al,2007;kufe et al,2009). Other risk factors include birth control pills, having many sexual partners, smoking , starting sex at a young age, and a weak immune system (CCT,2014).

Worldwide, cervical cancer is the fourth-most common cancer and cause of death in women (WHO,2014). About 70% of cervical cancers occur in developing countries like Nigeria etc (WCR,2014;WHO,2014) . In developed countries, the widespread use of cervical screening programs has dramatically reduced rates of cervical cancer (Canavan et al,2000). Cervical cancer chemotherapy is one of the best approaches to eradicate cancer, its success is far from satisfactory due to mostly drug related problems.

Drug-related problem(s) (DRP) is defined as an event or circumstance involving medication therapy that actually or potentially interferes with an optimum outcome for specific patients (ASHP, 1993). The increase in number of available drugs and drug users as well as more complex drug regimens (cervical cancer) lead to more side effects and drug interactions, and

complicate follow-up (Ruths et al., 2007). DRPs include adverse drug reactions (ADRs), unnecessary drug therapy, inappropriate choice of drugs, and untreated conditions. DRPs can lead to substantial morbidity and mortality. Drug toxicity is also a major limitation in providing healthcare to patients at a global level. It affects the patient's recovery as well as the economy of healthcare (Ruths et al., 2007; Leendertse et al., 2008). An inclusive study of DRPs in cervical cancer patients receiving chemotherapy could provide valuable insights for the healthcare professionals to reduce the incidence of DRPs.

The aim of this study is to investigate DRPs in cervical cancer patients receiving chemotherapy. Other objectives are to identify the types and frequencies of DRPs in cervical cancer patients, to investigate the factors influencing DRPs in cervical cancer patients, to identify the drugs implicated in the DRPs in cervical cancer patients, to highlight possible interventions on DRPs in cervical cancer patients.

2. Literature Review

2.1 Cancer

Cancer also known as malignancy, neoplasm or tumour, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumours are cancerous; benign tumours do not spread to other parts of the body (WHO, 2014). A tumour is a cluster of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely (NCI, 2014).

The main features of cancer have been proposed to include; self-sufficiency in growth signalling, insensitivity to anti-growth signals, evasion of apoptosis, enabling of a limitless replicative potential, induction and sustainment of angiogenesis, and activation of metastasis and invasion of tissue. The development from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression (Hanahan and Weinberg, 2011).

Many treatment options for cancer exist, with the primary ones including surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care. Which treatments are used depends upon the type, location, and grade of the cancer as well as the person's health and wishes. The treatment intent may be curative or not curative.

2.1.1 Classification

Cancers are classified by the type of cell that the tumour cells resemble and are therefore presumed to be the origin of the tumour. These types include:

Carcinoma: Cancer derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged, and includes nearly all those developing in the cervix, breast, prostate, lung, pancreas, and colon.

Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.

Lymphoma and leukaemia: These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukaemia is the most common type of cancer in children accounting for about 30% (Varricchio, 2004).

Germ cell tumour: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults.

Benign tumors (which are not cancers) For example, a benign tumor of smooth muscle cells is called a leiomyoma (the common name of this frequently occurring benign tumor in the uterus is fibroid).

2.2 Cervical cancer

Cancer of the cervical develops from the cervix (CCT,2014). It is due to irregular growth of cells that have the capacity to invade or feast to other parts of the body (NCI,2014). Initially, no symptoms are seen. Later symptoms may comprises abnormal vaginal bleeding, pelvic pain or pain during sexual intercourse (CCT,2014). Human papillomavirus (HPV) are virus that appears to be involved in the development of more than 90% of cases;(Kumar et al,2007;kufe et al,2009). Other risk factors include birth control pills, having many sexual partners, smoking , starting sex at a young age, and a weak immune system (CCT,2014). HPV vaccines protect against between two and seven high-risk strains of this family of viruses and may prevent up to 90% of cervical cancers (FDA,2015;HPV,2014;Tran et al 2014). As risk of cervical cancer still exists, guidelines endorse continuing regular Pap smears (HPV,2014). Treatment of cervical cancer may contain some combination of radiotherapy, chemotherapy and surgery (CCT,2014). Worldwide, cervical cancer is the fourth-most common cancer and cause of death in women (WHO,2014).

2.2.1 Signs and Symptoms

The initial stages of cervical cancer may likely be free of symptoms (kumar et al,2007;Canavan et al,2000). Vaginal bleeding, contact bleeding (bleeding after sexual intercourse), or (rarely) a vaginal mass may indicate the presence of malignancy. However, reasonable pain during sexual intercourse and vaginal discharge are indications of cervical cancer. In advanced disease, metastases may be present in the abdomen, lungs, or elsewhere.

Advanced cervical cancer may have the following symptoms: heavy vaginal bleeding, leg pain, loss of appetite, weight loss, fatigue, pelvic pain, back pain, swollen legs, bone fractures, and/or (rarely) leakage of urine or feces from the vagina (Nanda et al,2007).

2.2.2 Causes

HPV is the greatest risk factor for cervical cancer, followed by smoking. HIV infection is also a risk factor (Gadducci et al,2011). Not all of the causes of cervical cancer are known. However, several other contributing factors have been implicated (Stuart et al,2006).

Human papillomavirus(HPV)

Of the 150-200 types of HPV known,(MDL,2007;Gottlieb et al 2007) 15 are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three of them are probable high-risk (26, 53, and 66), and 12 of them are low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) (Munoz et al,2003).

HPV types 16 and 18 are the cause of 75% of cervical cancer cases globally. Furthermore, HPV 31 and 45 are the causes of another 10% (Robert et al, 2009).

Women who have many sexual partners (or who have sex with men who have had many other partners) have a greater risk (ACS,2006 ;Marrazzo et al,2001).

Infection with HPV is generally believed to be required for cervical cancer to occur (Snijders et al,2006).

Smoking

Both active and passive smokers have high risk of developing cervical cancer. Among HPV-infected women, current and former smokers have roughly two to three times the occurrence of invasive cancer (CCP,2015).

Smoking can increase the risk in women, which can be direct or indirect methods of inducing cervical cancer (Luhn et al,2013;Remschmidt et al,2013). A direct way of contracting this cancer is a smoker has a higher chance of CIN3 occurring which has the potential of forming cervical cancer (Luhn et al,2013). When CIN3 lesions lead to cancer, most of them have the assistance of the HPV virus, but that is not always the case, which is why it can be considered a direct link to cervical cancer (Remschmidt,2013). Heavy smoking and long-term smoking seem to have more risk of getting the CIN3 lesions than lighter smoking or not smoking at all (Jensen et al,2012). Although smoking has been linked to cervical cancer, it aids in the development of HPV which is the leading cause of this type of cancer (Gadducci et al,2011). Also, not only does it aid in the development of HPV, but also if the woman is already HPV-positive, she is at an even greater likelihood of contracting cervical cancer (Jensen et al,2012).

Oral contraceptives

Long-term use is related with increased risk of cervical cancer. The used of oral contraceptives for 5 to 9 years have about three times incidence of aggressive cancer. Using them for 10 years or longer have about four times the risk (CCP,2015).

Multiple pregnancies

Having numerous pregnancies is related with an increased risk of cervical cancer. Among HPV-infected women, those who have seven or more full-term pregnancies have around four times the risk of cancer compared with women with no pregnancies (CCP,2015).

2.2.3 Diagnosis

Biopsy

The Pap smear can be used as a screening test but is false negative in up to 50% of cases (Cecil medicine,2015;Berek et al,2014) . Confirmation of the diagnosis requires a biopsy of the cervix. This is often done through colposcopy, a magnified visual inspection of the cervix aided by using a dilute acetic acid (e.g. vinegar) solution to highlight abnormal cells on the surface of the cervix (Kumar et al,2009).

Before the biopsy, the doctors ask for medical imaging to rule out other symptoms. Imaging modalities such as ultrasound, CT scan and MRI have been used to look for alternating disease (Pannu et al,2001).

Precancerous lesions

The potential precursor to cervical cancer are cervical intraepithelial neoplasia(CIN). The term, cervical intraepithelial neoplasia (CIN) was developed to place emphasis on the spectrum of abnormality in these lesions, and to help standardise treatment (Demay et al,2007). The World Health Organization classification (CR UK website,2009;Demay et al,2007) system was descriptive of the lesions, naming them mild, moderate, or severe dysplasia or carcinoma in situ (CIS). It classifies mild dysplasia as CIN1, moderate dysplasia as CIN2, and severe dysplasia and CIS as CIN3. More recently, CIN2 and CIN3 have been combined into CIN2/3. These results are what a pathologist might report from a biopsy.

2.2.4 Cancer subtypes

Histologic subtypes of invasive cervical carcinoma include the following: (Garcia et al,2006)

- squamous cell carcinoma (about 80-85%)
- adenocarcinoma (about 15% of cervical cancers in the UK)
- adenosquamous carcinoma
- small cell carcinoma

- neuroendocrine tumour
- glassy cell carcinoma
- villoglandular adenocarcinoma

Non carcinoma malignancies is uncommon and occur in the cervix which include melanoma and lymphoma. The FIGO stage does not include lymph node participation in contrast to the TNM staging for most other cancers

2.2.5 Staging

Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) which is based on clinical examination. It permits only these diagnostic tests to be used in determining the stage: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, X-ray examination of the lungs and skeleton, and cervical conization.

2.2.6 Prevention

Screening

Using the Papanicolaou test or Pap smear for cervical cancer has been attributed with dramatically reducing the number of cases as well as mortality in developed countries (Canavan et al,2000). Pap smear screening every 3–5 years with suitable follow-up can decrease cervical cancer occurrence up to 80% (Arbyn et al,2010). Irregular results may propose the presence of

precancerous changes. It allows examination and likely preventive treatment. The treatment of low-grade lesions may adversely affect subsequent fertility and pregnancy (CCP,2015). European guidelines 2010, the age at which to start screening ranges between 20 and 30 years of age, "but preferentially not before age 25 or 30 years" (Arbyn et al,2010).

In America, screening is recommended to initiate at age 21 and regardless at which a woman began having sex or other risk factors. Pap tests should be done every three years between the ages of 21 and 65 (CCSG,2014). Women who are over the age of 65 years, screening may be discontinued if no abnormal screening results were seen within the previous 10 years and no history of CIN 2 or higher exists (CCSG,2014). HPV vaccination status does not change screening rates . Screening can occur every 5 years between ages 30 and 65 when a combination of cervical cytology screening and HPV testing is used and this is preferred (CCSG,2014).

Another screening method called Liquid-based cytology. It actually intended to improve on the accuracy of the Pap test. This reduces the need to recall women for a further smear. The United States Preventive Services Task Force supports screening every 5 years in those who are between 30 and 65 years when cytology is used in combination with HPV testing (Moyer,2012). In developing countries like Nigeria etc Pap smears have not been as effective as it should be . This is so because numerous of these countries like (Nigeria etc) have an impoverished health care infrastructure, insufficient trained and skilled professionals to obtain and interpret Pap smears (WHO,2014).

Barrier protection

Spermicidal gel or Barrier protection use during sexual intercourse reduce cervical cancer risk (CCP,2015). Condoms offer protection against cervical cancer. Indication on whether condoms protect against HPV infection is diverse but they may protect against genital warts and the precursors to cervical cancer (Manhart et al,2014). They also provide protection against other STIs which are related with greater risks of developing cervical cancer.

Vaccination

Two HPV vaccines (Gardasil and Cervarix) decrease the risk of cancerous or precancerous changes of the cervix and perineum by about 93% and 62%, respectively. The vaccines are between 92% and 100% effective against HPV 16 and 18 up to at least 8 years (CCP,2015).

HPV vaccines are typically given to age 9 to 26 as the vaccine is only effective if given before infection occurs. The vaccines have been shown to be effective for at least 4 to 6 years (Harper et al ,2008). The high cost of this vaccine has been a cause for concern. Several countries like Nigeria, Niger etc have consider (or are considering) programs to fund HPV vaccination.

2.2.7 Treatment

Worldwide, cervical cancer treatment varies largely due to access to surgeons skilled in radical pelvic surgery and the appearance of "fertility-sparing therapy" in developed countries. Cervical cancers are radiosensitive at all stages where surgical options do not exist.

Micro invasive cancer (stage IA) may be treated by hysterectomy (removal of the whole uterus including part of the vagina). Then stage IA2, the lymph nodes are removed as well. Alternatives comprise of local surgical procedures such as a loop electrical excision procedure or cone biopsy (Erstad et al ,2007). For 1A1 disease, a cone biopsy (cervical conization) is considered curative.

Initial stages (IB1 and IIA less than 4 cm) can be treated with radical hysterectomy with removal of the lymph nodes or radiation therapy. Radiation therapy is given as external beam radiotherapy to the pelvis and brachytherapy (internal radiation). Women treated with surgery who have high-risk features found on pathologic examination are given radiation therapy with or without chemotherapy to reduce the risk of relapse.

Largely initial-stage tumors (IB2 and IIA more than 4 cm) may be treated with radiation therapy and cisplatin-based chemotherapy, hysterectomy (which then usually requires adjuvant radiation therapy), or cisplatin chemotherapy followed by hysterectomy. When cisplatin is present, it is thought to be the most active single agent in periodic diseases (FDA,2006).

Advanced-stage tumors (IIB-IVA) are treated with radiation therapy and cisplatin-based chemotherapy. On June 15, 2006, the US Food and Drug Administration approved the use of a mixture of two chemotherapy drugs, hycamtin and cisplatin, for women with late-stage (IVB) cervical cancer treatment (FDA,2006). Mixture treatment has significant risk of neutropenia, anemia and thrombocytopenia side effects.

For surgery to be curative, the whole cancer must be removed with no cancer found at the margins of the removed tissue on examination under a microscope. This procedure is known as exenteration (Sardain et al,2015).

Treatment Protocols

Treatment protocols for cervical cancer are provided below, including treatment by stage, chemoradiation therapy, and chemotherapy.

Treatment recommendations for early stage disease

Stage IA1 disease:

- Primary treatment of early stage cervical cancer is surgery or radiation therapy
- Treatment recommendations include extrafascial hysterectomy, modified radical trachelectomy, or hysterectomy with pelvic node dissection

Treatment recommendations for stage IA2

Stage IA2 disease:

- Patients with stage IA2 tumors are treated with radical hysterectomy or radical trachelectomy with pelvic lymph node dissection
- Alternative options include brachytherapy with or without pelvic radiation therapy (total point A dose: 75-80 Gy)

Treatment recommendations for stage IB and IIA

Stage IB and IIA:

- Patients with stage IB or IIA disease can be treated with surgery (radical trachelectomy, pelvic lymphadenectomy, radical hysterectomy plus bilateral pelvic lymph nodes dissection), pelvic radiotherapy or chemoradiation
- If lymph nodes are positive, then a hysterectomy is not recommended; instead patient should receive chemoradiation
- Patients with stage IB or IIA may also be given pelvic radiotherapy and brachytherapy with or without concurrent cisplatin-based chemotherapy
- Cisplatin 40 mg/m^2 IV once weekly (not to exceed 70 mg/wk) **plus** radiation therapy 1.8-2 Gy per fraction (minimum 4 cycles; maximum 6 cycles) **or**
- Cisplatin 50-75 mg/m^2 IV on day 1 **plus** 5-fluorouracil (5-FU) 1000 mg/m^2 continuous IV infusion on days 2-5 and days 30-33 (total dose 4000 mg/m^2 each course)
- Cisplatin 50-75 mg/m^2 IV on day 1 **plus** 5-FU 1000 mg/m^2 continuous IV infusion over 24 h on days 1-4 (total dose 4000 mg/m^2 each cycle) every 3wk for a total of 3-4 cycles

Treatment recommendations for advanced stage disease

Stage IIB, IIIA, IIIB, and IVA:

- Traditionally, advanced disease includes stages IIB-IVA; however, many oncologists now also include patients with IB2 and IIA2 in the advanced disease category
- Treatment recommendations for advanced disease include concomitant chemoradiation and brachytherapy
- Cisplatin 40 mg/m^2 IV once weekly (not to exceed 70 mg/wk) **plus** radiation therapy 1.8-2 Gy per fraction (minimum 4 cycles; maximum 6 cycles) **or**
- Cisplatin 50-75 mg/m^2 IV on day 1 **plus** 5-fluorouracil (5-FU) 1000 mg/m^2 continuous IV infusion on days 2-5 and Days 30-33 (total dose 4000 mg/m^2 each course)
- Cisplatin 50-75 mg/m^2 IV on day 1 **plus** 5-FU 1000 mg/m^2 continuous IV infusion over 24 h on days 1-4 (total dose 4000 mg/m^2 each cycle) every 3wk for a total of 3-4 cycles

Treatment recommendations for metastatic disease

Stage IVB:

- Patients with metastatic disease are primarily treated with cisplatin-based chemotherapy
- In addition, individualized radiation therapy should be considered for control of pelvic disease and other symptoms

First-line therapy for stage IV recurrent or metastatic disease:

- Bevacizumab 15 mg/kg IV over 30-90 min **plus** cisplatin 50 mg/m^2 IV over 30-90 min on days 1 or 2 **plus** paclitaxel 135 or 175 mg/m^2 IV over 3 or 24 h on day 1 every 3 wk **or**
- Bevacizumab 15 mg/kg IV over 30-90 min **plus** paclitaxel 175 mg/m^2 IV over 3 h on day 1 **plus** topotecan 0.75 mg/m^2 IV over 30 min on days 1-3 every 3 wk **or**
- Paclitaxel 135 mg/m^2 IV over 24h (dosing at 175 mg/m^2 IV over 3h is also acceptable) **followed by** cisplatin 50 mg/m^2 IV on day 1 every 3wk **or**
- Topotecan 0.75 mg/m^2 IV (or 0.6 mg/m^2 IV if prior radiation therapy) on days 1-3 **followed by** cisplatin 50 mg/m^2 IV on day 1 every 3wk **or**
- Paclitaxel 175 mg/m^2 IV over 3h on day 1 every 3 wk

Second-line therapy for stage IV recurrent or metastatic disease:

- The National Comprehensive Cancer Network (NCCN) recommends agents such as docetaxel, gemcitabine, ifosfamide, 5-FU, mitomycin, irinotecan, and topotecan, which are listed as category 2B (recommendations based on lower level of evidence)

Category 3 (recommendations based on any level of evidence) recommended drugs include pemetrexed and vinorelbine

2.2.8 Prognosis

Prognosis depends on the phase of the cervical cancer. Survival rate is around 100% high for women with cervical cancer type with microscopic forms (CCEWH,2007). Treatment, the five-

year relative survival rate for the earliest phase of invasive cervical cancer is 92% and the overall (all phases combined) five-year survival rate is about 72%.

With treatment, women with stage I and stage II cancer can live for 5 years after diagnosis (80 to 90% and 60 to 75% respectively) . Survival rates decrease for women in stage III and stage IV cancer 5 years after diagnosis (30 to 40% and 15% respectively) (CFRS,2007) . Survival rate improves with radiotherapy and cisplatin-based chemotherapy according to the International Federation of Gynecology and Obstetrics (CPBG,2002).

Prognosis drops dramatically as the cancer metastasizes because treatment of local lesions is generally more effective than whole-body such as chemotherapy. It is imperative for Interval evaluation of women after therapy. Recurrent cervical cancer detected at its earliest stages might be successfully treated with surgery, radiation, chemotherapy, or combination of the three. About 35% of women with invasive cervical cancer have persistent or recurrent disease after treatment. Steady screening has meant that precancerous changes and early-stage cervical cancers have been detected and treated early. Figures suggest that cervical screening is saving 5,000 lives each year in the UK by preventing cervical cancer (CCSP,2007). About 1,000 women per year die of cervical cancer in the UK.

2.2.9 Epidemiology

Worldwide

Worldwide, cervical cancer is fourth-most common cause of cancer and deaths in women. In 2012, 528,000 cases of cervical cancer were estimated to have occurred and 266,000 deaths (WHO,2014). It is the second-most common cause of female-specific cancer after breast cancer. About 80% of cervical cancers occur in developing countries (Kent,2010).

Developing countries

Nigeria is among the numerous developing countries that have an impoverished health care infrastructure, insufficient trained and skilled professionals. In 2015, No fewer than 9000 Nigerian women die yearly as a result of cervical cancer. Cervical cancer had killed more people worldwide than HIV/AIDs, tuberculosis and malaria put together. However, more than 14,550 Nigerian women are infected with human papilloma virus (HPV), the major cause of cancer of the cervix. In spite of this statistics, there is evidence that utilisation of screening for prevention of the disease is poor in Nigeria (Okunade, 2015).

United States

In 2015, there is an estimated 12,900 new cervical cases and 4,100 cervical deaths (CCP,2015) . In the States, it is the eight-most common cancer of women. The median age at diagnosis is 48. Hispanic women are significantly more likely to be diagnosed with cervical cancer than the

general population (Howlader,2014). In 1998, around 12,800 women were diagnosed in the US and about 4,800 died (Canavan et al,2000). In 2014, an estimated 12,360 new cases were expected to be diagnosed, and about 4,020 were expected to die of cervical cancer (Howlader,2014). Cervical cancer deaths decreased by approximately 74% in the last 50 years, largely due to widespread Pap smear screening. The annual direct medical cost of cervical cancer prevention and treatment prior to introduction of the HPV vaccine was estimated at $6 billion (Armstrong,2010).

UK

In UK, cancer of the cervix is the 12th-most common cancer in women (around 3,100 women were diagnosed with the disease in 2011) and accounts for 1% of cancer deaths (around 920 died in 2012) (CCS,2014). With a 42% decrease from 1988-1997, the NHS-implemented screening programme has been highly successful, screening the highest-risk age group (25–49 years) every 3 years, and those ages 50–64 every 5 years.

Canada

In Canada, about 1,300 women have been diagnosed with cancer of the cervix in 2008 and 380 have died (MacDonald et al,2008).

2.3 Drug related problems or Drug therapy problems

Drug related problems or drug therapy problems are any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interfere with a desire patients outcome (PCNE, 2010). The term is used to denote a drug related event amenable to detection, treatment or prevention. A drug therapy problem may be potentially which is likely to occur or actual in which the patients is already experiencing it (Oparah,2010). Drug related problems are consequence of patients drug related needs that have gone unmet. Drug related problem is also a situation that left unresolved prevents the patient from realizing the full benefits of their drug therapy (Cipolle et al.,2004).

Drug related problem can be define in more as a situation in which drug therapy can cause problems. These problems are then identified, prevented and resolve primarily by pharmacists, especially those providing pharmaceutical care (Nickerson,2005). Physicians are faced with a lot of problems such as the risk of patients building tolerance to prescribed drugs taken (such as morphine to control pain as in cancers) which leads to the patient's body requiring higher doses for the drug to be effective, and eventually lead to drug overdoses. So also, side effects of drugs may inhibit the body from absorbing necessary nutrients (Cipolle et al.,1998; Ruscin 2013,).

2.3.1 Prevalence

It is acknowledged that accurate information on the prevalence of drug related problems is difficult to obtain more especially in cancer cases. More people die of inappropriate drug

treatment than from cervical cancer, breast cancer, AIDS and traffic accidents all together (Kohn et al.,1999). Adverse drug reactions are 4 to 6 most frequent cause of death in USA (Lazarous et al.,1998). Twice as much money are used to solve drug related problems and adverse drug events than on the drug themselves (Ernst and Grizzle,2000). Although drug related problems occur in all categories of patients, older people are more likely to suffer from multiple conditions as they are the greatest consumer of prescription medicines. Older people are more susceptible to drug related problems due to altered pharmacokinetic and pharmacodynamics properties of drugs (Nikolaus,1996) . An elderly patient is more likely to take a medication that has been prescribed inappropriately, so also unnecessary and ineffective or potentially dangerous drugs. All these led to an adverse drug reaction (Simon et al.,2005).

Pediatric population is more vulnerable to DTPs group than the adults. Though this population suffers similar adverse drug reactions as in adults, the prevalence is higher and detection of adverse drug reaction in children is more difficult because infants cannot communicate their problems and hence the health behavior is dependent on the mother (Oparah,2010). Children especially neonate may also suffer from drug related problem because their metabolic and excretory system are not being fully developed. For example, newborns cannot metabolize and eliminate the antibiotic chloramphenicol. If tetracycline is given to infants and young children during the period when their teeth are being formed (up to about age 8), it may permanently discolor tooth enamel (Ruscin,2013). Pregnant women suffer drug related problems because of impaired immunity and increase risk of disease, thus multiple drug usage.

2.3.2 Causes of Drug Related Problems

The cause of drug related problems are multifactorial and their assessment has been based on factors such as inappropriate delivery, inappropriate patient behavior, patient idiosyncrasy and inappropriate monitoring (Worjnar – Horton et al.,1998).

2.3.3 Type of Drug Related Problems

Unnecessary drug therapy

This could occur when the patient has been placed on too many medications for their condition and the drug is simply not needed. Multiple drug products are being used for a medical condition that requires single drug therapy. Sometimes the medical condition can be appropriately treated with nondrug therapy or lifestyle changes. Drug therapy is being taken to treat an avoidable adverse event associated with another medication. For example, a patient is using three different laxative products in an attempt to treat his constipation. A patient is using furosemide to prevent swollen ankles. A patient uses a proton pump inhibitor to treat dyspepsia associated with alcohol abuse (Leendertse et al.,2011).

Wrong drug

This could occur when patient is given medication that does not treat the patient's condition. The patient has a medical condition for which wrong drug is being taken. Common causes of wrong drug include dosage form inappropriate, contraindication present, condition refractory to drug,

drug not indicated for condition, more effective drug available. Example is seen when a heart medication is used to treat an infection (Oparah,2010).

Dosage too low

This could occur when a patient is given medication that is not strong enough to get beneficial or therapeutic effects. The patient has a medical condition for which too little of the correct drug is being taken (dose, frequency and duration). Common causes of dosage too low include, dose is too low to produce the desired outcome, the dosage interval is too long to produce the desired outcome, and the duration of the drug therapy is too short to produce the desired outcome. Examples a patient uses 500 mg paracetamol only twice a day to control chronic pain in osteoarthritis. A patient uses 375 mg amoxicillin only once a day to treat an air way infection (Leendertse et al.,2011).

Dosage too high

This could occur when a patient is given medication that is too strong and is causing detrimental effects or is simply not necessary. The patient has a medical condition for which too much of the correct drug is being taken. Common causes include, the dosing frequency of the drug is too short, the duration of drug therapy is too long ,the dose of the drug was administered too rapidly, the dose is too high in the patient because of its characteristics (excretion). Examples, a patient develops hyperkalemia after a dose of amiloride 10mg three times a day. A patient with impaired

renal function (Creatinine clearance 20 ml/min) is prescribed a normal dose of 300 mg allopurinol a day cause's nausea (Leendertse et al.,2011).

Adverse drug reaction

This could occur when a patient has an allergic response to a medication. The patient has a medical condition resulting from an adverse drug reaction. Common causes include, the drug causes an undesirable reaction that is not dose related. Common causes include; the drug causes an undesirable reaction that is not dose related. The drug causes an allergic reaction. The drug is contraindicated due to the risk factors or other diseases. A drug interaction with another drug or food causes an undesirable reaction that is not dose related. A safer drug is required due to risk factors. Examples, a patient on a low dose of aspirin is experiencing bruises. An elderly patient uses terazepam to sleep and is experiencing drowsiness at day time. A positive ketone test in urine due to captopril use. A patient had high blood glucose levels due to the start of prednisolone therapy (Leendert et al.,2011).

Inappropriate Adherence

Drug effectiveness is often compromised by lack of patient adherence. This could occur when a patient chooses not to or forget to take a medication. In this case, the patient has a medical condition resulting from not taking the drug appropriately (explore missed doses and reasons). A regimen using too complicated for patients to follow. Common causes include; directions not understood, patient prefers not to take drug, patient forgets to take drug, drug production too

expensive, drug product not available, patient cannot swallow or administer drug (Oparah,2010). For examples, a patient is not able to fetch the medication at the pharmacy. The patient forgets to take his antihypertensive medication. The patient is unable to administer the timolol eye drops for his glaucoma (Leendertse et al.,2011).

Needs additional drug therapy

This could occur when a patients needs more medication to treat their condition. i.e. the patient has a medical condition that requires the intiation of new or additional therapy (untreated indication). Common causes include, a medical condition which requires the initiation of drug therapy, preventive drug therapy is required to reduce the risk of developing a new condition (according to the national guidelines). A medical condition requires additional pharmacotherapy to produce an additive of synergistic effect. Examples, the patient is suffering from pain with no analgesic therapy. A patient with atrial fibrillation without antithrombotic therapy. Calcium and vitamin D supplements for a patient with osteoporosis who is already taking a bisphosphonate (Leendertse et al.,2011).

Drug interactions

The patient has a medical condition resulting from clinically significant drug interactions. Drug can interact in the following ways; Drug –drug (aminoglycoside and penicillin), drug-food (tetracycline and unlike product), drug-laboratory values (penicillin,salicylate and lecodops interact with urine and glucose test), drug-supplement (milk prevent absorption of oral iron

preparation), drug- disease interaction (beta 2 blocker in asthmatic patient), all these lead to adverse effects or decreased efficacy (Ruscin,2013).

Improper drug selection

Situation where patient is treating with medication that can show effective treatment, contraindicated in the disease condition, allergic to the patient or patient receiving an expensive drug instead of cheaper and equally effective drug, or patient receiving combination therapy instead equally affective single therapy (Oparah,2010).

Inadequate monitoring

A medication problem is being treated with the correct drug, but the patient is not monitored for complications, efficacy or both. Monitoring drug use involves, documenting the indication for a new drug, keeping a current list of drugs used by the patient in medical records, monitoring for achievement of therapeutic goals and other responses to new drugs, monitoring necessary laboratory tests for efficacy or adverse effects ,periodically reviewing drugs for continued need. Lack of close monitoring , especially after new drugs are prescribed, increases risk of adverse effects and ineffectiveness (Ruscin,2013).

Ineffective drug therapy

This could occur when a patient is treated with drug which is not effective for the medical condition. Common causes include; the drug product is not the most effective for the indication being treated. The drug is not effective because of the characteristics of the patient (example renal impairment, hepatic function). The formulation of the drug products is inappropriate. Examples, a patient is using antibiotic for common cold (viral infection). A patient with renal impairment uses a thiazide to lower the blood pressure. A patient with severe chronic obstructive pulmonary disease (COPD) uses salbutamol in turbuhaler (Leendertse et al.,2011).

Errors occur as a result of wrong product strength, expired order, wrong documentation, wrong product, wrong time ,wrong patient, wrong duration, monitoring error, and laboratory work error, wrong technique, wrong form of product, expired product, wrong rate of administration, wrong means of administration and so on (Van den et al.,2000,Oparah,2010).

2.3.4 Possible Causes of Drug Related Problems

Drug related problems can originate when prescribing, dispensing, or taking /administering medicines. Drug related problems can also be caused by the following; basic human error, prescription error, frequent distractions or care changes, poor communication, pharmacy dispensing, medication unavailable, too much workload or overtime ,wrong labeling, pharmacy delivered wrong medication, wrong packaging design, inadequate information, improper training,

illegible hand writing and so on . Careful monitoring can reduce the rate at which drug related problems occur (Van den et al.,2000,Oparah 2010).

2.3.5 Methods of identifying drug related problem

Identification of drug related problem requires obtaining relevant patient data and critical thinking skills. The data obtained are then analyzed. All medications are to be compared with the medical conditions/complaints to ascertain that every medication is treating a condition and that every condition is being treated with or without a medication:

Is there a need for a medication (To ensure indication)

If no ,unnecessary drug therapy

If yes, is the medication safe and efficacious for the condition? If no wrong drug.

If yes, are the dose, frequency and duration appropriate? If no , dosage too low or dosage too high.

If yes, is the patient likely to experience adverse drug reaction? If yes, adverse drug reaction.

Is there a likelihood of drug interaction? If yes, drug interaction.

Is patient adherence appropriate? If no, inappropriate adherence.

Is there any condition or complaint that requires a medication but receiving none? If yes, untreated indication/ additional drug therapy(Oparah,2010).

2.3.6 Implementation of pharmaceutical care

The pharmaceutical care plan is a written, individualized, comprehensive medication therapy plan based on clearly defined therapeutic goals. The pharmaceutical care plan is available to all pharmacists caring for a patient. It is updated with each major change in patient status. It is important that the physician be informed about the care plan to ensure common goals. Patients should also be informed about the general content of the care plan as means of gaining their agreement regarding drug therapy. Pharmaceutical care plan is a systematic and comprehensive process with three primary functions that involves, identifying a patient's actual and potential drug related problems, resolve this patient's actual drug related problems and prevent the patient's potential drug related problems (Igbinomwanhia et al.,2010).

2.3.7 Steps involve in Pharmaceutical care implementation

The first step in the care planning process is the creation of a comprehensive patient database, which include a minimum of the following information.

Some minimum contents of patient specific data

Patient demographics name, age ,gender , contact address etc.

Diagnoses and past medical history

Present medications and medication history including herbal medicines

Medication allergies/intolerances

Smoking/alcohol/caffeine/drug use history

Abnormal laboratory and physical examination results

Renal and liver function (Oparah,2010).

Then pharmacist should evaluate the patients' drug therapy outcomes

Determine whether drug related problems are present or not.

Determine whether current drug therapy is appropriate.

Determine whether additional drug therapy is needed

Determine if any of the drug related problems may have been caused by medication.

Assessment of Drug – Related Problems

To assess drug related problems an understanding of patient of drug related need and the types of drug related problems that may occur help facilitates the evaluation process (Becker et al.,2008). The identification of drug related problem is the focus of the assessment. This represents the key decisions made in that step of the patient care process. Although drug related problem identification is technically part of the assessment process, it represents the truly unique contribution made by pharmaceutical care pharmacists (Cipolle et al.,2004). Drug related problems should also be assessed for their severity, acuteness and significance to the patient to determine how quickly the resolution of the problem must occur (Strand et al.,2004).

2.3.8 Patient drug related need in drug therapy problem

The followings are some of the patients related need

1. Patient expectation

   What does your patient want ? What does your patient expectation of his or her medications ? Are they realistic ? or achievable, does patient have active participation of his or her pharmaceutical care (Strand et al.,1992).

2. Patient concern

   What does your patient knows about his or her health in general medical condition or drug therapy . What does your patient know about side effect, toxicity , allergy and cost . Patient should understand level of his medical problem, disease condition, drug therapy instruction and necessary participation actively to his or her care is needed (Nicholas and Poirier,2000).

3. Patient needs for drug therapy

   Every drug has an appropriate indication, drug therapy is effective , drug therapy is safe, patient can comply with drug therapy and no untreated indication is present. For a pharmacists to resolve drug related problems, he has to apply his problem solving skill and knowledge in managing the patient, for patient with actual or problems, the best is to treat the preventable potentials that have not occurred. However, knowing the cause of the drug related problems help to create care plan to fix it appropriately (Ruscin,2013).

   Establishment of therapeutic goals

Therapeutic goals must be established for each drug related problem so that the pharmaceutical care planning process can be effective. Therapeutic goals should be definite, realistic and if

possible, measurable. Most therapeutic goals related to approach normal physiology (i.e normalize blood pressure below 140/90mmHg,slow progression of disease), clear upper respiratory tract infection, alleviate symptoms (i.e optimize pain control), prevent adverse effects, control medication costs, educate the patient about his or her medication and specify monitoring parameters with end points and frequency.

Finally ,monitoring parameters must be specified so that the patients progress can be followed and it must include potential adverse effects. In order to determine desired and points for each parameter and frequency of monitoring, document patients progress. The pharmacist evaluates and documents the patient's progress in achieving the desired therapeutic goals and avoidance of potential adverse effects. The pharmaceutical care plan is updated with each major change in patient status (Bussieeres and Lepage,1991).

2.3.9 Care plan summary

The general steps involved in creating a pharmaceutical care plan include creation of a comprehensive patient database, assessment for actual and potential drug related problems, establishment of therapeutic goals ,specify monitoring parameters with end points and frequency, and document the patients' progress towards therapeutic goals (Oparah,2010). The care plan function is basically just a skeleton that one can expand on because plans will differ depending on the practice setting in which the program is being used. Acute, home care and long term care all have different monitoring parameters and schedules. The default care plan for a drug can be

change on the edit drug model function which care is accessed via the drop down menu tree or by the keyboard shortcut. The care plan field is free from text entry, you can enter anything you like in this field.

2.3.10 Follow up

Plan and schedule: This consist of a plan and schedule (When) encounter (face to face or telephone) with patient, which is designed to gather information to determine to what extent the recommended care plan is producing desired effect in achieving goal of therapy and not resulting in undesirable or intolerable side effect.

Follow up evaluation

This is a clinical judgment to how effective care plan and associated drug therapy has been achieved as regards to the goal of therapy for each patient medical condition from information gathered at follow up evaluation, evaluate the accual outcomes and document the progress (or lack of progress) in achieving the goal of therapy (Becker et al.,2008).

2.3.11 Prevention of drug therapy problem

Problem related to drug therapy may be averted by preventive interventions. Several possibilities for prevention exist, especially for the prevention of medication errors. Prescribing, transcription and interpretation errors can be reduced by using computerized physician order entry. Together with the use of automated dispensing systems and bar-code technology, this will aid in the

reduction of both dispensing and administration errors(Van den et al.,2000). Education of nursing staff involved in the process of drug distribution is another important measure for preventing medication errors (Van den et al.,2000). Certain strategies should be considered to document the indication for each new drug (to avoid using unnecessary drugs), consider age related changes in pharmacokinetics or pharmacodynamics and their effect on dosing requirements, choose the safest possible alternative (e.g for inflammatory arthritis,acetaminophen instead of an NSAID). Check for potential drug –disease and drug –drug interaction. Start with a low dose using the fewest drugs necessary. Note, coexisting disorders and their likelihood of contributing to adverse drug effect. So also explain the uses and adverse effects of each drug. Provide clear instructions to patients about how to take their drugs (including generics and brand names,spelling of each drug name ,indication for each drug and explanation of formulations that contain morethan one drug) (Cameron,1998).

Anticipate confusion due to sound-alike drug names and pointing out any names that could be confused (example Glucophage and glucovance). As soon as a drug is started it should be assumed that a new symptom may be drug related until proved otherwise (to prevent a prescribing cascade). Patients should be monitored for signs of adverse drug effects,including measuring drug levels and doing other laboratory tests as necessary. Response to therapy should be documented and increase doses as necessary until desired effect is achieved (Ruscin,2013).

Finally, the introduction of systems for the early detection of adverse drug reactions may help to reduce problems related to drug therapy. Identifying risk factors that contribute to the

development of adverse drug reactions may aid in the prevention of these reactions (Van den et al.,2000)

2.4 DRPs with Anticancer drugs

In systemic cancer therapy, drug regimens are administered following established protocols which have been carefully evaluated in clinical trials. The more complex drug therapy is the higher the risk of experiencing DRPs such as adverse effects, interactions, medication errors, and non-adherence. The use of anticancer drugs often results in the use of other agents to reduce or prevent side-effects of the anticancer treatment, thereby increasing the interaction potential due to polypharmacy. Furthermore, cancer itself increases the need for more medications. Cytotoxic agents have a narrow therapeutic window and a complex pharmacologic profile. In oncology patients, pharmacokinetic parameters can be altered by the disease itself or due to malnutrition, reduced levels of serum-binding proteins, edema, or hepatic and/or renal dysfunction. Patients with cancer are therefore more at risk for drug interactions (Jaehde, 2008). The increase in number of available drugs and drug users as well as more complex drug regimens lead to more side effects and drug interactions, and complicate follow-up. Drug related problems (DRPs), which includes adverse drug reactions (ADRs), unnecessary drug therapy, inappropriate choice of drugs, and untreated conditions, has been reported in up to 25% of hospitalized patients. DRPs can lead to substantial morbidity and mortality. Drug toxicity is also a major limitation in providing healthcare to patients at a global level. It affects the patient's recovery as well as the economy of healthcare. In systemic cancer therapy, drug regimens are administered following established protocols which have been carefully evaluated in clinical trials. The more complex

drug therapy is the higher the risk of experiencing DRPs such as adverse effects, interactions, medication errors, and non-adherence. The use of anticancer drugs often results in the use of other agents to reduce or prevent side-effects of the anticancer treatment, thereby increasing the interaction potential. Furthermore, cancer itself increases the need for more medications. Cytotoxic agents have a narrow therapeutic window and a complex pharmacologic profile. In oncology patients, pharmacokinetic parameters can be altered by the disease itself or due to malnutrition, reduced levels of serum-binding proteins, edema, or hepatic and/or renal dysfunction. Patients with cancer are therefore more at risk for drug interactions (DRP). Therefore it must be the goal of all health care providers to minimize treatment-associated risks as much as possible in these patients. A more comprehensive study of DRPs in cancer patients would provide valuable insights for the healthcare professionals trying to reduce the incidence of DRPs. However there is scarcity of data on comprehensive DRPs among cancer patients.

3. Materials and Methods

3.1 Materials

Data collection Form, PCNE V6.2

Patients Treatment Charts

Patients Register

Lexicomp Database

Drug Monographs

National Comprehensive Cancer Network(NCCN) Guidelines

3.2 The Study Design

It was a retrospective cross sectional study on patients receiving cervical cancer chemotherapy at Ahmadu Bello University Teaching Hospital, Kaduna-Nigeria. Patients' medication charts were reviewed for a period of twelve months (July, 2015 to June, 2016). The study was approved by the hospital research ethics committee (HREC).

ABUTH is one of the largest tertiary hospitals in Nigeria, and is located in the North West Geopolitical Zone of Nigeria. The Hospital Oncology Unit is a center of excellence for oncology in the said region there by serving host to majority of oncology patients in the Region

3.3 Data Collection

Data were collected on potential and manifested DRPs using the Pharmaceutical Care Network Europe Classification V 6.2. DRPs were identified by cross-checking the data with the standard protocol like Pharmacy Guide to Chemotherapy-Clinical Assessment, drug monographs and drug interaction databases.

3.4 Study Population

All charts of consented patients who received treatments in the oncology unit, who were diagnosed with cervical cancer, whose age is 18 and above and who had taken chemotherapy for at least one course were included in the study. Patients who had not taken chemotherapy for at least six months within the study period were excluded from the study.

3.5 Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software. Pearson chi-square test were used to determine the association between patients factors like age ,comorbidities and number of medications with presence or absence of DRPs. Statistical significance were considered at $P<0.05$

4. Results

Seventy six (76) patients were screened in this study; only sixty five (65) patients were included in the final analysis as eleven (11) patients were excluded due to missing data. However, fifty eight (58) patients out of sixty five (65) patients were found to have at least a DRP.

4.1. Demographics

a. Age distribution:

Table (1) show the demographic and patients population studied. The study analyzed a total of 65 female cervical cancer patients records out of 76 screened, majorities of the patients (27.69%) fell within 40 – 49 years. However, the least patients (3.08%) fell within 70 -79 years. The mean age was found to be 48.3 ± 4.2 years.

S/No.	Age (Years)	Number of patients (DRPS)	Percentage (%)
1.	20 – 29	9(7)	13.85
2.	30 – 39	12(10)	18.46
3.	40 – 49	18(16)	27.69
4.	50 – 59	10(9)	15.38
5.	60 – 69	9(9)	13.85
6.	70 – 79	2(2)	3.08
7.	80 and above	5(5)	7.69
	Total	**65(58)**	**100**

b. Comorbidity:

In the second (2) table, we obtained a total of 49 patients that have comorbidities while 16 did not have. The common comorbidities are recorded and noted. Cardiovascular disease that is hypertension has the highest percentage (29.77%) while the least is renal failure with (7.14%).

S/No.	Comorbid disease	Frequency	Percentage (%)
1.	Diabetes	23	27.38
2.	Hypertension	25	29.77
3.	Renal failure	6	7.14
4.	Hyperlipidemia	8	9.52
5.	Hepatitis	8	9.52
6.	Peptic ulcer	14	16.67
	Total	**84**	**100**

c. Number of comorbidities

Table (3), Comorbidity is the existence of one or more additional diseases or disorders co-occurring with a primary disease. It was discovered according to this study that number of comorbidities zero (0) had NO comorbidities which have the percentage (24.62%) which means that 16 patients out up 65 do not have comorbidities. Meanwhile, number of comorbidities one (1) have the highest comorbidities among others with the percentage (33.85%).

S/No.	Number of Comorbidities	Frequency(DRPS)	Comorbidities	Percentages (%)
1.	0	16(12)	0	24.62
2.	1	22(21)	22	33.85
3.	2	21(20)	42	32.31
4.	3	4(3)	12	6.15
5.	4	2(2)	8	3.08
	TOTAL	**65(58)**	**84**	**100**

d. Number of Medications

In table (4). More than 50% of the patients had 5 drugs and above. The Majority of the patients had 7-8 drugs.

Table 6: Number of Medications

S/No.	Number of Medications	No. of patients (DRPs)	Percentage (%)
1.	1-2	6 (2)	9.23
2.	3-4	6 (3)	9.23
3.	5-6	16 (16)	24.62
4.	7-8	20 (20)	30.77
5.	9-10	12 (12)	18.46
6.	Above 10	5 (5)	7.69
	Total	**65 (58)**	**100**

4.2. Drugs used in Chemotherapy:

In table (5) Drug type: Majority of the patients was on Cisplatin + 5- Fluorouracil regimen that has the highest percentage (43.08%) then followed by Cisplatin and Cisplatin + Paclitaxel has equal percentages (15.38%) respectively.

S/No.	**Regimens**	**Number of patients (DRPS)**	**Percentage (%)**
1.	Cisplatin alone	10(6)	15.38
2.	Cisplatin + 5-FU	28(28)	43.08
3.	Cisplatin + Paclitaxel	10(10)	15.38
4.	Paclitaxel	4(2)	6.15
5.	Others	13(12)	20.0
	Total	**65(58)**	**100**

4.3. Type of problem

This table (6) shows a total of 224 DRPs identified in 58 cervical cancer patients out of the total of 65 patients screened with a prevalence of 89.2%. Adverse drug reactions have the highest percentage (29.02%) when compare with other problems, followed closely by treatment effectiveness (28.13%).

S/No.	Type of problem	Freq.	Percentage (%)
	Treatment effectiveness	**63**	**28.13**
1.	No effect of drug treatment / therapy failure	25	39.68
2.	Effect of drug treatment not optimal	18	28.57
3.	Wrong effect of drug treatment	10	15.87
4.	Untreated indication	10	15.87
	Adverse reactions	**65**	**29.02**
1.	Adverse drug event (non-allergic)	62	95.38
2.	Adverse drug event (allergic)	3	4.62
3.	Toxic adverse drug event	-	
	Treatment costs	**60**	**26.79**
1.	Drug treatment more costly than necessary	51	85
2.	Unnecessary drug treatment	9	15
	Others	**36**	**16.07**

1.	Patient dissatisfied with therapy	30	83.33
2.	Unclear problem / complaint	6	16.67
	Total	**224**	**100**

4.4. Cause of problem

This table (7), below shows that the dose selection has the highest percentage which is (29.02%) then followed by drug selection (28.13%).

S/No.	**Cause of problem**	**Freq.**	**Percentage (%)**
	Drug selection	**63**	**28.13**
1.	Inappropriate drug (incl. contra-indicated drug)	20	31.75
2.	No indication for drug	5	7.94
3.	Inappropriate combination of drugs or drug and food	17	26.98
4.	Inappropriate duplication	4	6.35
5.	Unnoticed indication	-	-
6.	Too many drugs for indication	10	15.87
7.	More cost-effective drug available	7	11.11
8.	Synergetic or preventive drug required	-	-
9.	New indication presented	-	-

	Drug form	-	-
1.	Inappropriate drug form	-	-
	Dose selection	**65**	**29.02**
1.	Drug dose too low	8	12.31
2.	Drug dose too high	12	18.46
3.	Dosage regimen not frequent enough	-	-
4.	Dosage regimen too frequent	-	-
5.	No therapeutic drug monitoring	23	35.38
6.	Pharmacokinetic problem requiring dose adjustment	12	18.46
7.	Deterioration/improvement of disease requiring dose adj.	10	15.38
	Treatment duration	-	-
1.	Duration of treatment too short	-	-
2.	Duration of treatment too long	-	-
	Drug use / administration process	**35**	**15.63**
1.	Inappropriate timing of administration / dosing intervals	10	28.57
2.	Drug underused / under-administered	-	-
3.	Drug overused / over-administered	-	-
4.	Drug not taken / administered at all	25	71.43
5.	Wrong drug taken / administered	-	-
6.	Drug abused (unregulated overuse)	-	-

7.	Patient unable to use drug / form as directed	-	-
	Logistics	**20**	**8.93**
1.	Prescribed drug not available	15	75
2.	Prescribing error (information wrong or missing)	5	25
3.	Dispensing error (wrong drug or dose)	-	-
	Patient	**5**	**2.2**
1.	Patient forgets to take drug	-	-
2.	Patient uses unnecessary drug	5	100
3.	Patient takes food that interacts	-	-
4.	Patient stored drug inappropriately	-	-
	Other	**36**	**16.07**
1.	Other cause	30	83.33
2.	No obvious cause	6	16.67
	Total	**224**	**100**

4.5 Contraindications involving drugs use in cervical cancer patients

In this table (8) ,contraindications are factors that serve as a reason to withhold a certain medical treatment due to the harm that it would cause the patients. Contraindication is the opposite of indication. Cisplatin is the drug of choice according to the NCCN guidelines but it is highly contraindicated in patients with renal failure which fall in line with this study that was carried out which shows that it had the highest percentage (15%).

S/No.	Contraindications	Drugs	Frequency	Percentage (%)
		Anticancer drugs		
1.	Renal failure	Cisplatin	3	15
2.	Hepatitis	Cisplatin	2	10
3.	Pregnancy	5-Fluorouracil	2	10
4.	Pregnancy	Paclitaxel	1	5
		Supportive drugs		
5.	Hypertension	Corticosteroids	2	10
6.	Diabetes	Corticosteroids	1	5
7.	Peptic ulcer	Corticosteroids	2	10
8.	Renal Failure	Metoclopramide	1	5
		Others		
9.	Diabetes	ACE – Inhibitors (Lisinopril)	2	10
10.	Diabetes	Beta – blockers (Atenolol)	1	5
11.	Hypertension	Antiplateletes (Aspirin)	2	10
12.	Peptic ulcer	NSAIDS (Diclofenac)	1	5

		Total	**20**	**100**

4.6 Interactions involving drugs use in cervical cancer patients

In table (9), a drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. Typically, interaction between drugs comes to mind (drug-drug interaction). However, interactions may also exist between drugs & foods (drug-food interactions), as well as drugs & herbs (drug-herb interactions). These may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances. However, 5-Fu, Paclitaxel,corticosteroid and ACE- inhibitors have the highest percentages (11.76%) respectively while the lowest percentage (5.88%) which are the cisplatin, beta blockers and diuretics.

S/No.	**Drugs**	**Interacting Drugs**	**Mechanism of interaction**	**Effect**	**Severity**	**Frequency**	**Percentages (%)**
	Anticancer						
1.	Cisplatin	Furosemide	Pharmacodynamic Inter.	Ototoxicity	Moderate	1	5.88
2.	Cisplatin	Phenytoin	?	?	Moderate	1	5.88
3.	5 – Fu	Diclofenac	Pharmacodynamic Inter.	Hepatotoxicity	Moderate	2	11.76
4.	5 – Fu	Metronidazole	Pharmacokinetic	Anemia	Moderate	2	11.76

			inter.				
5.	Paclitaxel	Cimetidine	Pharmacokinetic Inter.	Nausea	Moderate	1	5.88
6.	Paclitaxel	Dexamethason	Pharmacokinetic Inter.	Anemia	Moderate	2	11.76
7.	Paclitaxel	Phenytoin	Pharmacokinetic Inter.	Therapy failure	Moderate	1	5.88
S/No.	**Drugs**	**Interacting Drugs**	**Mechanism of interaction**	**Effect**	**Severity**	**Frequency**	**Percentages (%)**
	Anticancer						
1.	Cisplatin	Furosemide	Pharmacodynamic Inter.	Ototoxicity	Moderate	1	5.88
2.	Cisplatin	Phenytoin	?	?	Moderate	1	5.88
3.	5 – Fu	Diclofenac	Pharmacodynamic Inter.	Hepatotoxicity	Moderate	2	11.76
4.	5 – Fu	Metronidazole	Pharmacokinetic inter.	Anemia	Moderate	2	11.76
5.	Paclitaxel	Cimetidine	Pharmacokinetic Inter.	Nausea	Moderate	1	5.88
6.	Paclitaxel	Dexamethason	Pharmacokinetic Inter.	Anemia	Moderate	2	11.76

4.7 Adverse drug reaction

In table (10), it is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modifications of physiological function. In this study, it was shown that almost all the anticancer drugs causes nausea and vomiting which indicate it has the highest percentage (46.15%) then followed by diarrhea which has (18.46%) meanwhile, others have the least percentages.

S/NO	**Adverse(ADR)**	**Suspected Drugs**	**Frequency**	**Percentages (%)**
1.	Hypersensitivity reaction	Cisplatin	3	4.62
2.	Nausea and Vomitting	Cisplatin /Paclitaxel/5-Fu	30	46.15
3.	Diarrhoea	Cisplatin/Paclitaxel	12	18.46
s4.	Loss of hearing	Cisplatin	3	4.62
5.	Mucositis	Cisplatin/5FU/paclitaxel	6	9.23
6.	Seizure	Cisplatin	2	3.08
7.	Loss of hair	Cisplatin/5Fu/Paclitaxel	3	4.62
8.	Nephrotoxicity	Cisplatin	3	4.62
9.	Hypotension	Paclitaxel	3	4.62
		TOTAL	**65**	**100**

Relationship between patients factors and DRPs.

In this table (11), it shows the relationship between patients factors such as age, number of medications and comorbidity which indicate the p value is < 0.05.

Patients Factor		Drug Related Problems(DRPs)		P Value
		Yes	No	
Age	< 50 years	33	6	0.006
	≥50 years	25	1	
Comorbidity	< 3	53	6	0.002
	≥ 3	5	1	
Number of medication	<5	5	7	0.01
	≥5	53	0	

Table 12: Pharmacist possible intervention

Many interventions were made as such pharmacists possible recommendations were shown below.

S/NO	Drugs	Recommendations
1.	Cisplatin + Ferosemide	Generally avoid (unless benefit out weight risk).
2.	Cisplatin + Phenytoin	Increase phenytoin dosage during chemotherapy and decrease it after.
3.	5-Fu + NSAID	Not to use for a prolong period of time (less than a week)
4.	5-Fu + Metronidazole	Generally avoid (unless benefit out weight risk)
5.	Paclitaxel + Cimetidine	Increase blood level of paclitaxel so cimetidine is replace with PPI
6.	Paclitaxel + Dexamethasone	Increase the dose of Paclitaxel during chemotherapy.
7.	Paclitaxel + Phenytoin	Increase phenytoin dosage during chemotherapy and decrease it after.
8.	Corticosteroid + NSAID	Patients should take with food and immediately report signs and symptoms of G.i ulcer and bleeding. Selective use of prophylactic anti-ulcer therapy.
9.	Ace-inhibitors + NSAID	Interactions are not expected with low dose but prolong use of Nsaid required blood pressure monitoring more closely.
10.	Beta blockers + NSAID	Interaction is associated with prolong use but can be used for less than a week
11.	Beta blockers + Antidiabetic	Cardioselective beta blockers are preferred over non- selective in diabetic patients.
12.	Diuretics + NSAIDs	Avoid dehydration and carefully monitoring patient's renal function and blood pressure. If hyperkalemia occur both drugs should be discontinue until conditions are corrected.

5. Discussions

Worldwide, cervical cancer was reported to be the fourth-most common cancer and cause of death in women (WHO, 2014). About 70% of cervical cancers occur in developing countries (WCR, 2014;WHO, 2014). In developed countries, the widespread use of cervical screening programs has dramatically reduced rates of cervical cancer (Canavan et al, 2000).

This work was a retrospective study aimed at investigating DRPs in cervical cancer patients receiving chemotherapy. Drug related problems are significant healthcare problems and great proportions are preventable.

Our study identifies significant cases of cervical cancer. Majority of the women captured in this our study were between the age of 30 and 60 years. This number could be attributed to the wide prevalence of human papilloma virus and lack of its vaccination among developing countries. It was also discovered that women in the said region don't go for routine screening.

Cervical cancer chemotherapy is one of the best approaches to eradicate the cancer and its success is far from satisfactory due to mostly drug related problems. Drug regimens are administered following established protocols in cervical cancer chemotherapy. The more complex drug therapy is the higher the risk of experiencing drug related problems (DRPs) such as adverse effects, comorbidities, interactions, medication errors, and non-adherence.

A study conducted in Ethiopia, about 474 DRPs was identified out of 367 (0.77) patients, also a prospective study in Netherland showed that a total of 952 DRPs detected in 546 (0.57) patients. In Portugal, a retrospective study was also conducted such that the DRPs were 43 detected in 56

patients (1.30). In Ethiopia, a study showed a statistically significant association between numbers of medications and presence of comorbidities with occurrence of DRPs. Meanwhile, a study conducted in Norway indicates that the number of DRPs per patients increased approximately linearly with the increase in number of drugs used.

In our study, we were able to identify 224 DRP in 65 (0.29) patients. This could be explained due to the fact that our study setting falls in a less developed country and patient management is believed to be not as standard when compared to those in developed countries mentioned above.

The most common cause of DRPs as determined in our study is adverse drug reaction, treatment effectiveness and dose selection. And this could be attributed to the ability of cytotoxic drugs to attack both cancer and normal cells. Management of such reactions is poor in the targeted facility.

However, most of the cervical cancer patients fall within the age range of 40 – 49 years. Drug related comorbidities are important healthcare issues. Cardiovascular and diabetic diseases are the highest comorbidities recorded in our study accounting for about 29.77% and 27.38% respectively. It also showed that one patient can have more than two comorbidities. Furthermore, majority of the patients are on cisplatin and 5- fluorouracil as a choice of drug chemotherapy in the facility. It shows that the more comorbid the patient has the higher the tendency of DRPs as discuss before. Cisplatin is the drug of choice according to the NCCN guidelines but it is highly contraindicated in patients with renal failure which fall in line with this study that was carried out which shows that it had the highest percentage (15%).

In a study that was carried out in Singapore, Drug – Drug interactions (DDI) was the most common DRPs detected and 162 patients with 55.1% were identified with at least one potential DDI. The prevalence of potential DDI in the above mention study in patient's population could

be connected to polypharmacy. In contrast, DDI in our study was not the most common DRPs detected but about 26.98% was identified from 65 patients. A possible explanation could be that our study was concern with only cervical cancer not general cancer. The association between increasing number of drugs and higher incidence of DDI has been established by several studies. In our study, the prevalence of DDI may be attributed to many combination of drugs used by the patients such as cisplatin and furosemide which could lead to pharmacodynamics interactions causing kidney damage and hearing loss, 5-Fu and NSIDs may result to alteration of dihydropyrimidine dehydrogenase (DPD) enzyme activity resulting in an enhanced cytotoxic effect that is NSAIDs enhanced in a synergistic manner the cytotoxic effect of 5- Fu. Paclitaxel and dexamethasone in which dexamethasone may reduce the blood levels and effect of paclitaxel. Dexamethasone will increase the levels or effect of paclitaxel. Paclitaxel levels or toxicity may increase when co-administered with CYP2C8 inhibitor. In the case of 5-Fu and metronidazole the metronidazole may slow down how quickly your body removes fluorouracil (pharmacokinetics). It also shows that combining corticosteroid and NSAID may either increase toxicity of the other by pharmacodynamics synergism also increased risk of GI ulceration.

The use of anticancer drugs often results in the use of other agents to reduce or prevent side-effects of the anticancer treatment, thereby increasing the interaction potential due to polypharmacy. Furthermore, cancer itself increases the need for more medications. Cytotoxic agents have a narrow therapeutic window and a complex pharmacologic profile. In oncology patients, pharmacokinetic parameters can be altered by the disease itself or due to malnutrition, reduced levels of serum-binding proteins, edema, or hepatic and/or renal dysfunction. Patients with cancer are therefore more at risk for drug interactions (Jaehde, 2008).

The use of non-anticancer drug is not uncommon in our study. Cancer patients were mostly having co-mobid states, and will have to be on many other medications. This at large could lead to polypharmacy drug interaction and eventually treatment failure.

In chemotherapy, ADRs have strong connection to the treatment itself. In fact, most cytotoxic agents cannot differentiate between cancer and normal cells, most ADRs seem to be unavoidable. They are often accepted by both the patients and the health care professionals. In a study, that was carried out in Florida among elderly patients found actual ADRs in 56.3% of the study participants. Also a study conducted in Ethiopia, shows that ADRs is the most prevalent among the DRPs which occurred in 45.5% of the population (34.4%) of the total number of DRPs. Likewise a study was carried out in Thailand that indicate ADRs was the most common DRPs which was seen in 44 of 68 cancer patients (64.70%). The most common ADRs identified were vomiting, nausea and alopecia was observed in the study except diarrhea.

In our study, a substantial portion of DRPs identified were adverse drug reaction (ADR) which had the highest percentage (29.02% with regard to the problems type), mostly linked with chemotherapeutic agents. A possible explanation of these could be as a result of mechanisms of action and narrow therapeutic window; ADRs are common in patients receiving chemotherapy. The most common ADRs identified in our study were nausea, vomiting and diarrhea with the percentage (46.15% and 18.46% respectively). However, possible recommendations were made in order to avoid serious problems as the case may be. In the case of certain medications it should be avoided generally (Cisplatin + Furosemide) except when the benefit outweigh the risk. In some medications there is needs for change of drugs completely.

6. Study Limitations

1. The first limitation concerns the retrospective nature of this study using medical records, established references, and a literature review. The prevalence of DRPs might be underestimated, as some important data including physicians' and patients' perceptions could not be found in the medical records.

2. The second limitation is that the record was only able to generate the list of cervical cancer patients who were registered from June 2015 to June 2016. Therefore, the findings of this study may not be generalized to the actual population of Nigeria, because of the relative small sample size.

3. Finally, this study used only part of the PCNE Classification in assessing DRPs. Interventions by pharmacist as well as the outcome of interventions listed in the tool were not included.

7. Conclusion

This study showed that DRPs in cervical cancer patients receiving chemotherapy were common in at the oncology clinic of interest. The risk factors associated with DRPs are the presence of comorbidities and polypharmacy. Our study have shown that cancer patients are one of the groups who are most at risk of developing DRPs. Potential DDI, treatment effectiveness, treatment cost, drug selection, dose selection and ADRs were the most common DRPs detected in this study. This calls for interventions which could lead to involvement of a pharmacist in management of cervical cancer patients to detect and intervene in DRPs in order to ensure a better therapeutic result.

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Appendix I: Data Collection Form

Patient ID: Age: Diagnosis: History:			**2. Cause of problem** (one problem can have more than one cause)				
			C1☐	**Drug selection**	C5☐	**Drug use / administration process**	
Medication and dosing regimen			C1.1 ☐	Inappropriate drug (incl. contra-indicated drug)	C5.1☐	Inappropriate timing of administration / dosing intervals	
			C1.2 ☐	No indication for drug	C5.2☐	Drug underused / under-administered	
			C1.3 ☐	Inappropriate combination of drugs or drug and food	C5.3☐	Drug overused / over-administered	
			C1.4 ☐	Inappropriate duplication	C5.4☐	Drug not taken / administered at all	
DRP potential ☐ manifest ☐			C1.5 ☐	Unnoticed indication	C5.5☐	Wrong drug taken / administered	
			C1.6 ☐	Too many drugs for indication	C5.6☐	Drug abused (unregulated overuse)	
1. Type of problem (tick one box only)			C1.7 ☐	More cost-effective drug available	C5.7☐	Patient unable to use drug / form as directed	
P1☐	**Treatment effectiveness**		C1.8 ☐	Synergetic or preventive drug required	C6☐	**Logistics**	
P1.1 ☐	No effect of drug treatment / therapy failure		C1.9 ☐	New indication presented	C6.1☐	Prescribed drug not available	
P1.2 ☐	Effect of drug treatment not optimal		C2☐	**Drug form**	C6.2☐	Prescribing error (information wrong or missing)	
P1.3 ☐	Wrong effect of drug treatment		C2.1☐	Inappropriate drug form	C6.3☐	Dispensing error (wrong drug or dose)	
P1.4	Untreated indication		C3☐	**Dose selection**	C7☐	**Patient**	

	☐							
P2☐	**Adverse reactions**			C3.1☐	Drug dose too low		C7.1☐	Patient forgets to take drug
	P2.1 ☐	Adverse drug event (non-allergic)		C3.2☐	Drug dose too high		C7.2☐	Patient uses unnecessary drug
	P2.2 ☐	Adverse drug event (allergic)		C3.3☐	Dosage regimen not frequent enough		C7.3☐	Patient takes food that interacts
	P2.3 ☐	Toxic adverse drug event		C3.4☐	Dosage regimen too frequent		C7.4☐	Patient stored drug inappropriately
P3☐	**Treatment costs**			C3.5☐	No therapeutic drug monitoring	C8☐	**Other**	
	P3.1 ☐	Drug treatment more costly than necessary		C3.6☐	Pharmacokinetic problem requiring dose adjustment		C8.1☐	Other cause (specify in notes)
	P3.2 ☐	Unnecessary drug treatment		C3.7☐	Deterioration/improvement of disease requiring dose adj.		C8.2☐	No obvious cause
P4☐	**Others**		C4☐	**Treatment duration**				
	P4.1 ☐	Patient dissatisfied with therapy		C4.1☐	Duration of treatment too short			
	P4.2 ☐	Unclear problem / complaint		C4.2☐	Duration of treatment too long			