EFFECTIVENESS OF MANNITOL IN PREVENTING ACUTE KIDNEY INJURY AMONG PATIENTS WITH CERVICAL CANCER STAGE 1B TO 2B RECEIVING CONCURRENT CHEMORADIATION AT MOI TEACHING AND REFERRAL HOSPITAL AND ELDORET HOSPITAL

By

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A THESIS SUBMITTED TO THE SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR AN AWARD OF THE DEGREE OF MASTER OF MEDICINE IN REPRODUCTIVE HEALTH OF MOI UNIVERSITY

DECLARATION

Student Declaration

I declare that this thesis is my original work and has not been presented in any other university or institution for the award of the degree or any academic credit.

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DEDICATION

I dedicate this study to my darling daughter, my family and to all women with cervical

cancer.

ACKNOWLEDGMENT

I wish to thank my supervisors Prof. Omenge Orango and Dr. Peter Itsura for their invaluable advice, and guidance in the development of this thesis.

I would also like to thank my colleagues in the Department of Reproductive Health for their input and constructive criticism.

Finally, I thank my entire family for their support and prayers.

ABBREVIATIONS

ACOG   American College of Obstetricians and Gynecologists

CCRT   Concurrent Chemoradiation Therapy

CDC   Centers for Disease Control and prevention

CDDP   Cisplatin

CRT   Chemotherapy

DFS   Disease-free survival

FIGO   International Federation of Gynecology and Obstetrics

GFR   Glomerular Filtration Rate

HPV   Human Papilloma Virus

IREC   Institutional Research and Ethics Committee

KDHS   Kenya Demographic and Health Survey

LACC   Locally Advanced Cervical Cancer

LVSI   Lymphovascular space invasion

MBChB   Bachelor of Medicine and Surgery

MMED   Master of Medicine (Degree)

MTRH   Moi Teaching and Referral Hospital

NACT	Neoadjuvant Chemotherapy
OS	Overall Survival
PGRH	Post Graduate Reproductive Health
RBF	Renal Blood Flow
RH	Reproductive Health
RIFLE	Risk, Injury, Failure, Loss and End-stage Renal disease
ROS	Reactive oxygen species
RT	Radiotherapy
RVR	Renal Vascular Resistance
SNOSE's	Sequentially, Numbered, Opaque & Sealed Envelopes
SOM	School of Medicine
SSA	Sub Saharan Africa
TNM	Tumor (T), nodes (N), and metastases (M)
UN	United Nations
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Acute Kidney Injury - Defined as abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes

Chemoradiation : Combination treatment of chemotherapy and radiotherapy

Double blind study: an experimental procedure in which either the subject or the person administering the experimnt know the crtical aspect of the experiment

Microinvasive: the extension of cancer cells beyond the basement membrane into adjacent tissue with a focus of no more than 10mm in greatest dimension.

Neoadjuvant : Induction treatment (chemotherapy, radiation therapy, or hormone therapy) given as a first step to shrink a tumor before the main treatment, which is usually surgery.

Nephrotoxicity: Defined as rapid deterioration in the kidney function due to toxic effect of medications and chemicals, such as Cisplatin.

Standard of Care: A general or specific medical treatment based on scientific evidence and collaboration between medical professionals involved in the treatment of a given condition

Total body Irradiation (TBI) - Involves irradiation of the whole body, typically 10-15Gy but can be more.

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ABSTRACT

Background: Cervical cancer is the leading cause of cancer deaths in women with 90% occurring in low and middle-income countries. The gold standard of treatment for locally advanced cervical cancer is concurrent chemoradiation with cisplatin, cisplatin serves as a radiosensitizer.However, cisplatin is known to be toxic to the kidney, leading to dose delays and treatment cessation. This study aims to determine whether mannitol prevents Cisplatin induced acute kidney injury during chemoradiation therapy for cervical cancer.

Objective: To evaluate the effectiveness of Mannitol using the rate of averted acute kidney injury and completion rate among patients with cervical cancer undergoing chemoradiation treatment in MTRH and Eldoret Hospital.

Methods: It was a double blind randomized clinical trial study involving 50 women with cervical cancer stage 1B up to 2B underwent chemoradiation at MTRH and Eldoret Hospital. Patients were naive to chemotherapy and radiotherapy. Patients were randomly assigned into two arms of 25 each (intervention and control). Intervention arm received mannitol 20% (200mls) with standard chemotherapy regimen (Cisplatin 40mg/m^2) and the control arm received standard chemotherapy regimen as per the protocol along with 200mls of Normal Saline as placebo. All patients underwent 25 sessions of external beam radiation at 1 to 1.5 Grays per session. Weekly kidney function of patients was collected. Data was collected using structured questionnaire and analyzed. The outcome measured was the rate of averted acute kidney injury and the time of chemotherapy completion in both arms.

Results: The average age in the control and intervention group was 52.8 and 50.6 The rate of averted AKI was 96% in the intervention arm and 92% in the control arm.The time of chemoradiation completion was the same among both arms.

Conclusion: We do not have enough evidence to conclude that the proportion with averted AKI or the time to completion differed between the two groups.

Recommendation: Further studies should be done to evaluate the effectiveness of Mannitol in preventing of CIN and AKI.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Cervical cancer is the fourth commonest cancer among women in the world. In 2018, 570 000 new cases of cervical cancer were diagnosed, and 311 000 women died of the disease, nearly 90% of them in low- to middle-income countries. Without urgent attention, deaths due to cervical cancer are projected to rise by almost 25% over the next 10 years.

Before the 1990s, the gold standard treatment of stage II cervical cancer was external beam and internal radiation therapy with roughly 60% of patients with locally advanced cervical cancer survived 5 years from treatment with radiation therapy alone. More recently, however, the addition of chemotherapy (anti-cancer drugs) as a radio sensitizer has improved long-term outcomes in patients with this disease. In facilities that lack radiotherapy, neoadjuvant chemotherapy had been used to down size tumor to improve curability and safety of the surgery, as well as inhibit micrometastasis and distant metastasis.

Cisplatin or any other radio sensitive chemotherapy to radiotherapy (RT) have improved local tumor control, disease free survival rate, and overall survival in advanced cervical tumors through randomized trial. Therefore, concurrent chemoradiation is considered as standard treatment modality (Yamashita et al., 2010) Although cisplatin has been the gold standard in cervical cancer therapy,its use is limited by two factors: acquired resistance to cisplatin and severe side effects in normal tissues. Major limiting factor in the use of cisplatin is the side effects in normal tissues, which include neurotoxicity, ototoxicity, severe nausea and vomiting. This leads to

electrolyte imbalance mainly hypomagnesemia, hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia and finally nephrotoxicity.

A study done in Indonesia (Yenny prasaja et al 2014) concluded that, Cisplatin nephrotoxicity occurred in more than one-third of patients after the fourth cycle of chemotherapy and worsened after each cycle despite preventive strategies such as hydration.

Mannitol is a polyol (sugar alcohol) which is widely used in the food and pharmaceutical industries. Due to its low molecular weight (182.172 g/mol) , mannitol is freely filtered through the renal tubules. It does not get reabsorbed and continues to be osmotically active in the tubules and this accounts for its action as an osmotic diuretic. Mannitol also causes release of renal prostaglandins that lead to renal vasodilation and an increase in tubular urine flow that is believed to protect against renal injury by reducing tubular obstruction. It also acts as a free-radical scavenger and reduces the harmful effects of free radicals during ischaemia − reperfusion injury. Mannitol is a logical choice for reduction of cisplatin-induced nephrotoxicity as it is nontoxic and could reduce the half-life of cisplatin in the kidney.

1.2 Problem Statement

It is recognized that the prevalence of cisplatin associated nephrotoxicity is high, occurring in about one-third of patients undergoing cisplatin treatment.Cisplatin is commonly used in cancer of cervix as neoadjuvant therapy in settings without radiotherapy facility to down size tumour before radical surgery, in palliative setting, and as radiosensitizer in facilities with radiotherapy.   There is need to prevent this side effect in order to get better outcomes in cervical cancer treatment and management. Mannitol has shown scientific benefits as a renal protective agent in patients with high

risk of developing renal failure by increasing urine output hence decreasing toxic build ups from Cisplatin use.However we are lacking that evidence in our setting . In this study, we are looking at patients with cervical cancer stage 1B up to 2B undergoing chemoradiation with cisplatin and to determine whether mannitol will help in aversion of cisplatin induced kidney injury in our setting.

1.3 Justification

The rate of kidney injury as an adverse effect of cisplatin has a potentially significant impact on hospital resources, length of hospital stay, treatment outcome and prognosis of the patient. As such, we purpose to establish the effectiveness of mannitol on patients with cervical cancer receiving concurrent chemoradiation at Moi Teaching and Referral Hospital and Eldoret Hospital. Moi Teaching and Referral Hospital, Eldoret happens to be the second largest referral hospital in Kenya and serves as the main catchment area for patients with oncologic diseases in Rift Valley, hence the results of this study will benefit the target population of this region.. Additionally, our study seeks to robustly complement the findings of previous studies.

1.4 Research Hypothesis

Null Hypothesis (H0) - Use of Mannitol as a renal protective agent has no effect on rate of averted acute kidney injury among patients with stage 1B to 2B Cervical cancer in MTRH and Eldoret Hospital.

Alternative Hypothesis (H1) - Use of Mannitol as a renal protective agent has effect on the rate of averted acute kidney injury among patients with stage 1B to 2B Cervical cancer in MTRH and Eldoret Hospital.

1.5 Objectives

1.5.1 Broad objective

To determine the effectiveness of Mannitol in prevention of acute kidney injury in oncurrent chemoradiation regimen and rate of chemotherapy completion among cervical cancer patients stage 1B to 2B receiving chemoradiation treatment in MTRH and Eldoret Hospital

1.5.2 Specific objectives

1. To determine the socio- demographic and clinical characteristics of Patients with Cervical cancer receiving concurrent chemoradiation in MTRH, and Eldoret Hospital.

2. To determine the effect of Mannitol on the rate of averted acute kidney injury among cervical cancer patients stage 1B to 2B receiving Mannitol with concurrent chemoradiation in MTRH and Eldoret Hospital.

3. To determine the rate of completion of chemoradiation among the patients with cervical cancer stage 1B to 2B receiving Mannitol with concurrent chemoradiation in MTRH, and Eldoret Hospital

1.6 Outcomes

Primary outcome - Creatinine levels (mean) in both Intervention and control arm at initiation and end of study.

Secondary - Number of cycles completed and number of patients that completed the chemoradiation as per protocol in both intervention and control arm.

CHAPTER TWO

2.0 LITERATURE REVIEW

Cisplatin is known to be a very efficacious chemotherapy drug however the nephrotoxic effect limits its therapeutic use. The renal protective methods available currently is still insufficient for patients on cisplatin regimen , many studies done mainly focusing on new and better methods. Several routes are associated in resolving cisplatin induced renal injury and mainly target in renal protection proposes. There is several routes that causes kidney injury and cell apoptosis that has similiar modulators. The most common pathways is by oxidative stress that initiates and as a end result.

Cisplatin is usually accumulated and eliminated via the renal proximal tubules, leading to nephrotoxicity. This is restricted to patients with a creatinine clearance (CrCl) >60 mL/min; however, cisplatin-induced nephrotoxicity is frequent, hence it is dose limitiing and/or dose intensity. A study done, moderate to severe nephrotoxicity was noted in 25%–33% of patients receiving a single intravenous (IV) 50–75 mg/m2 dose. A majority of patients (50%–75%) who received cisplatin (15–20 mg/m2 IV daily) over five consecutive days also experienced moderate to severe nephrotoxicity. There was a higher incidence of severe and irreversible nephrotoxicity in patients who received high cisplatin doses (>100 mg/m2).

Mannitol, an osmotic diuretic, has been used in clinical practice for the prevention of AKI because of its potentially renal protective effects: removal of obstructing tubular casts, dilution of nephrotoxic substances in the tubular fluid, and reduction in the swelling of tubular elements via osmotic extraction of water.

2.1 Epidemiology of Cervical Cancer

Cervical cancer is known to be the 2nd most common gynecological cancer after breast cancer worldwide. In 2018, 569,847 new cases of cervical cancer have been diagnosed and 307,000 women died of the disease, that accounts for nearly 90% of them occurring among in low- to middle-income countries (GLOOBCAN, 2018). In Sub Saharan Africa (SSA), 60–75% of women who develop cervical cancer live in rural areas and many of these women go untreated, mostly due to limited access (financial and geographical) to health care facilities.

According to WHO 2018, 33 per 100,000 women in Kenya are diagnosed with cervical cancer and 22 per 100,000 of them succumb from the disease. Based on the data collection by Kenya cancer statistics and National Strategies, an estimate of 25 out of 100,000 women suffers from Cervical cancer and it is the 2nd leading type of cancer in Kenyan women after breast cancer. Unfortunately, 70-80% of the patients are diagnosed late due to lack of awareness, inadequate diagnostic facilities, lack of treatment facilities, high cost of treatment and high poverty (KDHS, 2019).

2.2 Treatment of Cervical Cancer

2.2.1 Management of Patients with Invasive Cervical Cancer
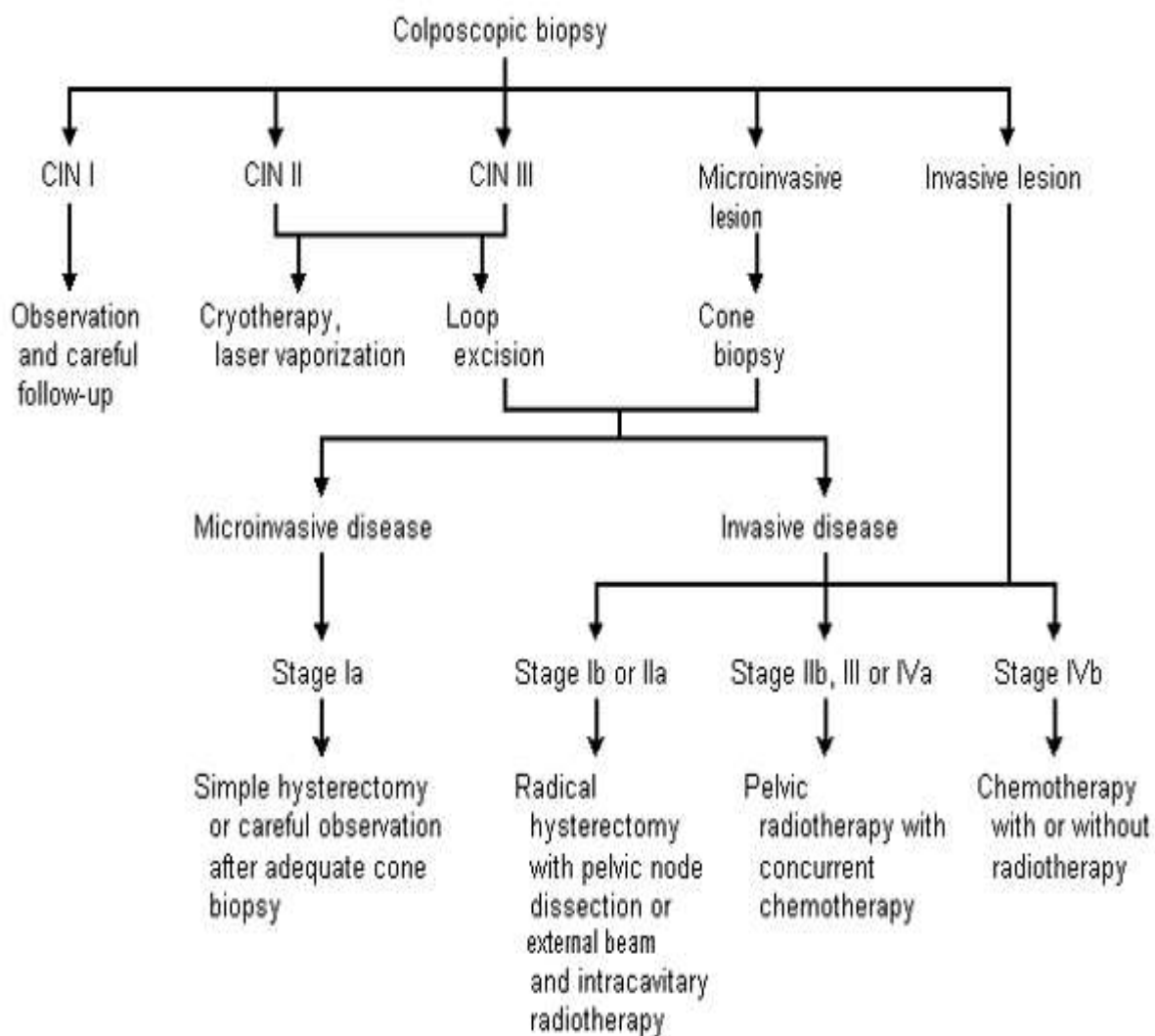
Figure 1: Algorithm for the management of Papanicolaou smear findings and invasive cervical cancer. (CIN = cervical intraepithelial neoplasia)Information from Cannistra SA, Niloff JM. Cancer of the uterine cervix. N Engl J Med 1996;334:1030–8.

2.2.2 Radiotherapy in Cervical Cancer

Despite improvements in screening and prevention, cervical cancer remains a significant cause of morbidity and mortality. Effective treatment is often challenging owing to the disease's propensity for local spread within the pelvis, in close proximity to critical normal tissues. In the last 2 decades there have been notable advances in surgical procedures, external radiation therapy (RT), brachytherapy techniques, and chemotherapy

Postoperative irradiation of the pelvis reduces the risk of local recurrence in patients with high-risk factors (Sedlis's criteria) ,ie, positive pelvic nodes, positive surgical margins, and residual parametrial disease. A randomized trial showed that patients with parametrial involvement, positive pelvic nodes, or positive surgical margins benefit from a postoperative combination of cisplatin-containing chemotherapy and pelvic irradiation.

Ionizing radiation may causes renal impairment and kidney injuries. It frequently occurs when the kidneys are irradiated, causing reactions to the renal tissues, it is usually dose dependant.

Acute renal injury causes by radiation occurs roughly 6- 12 months post radiotherapy and chronic injuries occurs years post radiations.

The classic renal injury caused by radiation happens when bilateral kidneys are irradiated and it is demonstrated as chronic kidney disease.

2.2.3 Chemoradiotherapy in locally advanced cervical cancer.

CRT has been the standard of care for patients with bulky IB2–IVA disease for almost two decades. The publication of five randomised trials, three in Locally Advanced Cervical Cancer, collectively demonstrated an improvement in both disease-free survival (DFS) and overall survival (OS) with concomitant chemotherapy and RT over

standard RT/hydroxyurea and it has changed clinical practice worldwide. However, concerns were raised about the applicability of the results in view of patient selection, protracted overall treatment time, the lack of a RT-only control arm and the poor outcome in the control group. A. The estimated absolute survival benefit for CRT compared with RT alone was 10% for those with FIGO stage I/II disease, compared with 3% for those with FIGO stage III/IVa.

More recently in Mexico, a large randomised phase III trial compared standard CRT with gemcitabine/cisplatin followed by an additional two cycles of adjuvant chemotherapy. A 9% improvement in progression free survival (PFS) at 3 years with treatment intensification was reported, but this approach has not been widely used amid concerns about toxicity.

Technical advances in imaging and in RT planning have facilitated the increased of precision in brachytherapy practice. This approach has been used by groups in Austria, Denmark and France with the dual aim of improving outcome through dose escalation while reducing the toxicity to the surrounding normal tissues. A recently published multicentre cohort study (RetroEMBRACE) demonstrated excellent local control rates of 93% and 79% for patients with FIGO stage IIB and IIIB disease, respectively, at 3 years .

Most clinicians favour: the use of combined modality therapy (surgery followed by chemotherapy or combined CRT) for limited-stage potentially resectable disease; definitive CRT for loco regionally advanced unresectable but non-metastatic disease; and palliative chemotherapy alone for those with metastatic disease, using chemotherapy regimens that are typically used for small-cell lung cancer.

A phase 3 randomized clinical trial done on 850 women with FIGO stage IIIB squamous cell carcinoma of the uterine cervix who were eligible for concurrent

cisplatin chemotherapy were randomly assigned to CT-RT and RT. The follow up period was 5 years. The primary end point was 5-year disease-free survival (DFS), defined as the time between the date of randomization and the date of any recurrence or death (whichever occurred first) in the intent-to-treat population.Results shows that chemoradiotherapy using weekly cisplatin has a better DFS and OS compared with RT in women with stage IIIB squamous cell carcinoma of the uterine cervix.

2.2.4 Lymph node staging and radiotherapy.

In patients with LACC, RT treatment planning relies on accurate staging information. Pelvic MRI and clinical examination is essential to determine the local extent of the tumour for both external beam RT and brachytherapy planning. Information on para-aortic nodal status is also important for treatment planning, particularly in determining the superior extent of the external beam RT portal.

Surgical series suggest that the incidence of para-aortic nodal involvement increases with stage from about 5% in patients with stage I disease to 25% in those with stage III disease. There is much debate concerning the best way to assess the para-aortic nodes. In some parts of the world, PET/CT is routinely used for staging while elsewhere there is a reliance on surgical exploration of the para-aortic region. This is particularly important in the light of the findings from a multicentre, randomised trial demonstrating an excellent outcome in patients with negative PET scans and metastasis <5mm detected histologically after surgical removal and subsequently treated with extended-field CRT.

2.3 Use of Chemoradiation in Cervical Cancer management and its side effect

2.3.1 Radiation Therapy for Cervical Cancer - Management and Side effects

Radiation therapy uses high energy x-rays to kill cancer cells. Depending on the stage of the cervical cancer, radiation therapy may be used:

Concurrent Chemoradiation- Radiation and chemo given together is the preferred treatment as the chemo helps the radiation work better.

To treat cervical cancer that has spread or that has come back after treatment- Radiation therapy may be used to treat cervical cancers that have spread to other organs and tissues.

The types of radiation therapy most often used to treat cervical cancer are:

External beam radiation

Brachytherapy

2.3.1 Concurrent Chemoradiation

Both radical RT and radical surgery are appropriate for patients with locally advanced carcinoma of the cervix. Choice between both treatments is influenced by the availability of specialists, the age of the patient, and perceived toxicities.

It is known that survival after radical hysterectomy is influenced by lymph node status, margin status and parametrial involvement. The depth of cervical stromal invasion, clinical lesion size, and patient age are considered to have its independent prognostic factors.

Postoperative pelvic RT are given to patients with positive pelvic lymph nodes. A GOG 92 compared RT after surgery with surgery alone in an intermediate-risk group; they found a reduction in the recurrence rate from 28% to 15% with the addition of RT. However,GOG 92 excluded patients with positive lymph nodes and it was suggested that RT has a role in adjuvant therapy.

For high-risk postsurgical patients, several retrospective studies have suggested a benefit to cisplatin-based CT either given alone or before RT. In a small randomized trial, Curtin et al compared CT with CT + RT and showed the same relapse rate in a high-risk patient group. Tattersall et al compared RT with CT followed by RT and found no difference in disease-free or overall survival. Concomitant CT with RT has proven to improve survival and reduce relapses in select groups of cervical cancer patients when compared with RT alone.. For bulky stage IB cervical cancer, the GOG found improvement in the recurrence-free interval and survival for patients treated with weekly cisplatin during irradiation compared with RT alone.

Ryu and Nagy et al. conducted a RCT compared weekly against 3 weekly cisplatin, the results shows triweekly cisplatin 75 mg/m2 every 21 days, concurrent with radiotherapy is more effective with an increase in overall 5 year survival of 18%, and a reduction in the risk of death by 62.5% (HR 0.375, p = 0.03). It was also overall less toxic than weekly cisplatin treatment. For instance, grade 3–4 neutropenia was approximately half of that seen with the weekly regimen (Ryu et al., 2011).

The results of Nagy et al. were similar, showed that daily cisplatin, 20 mg/m2 for 5 days every three weeks has a superior five-year local relapse-free survival (p b 0.01), lesser toxicity, and a similar 5-year survival rate compared with the standard weekly cisplatin treatment (Nagy et al., 2012).

2.3.3 Key Recommendation for radiotherapy in cervical cancer.

Postoperative RT with and without systemic therapy

High-risk surgico-pathologic findings

There is a strong evidence that adjuvant concurrent cisplatin-based chemoradiation improves overall survival and progression-free survival for patients with cervical cancer who have high-risk pathologic features after radical hysterectomy (eg, positive

margins or positive lymph nodes or extension into the parametrial tissue) ; the benefit of chemoradiation compared with RT alone is similar to the benefit observed for locally advanced patients with cervical cancer who undergo definitive chemoradiation compared with RT alone. For cases meeting these high-risk criteria, whole pelvic RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m2).

Intermediate-risk surgicopathologic findings

The Gynecologic Oncology Group (GOG) conducted an RCT (GOG 92) of 277 patients with cervical cancer (including both squamous cell and adenocarcinomas) treated by radical hysterectomy and intermediate-risk Sedlis criteria who were randomized to no further treatment versus adjuvant pelvic RT. Adjuvant radiation was associated with a 47% reduction in recurrence (a 12.6% absolute reduction) with acceptable morbidity and a 6% versus 2% grade 3 or 4 adverse event rate.

A 2012 meta-analysis, which included data from GOG 92, further supports the benefit of adjuvant RT for those with intermediate-risk factors, with a significantly lower risk of disease progression at 5 years. For cases meeting these intermediate-risk criteria, whole pelvic RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy per fraction or 4000 to 4400 cGy in 200 cGy per fraction.

Occult cervical cancer after total hysterectomy

For women who are found to have an occult invasive cervical cancer after total hysterectomy (either for benign disease or uterine cancer), further treatment is needed for stages greater than or equal to IA2 because a radical hysterectomy with lymph node dissection is required for curative surgery in these cases.

Options would be additional surgery (a parametrectomy, upper vaginectomy, and lymph node dissection) or RT. In practice, if additional surgery is expected to be technically difficult and/or potentially morbid, RT or chemoradiation may be offered as an alternative, particularly if RT is already indicated from surgicopathologic findings. Although prospective evidence is lacking, pelvic RT to 4500 to 5040 cGy, followed by a boost to the sites at high risk of additional occult disease (either with vaginal brachytherapy or external beam radiation therapy (EBRT) depending on location) is a reasonable approach. Concurrent chemotherapy may also be considered.

Definitive RT with and without systemic therapy; hysterectomy after RT

Multiple RCTs demonstrate an approximately 10% survival benefit at 5 years for radiation with concurrentplatinum-based chemotherapy compared with RT alone for women with stage IB3-IVA cervical cancer. If treatment of the extended field is indicated, concurrent chemotherapy with cisplatin is administered with appropriate symptom management, consideration of intensity modulated radiation therapy (IMRT) to spare bowel; close monitoring of laboratory tests with special attention to assess neutropenia, anemia, and thrombocytopenia; and a potential need to stop chemotherapy before the completion of 5 cycles. For definitive RT, whole pelvic RT or extended field RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m2). Additional nodal boosts may be included. This is followed by brachytherapy with a goal to limit the total treatment time to 7 to 8 weeks.

3. Hysterectomy after radiation

In the era of combined chemoradiation and image guided brachytherapy (IGBT), pelvic control is very high even for women with bulky stage IB3-IIB cervical cancer. Therefore adjuvant hysterectomy after radiation is not routinely recommended,

particularly when IGBT is available. When a lower dose of brachytherapy is given and IGBT is not available, hysterectomy may be considered, especially in the presence of cervix-confined residual disease. Despite high rates of local control, a small percentage of cancers do not respond well to chemoradiation and have evidence of residual disease after treatment. Time should be allowed for delayed response, with consideration of positron emission tomography imaging approximately 3 months after treatment completion. However, if recurrence and/or persistence of disease is confirmed by biopsy as early as 8 to 12 weeks after therapy, there may be a role for salvage hysterectomy or exenteration, if feasible, to improve local control and survival, at the risk of significant morbidity.

Intensity modulated radiation therapy

In the treatment of postoperative and definitive cervical cancer, dosimetric studies of IMRT have demonstrated decreased volumes of the bladder, rectum, bowel, and bone marrow receiving clinically significant doses of RT.Single and multi-institution series of postoperative RT have demonstrated a favorable toxicity profile with the use of IMRT.

Brachytherapy

Brachytherapy is an important component in definitive treatment for patients with locally advanced cervical cancer. Results from national databases found much improved outcomes using brachytherapy. In multiple large national retrospective data sets, the use of brachytherapy in women with cervical cancer declined between 2003 to 2011, whereas use of IMRT or SBRT instead increased during this period. The use of brachytherapy has been consistently associated with improved survival compared with

IMRT or SBRT as a boost. The omission of brachytherapy has a stronger negative effect on survival than the exclusion of chemotherapy.

Brachytherapy may be considered in the postoperative setting in the presence of a positive vaginal mucosal margin. For positive margins beyond the vaginal mucosa surface (ie, parametrial, paravaginal) or positive macroscopic margins, an advanced brachytherapy technique (eg, an intracavitary multichannel cylinder) or interstitial needles may be required to adequately deliver conformal doses to the areas at risk. For regions at risk not amenable to brachytherapy, a targeted external beam boost may be considered.
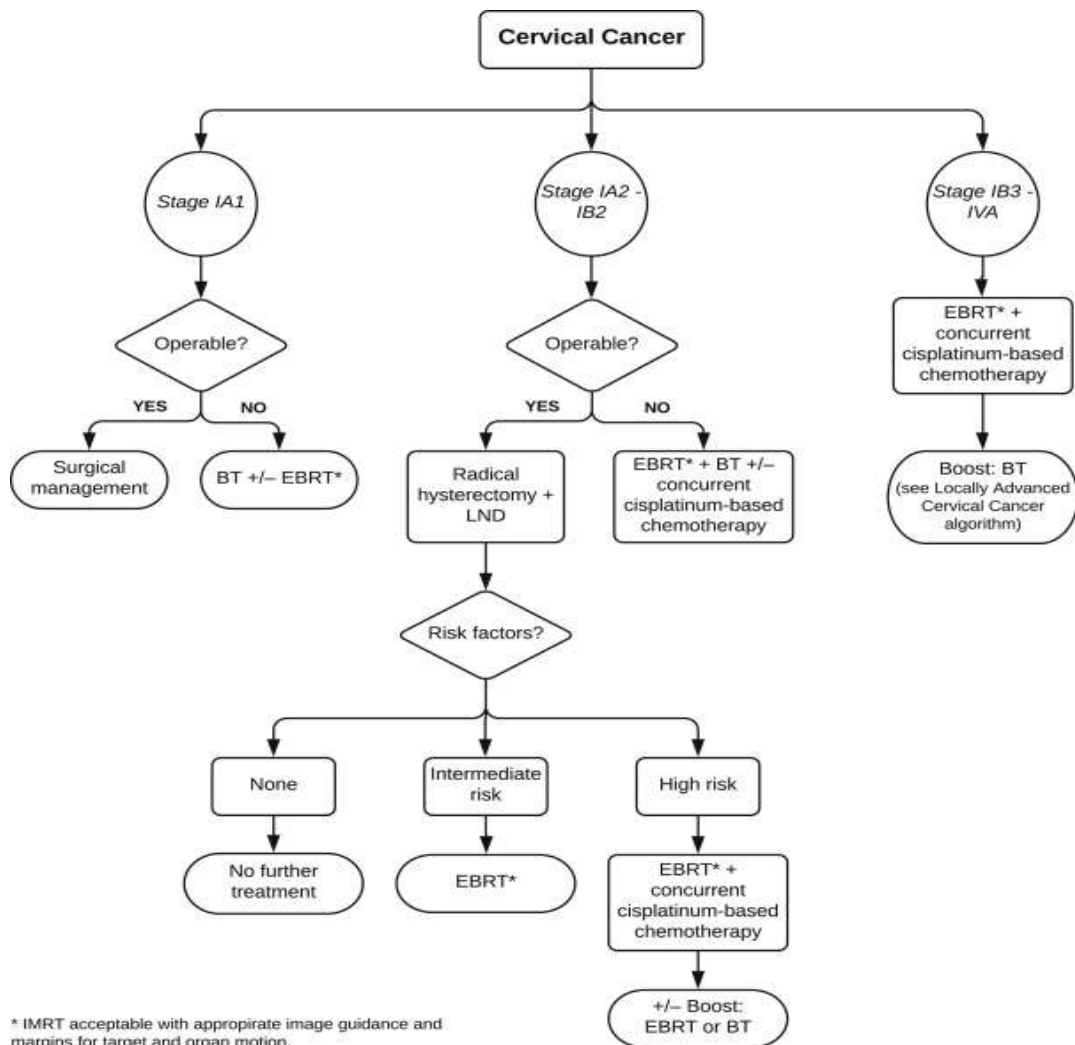
Figure 2: Algorithm for Management of Cervical Cancer with Radiotherapy

In various guidelines including the National Comprehensive Cancer Network, the National Cancer Institute, the European Society of Medical Oncology, and the Japan Society of Gynecologic Oncology, radiation therapy (RT) or concurrent chemoradiotherapy (CCRT), but not chemotherapy alone is recommended as the standard adjuvant therapy after radical surgery (RS) for early-stage cervical cancer.

Adjuvant RT or CCRT after RS can reduce the risk of local recurrence, but the main purpose of adjuvant therapy after RS is to reduce extrapelvic recurrence rather than local recurrence Because RS including extensive pelvic lymphadenectomy should be enough for local disease control even without adjuvant RT or CCRT in cases without gross residual tumors, adjuvant chemotherapy alone after RS may be an alternative strategy for the patients undergoing primary RS. Another possible reason to utilize adjuvant chemotherapy alone is that chemotherapy can reduce adverse effects of RT or CCRT. Adjuvant RT or CCRT is associated with an increased risk of severe acute complications, described below. And several studies suggest that QOL and sexual functioning of cervical cancer survivors treated with therapy including RT are worse than surgery alone or surgery followed by chemotherapy without RT (Srowkoski et al., 2014).

2.3.4 Side effect of Radiation

According to FIGO, the gold standard management for LACC (stage IIb to IVa) is concurrent chmoradiotherapy followed by brachytherapy.

Radiotherapy treatment can cause acute(within 90 days) and chronic toxicity (months or years after radiotherapy). Roughly 84% of patients will have some adverse effect from radiotherapy. Most common symptoms are hematological, gastrointestinal or genitourinary symptoms.

The extend and intensity of the adverse effect deoends on the radiation dose,fractionation regime, technique and duration of therapy. Individual patient characteristic also plays a role, such as age, stage of disease, genetic aspect, comorbidities and applied therapeutic modalities.

Side effects of EBRT

Short-term side effects of external beam radiation therapy for cervical cancer can include:

Fatigue (tiredness)

Upset stomach

Diarrhea or loose stools (if radiation is given to the pelvis or abdomen)

Nausea and vomiting

Skin changes (mild redness to peeling or flaking)

Radiation cystitis: Radiation to the pelvis can irritate the bladder (radiation cystitis), causing discomfort, an urge to urinate often, and sometimes blood in the urine.

Vaginal pain: Radiation can make the vulva and vagina more sensitive and sore, and sometimes causes a discharge.

Menstrual changes: Pelvic radiation can affect the ovaries, leading to menstrual changes and even early menopause

Low blood counts: Anemia (low levels of red blood cells) can make you feel tired. Neutropenia (low levels of white blood cells) increases the risks of serious infection. Thrombocytopenia (low levels of platelet counts) increases the risk of bleeding.

When chemotherapy is given with radiation, the blood counts tend to be lower and fatigue and nausea tend to be worse. These side effects typically improve in the weeks after treatment is stopped.

Other, long-term side effects are also possible with EBRT.

Possible short-term side effects of brachytherapy

Since the radiation only travels a short distance with brachytherapy, the main effects of the radiation are on the cervix and the walls of the vagina. The most common side effect is irritation of the vagina. It may become red and sore, and there may be a discharge. The vulva may become irritated as well.

Brachytherapy can also cause many of the same side effects as EBRT, such as fatigue, diarrhea, nausea, irritation of the bladder, and low blood counts. Often brachytherapy is given right after external beam radiation (before the side effects can go away), so it can be hard to know which type of treatment is causing the side effect.

Long-term side effects of radiation therapy

Women can experience side effects related to radiation months to years after treatment.

Vaginal stenosis: Both EBRT and brachytherapy can cause scar tissue to form in the vagina. The scar tissue can make the vagina narrower (called vaginal stenosis), less able to stretch, or even shorter, which can make vaginal sex painful.

A woman can help prevent this problem by stretching the walls of her vagina several times a week, either by having sex or by using a vaginal dilator

Vaginal dryness: Vaginal dryness and painful sex can be long-term side effects from radiation (both brachytherapy and EBRT). Estrogens used locally may help with vaginal dryness and changes to the vaginal lining, especially if radiation to the pelvis damaged the ovaries, and caused early menopause. These hormones are typically applied in the vagina and absorbed into the genital area, rather than taken by mouth. They come in gel, cream, ring, and tablet forms.

Rectal bleeding/Rectal stenosis: Radiation to the rectal wall can cause chronic inflammation of the area which can lead to bleeding and sometimes stenosis (narrowing) of the rectum which can be painful. An abnormal opening (called a fistula)

also may form between the rectum and vagina, causing stool to come out of the vagina. These problems typically happen during the first 3 years after radiation treatment. Additional treatments, such as surgery, may be needed to fix these complications.

Urinary problems: Radiation to the pelvis can cause chronic radiation cystitis (as mentioned above), blood in the urine, or an abnormal opening between the bladder and vagina (called a fistula). These side effects can be seen many years after radiation therapy.

Weakened bones: Radiation to the pelvis can weaken the bones, leading to fractures. Hip fractures are the most common, and might occur 2 to 4 years after radiation. Bone density tests are recommended to monitor the risk of fracture.

Swelling of the leg(s): If pelvic lymph nodes are treated with radiation, it can lead to fluid drainage problems in the leg. This can cause the leg to swell severely, a condition called lymphedema.

2.4 Cisplatin

Cisplatin (cisdiamminedichloroplatinum II, CDDP), an inorganic platinum compound, is one of the effective chemotherapeutic agents in the treatment of several types of cancer, including cervical carcinomas.

Cisplatin induced nephrotoxicity is dose dependent with major damage seen on the distal part of the proximal tubule or in the distal nephron segment of the nephrons.

Studies done on animals, particularly rats shows that prolonged injections of cisplatin causes tubular atrophy of cortical nephrons, cystic dilatation of inner cortical or medullary tubules and chronic renal failure due to tubulonephritis

Single courses of 2 mg/kg or 75 mg/m2 cisplatin are associated with nephrotoxicity in one-third of the patients treated. The cellular mechanism of platinum nephrotoxicity is

unknown. Levi et al. have reported a decrease in protein-bound sulfhydryl groups in the renal tissue in rats prior to the development of frank renal failure. In vitro studies showed no direct interaction of platinum with sulfhydryl groups of cysteine or renal homogenates. The decrease in sulfhydryl groups was similar in magnitude in the outer medulla and cortex, whereas platinum concentrations were higher in the medulla. Cysteamine, penicillamine and N-acetylcystein offered no protection against experimental platinum nephrotoxicity.

The mechanism of action of cisplatin is mediated by the interaction of cisplatin with DNA. The principle of action involves exerting its cytotoxicity upon cancer cells through the formation of DNA adducts that include mono-, inter, and intrastrand cisplatin DNA cross-links that arrest the cell cycle at S, G1 or G2-M thus induces apoptosis. This is because cisplatin results into the arrest of cells at G2, S or G1-phases of the cell cycle in an effort to repair the damage. The primary DNA adducts is the intrastrand crosslink adducts responsible for activation of apoptosis. This results into failure of adequate repair resulting into aberrant mitosis of the cells followed by apoptosis. Siddik et al. defines apoptosis as a series of death of cancer cells that is programed by the formation of DNA adducts. The resulting impairment of replication of the cancer cells DNA is responsible for the death of fastest proliferating cells which are carcinogenic. Apoptosis therefore involve various pathways that converge on a single non reversible phase in which nucleases and proteases digest the doomed cell.

Evidences from previous studies on apoptosis have singled out many factors within the cell that determines the survival of the cell. As stated by Hu et al, these factors are Bcl-2 family of proteins, p53-tumor suppressor and intracellular signal-transduction pathways that are often facilitated by protein kinases and phosphatidylinositol

3-kinase. It is therefore important to note that the understanding of the mechanism that drives the regulation of cell cycle and apoptosis gives new insights that can be targeted with the objective of enhancing the therapeutic activity of cisplatin. As outlined in the mechanism above, cisplatin mechanism of actions can be improved by preventing arrest of the cell cycle or through inhibition of protein kinase. According to Galluzzi et al, when the drug is administered, immediate displacement of one or two chloride atoms occurs; this gives an aqua-complex known as aquation. The condition within the cell encourages the dissociation of chloride because the lower intracellular concentration of chloride. The hydrolyzed product is an important electrophile that can react with nucleophile such as sulfhydryl groups on proteins and nitrogen donor atoms on the nucleic acids. The binding of cisplatin to the N7 reactive center on residues of purine results into destruction of the deoxyribonucleic acid (DNA) in cancer cells. This process is very important in cell division because DNA play a key role in transcription and replication. Since DNA is damaged, there is subsequent blockage of cell division which finally results into apoptotic cell death. According to Elise et al, evidence has shown that the most notable changes to the DNA that results into its death as a result of cisplatin administration is 1, 2-intrastrand cross-link purine bases. This represent approximately 90% of DNA adducts. However as stated by Yoshikawa et al other adducts such as inter-strand, 1, 3-intrastrand adducts and other nonfunctional adducts have been closely linked to toxicity of the drug.

However, current research on the mechanism connecting destruction of the DNA and pathway leading to death of the cell is not very clear. As stated by Torres, apoptosis is a critical process in the maintenance of the physiological processes with regard to response to stimuli. At the molecular levels, apoptosis is accomplished through caspases activation. Caspases refers to a group of intracellular cysteine proteases that

cleave substrates at aspartic acid residues. Once caspases have been activated, they target and invade both the nuclear and the cytoplasmic factors that are responsible for the maintenance of architecture of the cell and participate in the repair of the DNA, replication and transcription. This process is also enhanced by the fact that regulation of apoptotic pathways is enhanced in the presence of anti-apoptotic as well as apoptotic proteins. However, as Bagnobianchi states, certain cancer cells often don't respond to treatment by cisplatin in varying degrees. This is partly attributed to failure of cell death resulting from apoptosis and caspases pathways failure. Certain compounds referred to as inhibitor of apoptosis proteins (IAPs) is a group of intracellular apoptosis proteins that are responsible for blocking cell death through inhibition of caspases activation downstream. Generally, IPAs are the key obstacles of cancer medications such as cisplatin because they protect cancer cells from different extrinsic and intrinsic pathways that are triggered by cisplatin medication.

2.4.1 Cisplatin Side effect

Cisplation administration causes initial accumulation in the body tissue and in plasma levels for a longer time. Cisplatin levels in the plasma can be detected years after chemotherapy use as cisplatin reversibly binds with 90% of protein in the tissue. Brouwers and co-researchers conducted a 6-year follow-up observation, the results showed that the half life of Cisplatin in plasma level is roughly 28.5 months.The metabolization and clearance of cisplatin in all tissue differs as it is quicker in regenerating tissues compared to the non or slower regenerating tissues.

The levels of Cisplatin in plasma membranes depends on numerous factors such as : cumulative dose, follow- up time, patient's age , glomerular flitration rate (GFR) during the chemotherapy sessions, as well as the use of sodium thiosulphate (STS) and

method of chemotherapy administration. The higher initial dose of the drug causes a higher tissue concentration and a longer time for excretion, but research done shows that the use of STS binding to cisplatin reduces the initial tissue accumulation.

Cisplatin is eliminated by biliary (~10%) and urinary (90%) system. The clearance of Cisplatin by the kidney is characterized by an initial fast excretion phase (20 min), followed by a slower phase (60-70 min) and a very slow and finally an incomplete phase (24 h).

The adverse effect of cisplatin and its characteristic depends on pharmacological parameters such as the dosage (single and cumulative) and administration (schedule and means). However the systemic and individual conditions such as skin pigmentation, age, diet, blood pH and interactions with radiotherapy plays a major role on the level and characteristic of the adverse effect.

Most of the adverse effects are dose-dependent but it can only be controlled but not prevented.

The common side-effects of cisplatin usage are generally induced by oxidative stress due to strong electrophilic nature of activated cisplatin.

Cisplatin adverse effect can be classified according to the Common Terminology Criteria of Adverse Effect (CTCAE) v3.0 (National Cancer Institute , 2006) as follows: auditory/ear (ototoxicity), blood/bone marrow (haematological toxicity), constitutional symptoms, dermatology/skin (dermatological disorders), gastrointestinal (gastrointestinal disorders), hepatobiliary/pancreas (hepatic toxicity), neurology (neurotoxicity), pulmonary/upper respiratory (respiratory disorders), renal/genitourinary (nephrotoxicity) and sexual/reproductive function (genital

apparatus disorders). Changes in sleep-wake cycle were classifed in a separate category, termed sleep-wake disorders, as they are not clearly categorised by CTCAE.

Anemia observed with cisplatin use may be caused by a decrease in erythropoietin or erythroid stem cells. Cisplatin has been shown to sensitize red blood cells, sometimes resulting in a direct Coombs' positive hemolytic anemia.

Electrolyte disturbances can be serious and mainly includes hypomagnesemia, hypocalcemia and hypokalemia. Hypophosphatemia and hyponatremia have occurred in some patients receiving cisplatin combination regimens. These effects are due to renal tubular damage. Cisplatin greatly increases the urinary excretion of magnesium and calcium; increased excretion of potassium, zinc, copper and amino acids also occurs. Hypomagnesemia and or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany.

Emetogenic effects are common with cisplatin therapy and may be serotonin-mediated.Acute nausea and vomiting may occur within 1-6 (usually 2-3) hours after administration of cisplatin.This early period is the most severe and usually lasts 8 hours, but can last up to 24 hours. Various levels of nausea, vomiting and anorexia may persist for up to 5-10 days. Delayed nausea and vomiting can occur 24 hours or longer following chemotherapy when complete emetic control had been attained on the day of cisplatin therapy. The incidence and severity of cisplatin-induced nausea and vomiting appear to be increased in: females, the young, high doses, rapid infusion and combinations with other emetogenic drugs. Over 90% of patients will experience symptoms of nausea and vomiting and this symptoms are normally are counteracted by the administration of antiemetic drugs such as the antagonist of serotonin receptor 3 (5-HT3) and dexamethasone.

Nephrotoxicity is a major concern when prescribing cisplatin.. Nephrotoxicity included electrolyte alterations (hyperK+, hypoK+, hyperCa++, hypoNa+, hypoCl-, hypoMg+), an increase in blood nitrogen, creatinine and urea, pollakiuria (abnormally frequent urination), hematuria, oliguria, polyuria, urinary tract infections, and kidney spasms to renal insufficiency.

The nephrotoxic effect of cisplatin is dose limiting and is characterized by reduction of creatinine clearance and electrolyte imbalances, particularly hypomagnesemia,caused by acute cytotoxic effect of cisplatin on proximal and distal tubules, and on loop of Henle . Severe magnesium deficiency following cisplatin treatment could result in seizures. In both human and experimental studies have shown that the use of diuretics and hydration can substantially reduce cisplatin-associated nephrotoxicity.

Nervous system effects are usually peripheral neuropathies and sensory in nature (e.g., parethesias of the upper and lower extremities).They can also include motor difficulties (especially gait); reduced or absent deep-tendon reflexes and leg weakness may also occur. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow. Geriatric patients may be at greater risk for these cisplatin-induced neuropathies. Muscle cramps have been reported, and usually occurred in patients with symptomatic peripheral neuropathy who received relatively high cumulative doses of cisplatin. Lhermitte's sign (a sensation during neck flexion resembling electric shock) often is present with cisplatin-induced neuropathy. The occurrence of Lhermitte's sign may coincide with the onset of peripheral neuropathies, and can last for 2-8 months.

Otic effects include tinnitus, with or without clinical hearing loss, and occasional deafness. Ototoxicity is cumulative and irreversible and results from damage to the inner ear. These effects may be more severe in children than in adults.

Vestibular ototoxicity may increase with increasing cumulative dosage and may be more likely to occur in patients with pre-existing vestibular dysfunction. Sensitivity reactions can include anaphylactoid reactions consisting of facial edema, flushing, wheezing or respiratory difficulties, tachycardia, and hypotension. These reactions can occur within a few minutes after IV administration of cisplatin; diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, apprehension, and sensation of chest constriction may also occur. Cisplatin-induced anaphylactoid reactions usually have occurred after multiple cycles of cisplatin (e.g., at least 5 doses), but also can occur after the first dose.

2.4.2 Pathophysiology of Cisplatin induced Nephrotoxicity
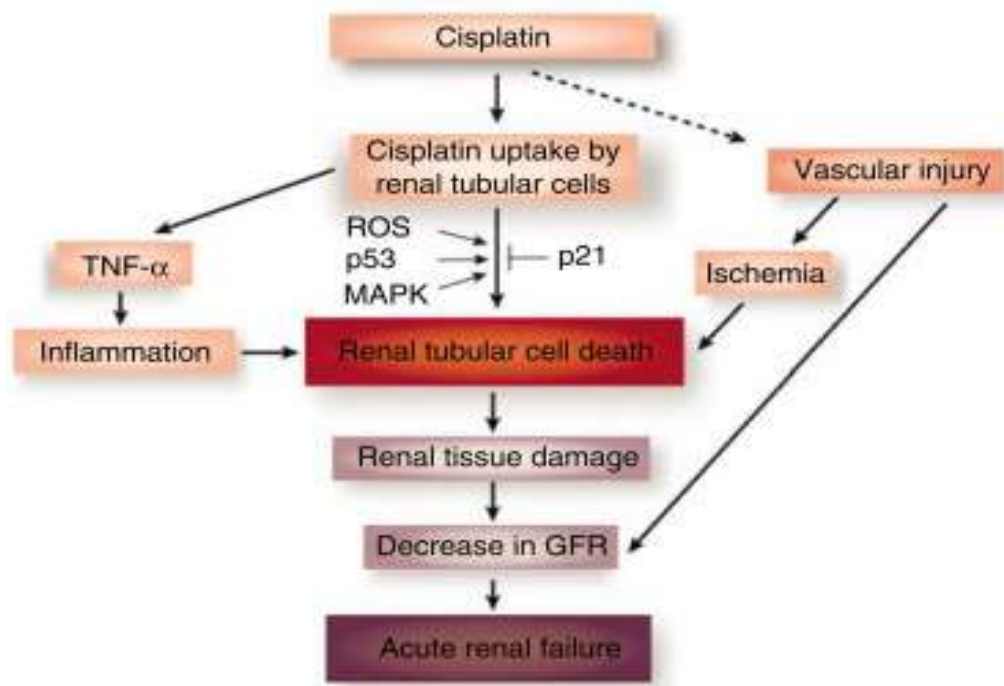
Figure 3: Pathophysiological map of the key molecular pathways demonstrated to play a role in the pathogenesis of cisplatin-induced acute kidney injury (AKI).

The mechanisms associated with cisplatin-induced AKI (CIAKI) are complex, and the relationship between the key pathways remains unknown. However, it is believed that the detrimental nephrotoxic effect of cisplatin in renal tissue is due to platinum accumulation.

The pathophysiology of cisplatin-induced AKI involves 4 major mechanisms: (1) proximal tubular injury, (2) oxidative stress, (3) inflammation, and (4) vascular injury in the kidney.

Proximal tubular injury involves several different mechanisms including apoptosis, autophagy, dysregulation of cell-cycle proteins, activation of the mitogen-activated protein kinase (MAPK) signaling pathways, direct toxicity to renal tubular epithelial cells, DNA damage , and mitochondrial dysfunction.

Generation of reactive oxygen species (ROS), accumulation of lipid peroxidation products in kidneys, and suppressed antioxidant systems are thought to be major mechanisms of cisplatin-induced AKI. Within the cell, cisplatin is converted into a highly reactive form rapidly reacting with thiol-containing antioxidant molecules such as glutathione. Consequently, depletion of glutathione leads to increased oxidative stress within the cells. Cisplatin may also cause mitochondrial dysfunction and increased ROS production through an impaired respiratory chain . Finally, cisplatin may induce ROS formation via the cytochrome P450 (CYP) system.

The proinflammatory nature of cisplatin-induced AKI has been well documented. Secretion of various cytokines such as IL-1-beta, IL-6, IL-18, monocyte chemotactic protein-1 (MCP-1), regulated upon activation normal T cell expressed and secreted (RANTES), macrophage inflammatory protein-2 (MIP-2), intercellular cell adhesion

molecule-1 (ICAM-1), and transforming growth factor beta (TGF-beta) has been shown to be increased in cisplatin-induced AKI. In the study by Faubel et al., cisplatin-induced AKI was associated with increases in the cytokines IL-1, IL-18, and IL-6; however, inhibition of IL-1, IL-18, and IL-6 could not prevent cisplatin-induced AKI.

Cisplatin increases both serum and urine concentrations of TNF-alpha. Genetic or pharmacological inhibition of TNF-alpha reduces the expression of other inflammatory cytokines and chemokines such as IL-1-beta, MCP-1, and RANTES in cisplatin models. Importantly, pharmacological inhibitors of TNF-alpha (GM6001 and TNF-neutralizing antibody) protected against cisplatin-induced AKI. Also TNF-alpha knockout mice were resistant to cisplatin nephrotoxicity. Salicylates, by the way of TNF-alpha inhibition, have also been reported to be protective against cisplatin-induced AKI. However salicylates had no beneficial effect in TNF-alpha knockout mice. In another study by Kim et al., pentoxifylline, a TNF-alpha inhibitor, protected against cisplatin nephrotoxicity in vivo.

In a study by Zhang et al., to determine the contributions of renal parenchymal cells and bone marrow-derived cells to the pathogenesis of cisplatin-induced AKI, chimeric mice in which the bone marrow was ablated and replaced with donor bone marrow cells from wild-type or from TNF-alpha knockout mice were used. Chimeras with TNF-alpha knockout kidneys showed significantly less serum TNF-alpha levels and cisplatin-induced AKI regardless of the immune cell source. It may be concluded that local production of TNF-alpha by resident kidney cells rather than by bone marrow-derived infiltrating immune cells is crucial in cisplatin-induced AKI).

Renal vasoconstriction caused by endothelial dysfunction and impaired vascular autoregulation is an important component of the pathophysiology of cisplatin-induced AKI. Cisplatin has been shown to induce acute ischemic damage with a reduction in medullary blood flow resulting in tubular cell injury. Instead of usual autoregulatory renal vasodilatation that occurs in ischemic kidney, a marked vasoconstriction develops in cisplatin-induced AKI causing further hypoxic injury. Cisplatin decreases effective renal plasma flow before any alteration in the GFR in humans. Similarly, in rats, renal blood flow has been demonstrated to be reduced 2-3 days after cisplatin administration. These renal hemodynamic alterations may be associated with an increase in cytosolic calcium in the glomerular arterioles. Consistently, calcium channel blockers were shown to reverse the renal vasoconstriction and attenuate cisplatin-induced renal dysfunction. Another possible cause of renal vasoconstriction induced by cisplatin is the reduced COX-2 and vasodilatatory prostaglandins.

Cisplatin is directly toxic to endothelial cells. In a study by Dursun et al., cultured pancreatic microvascular endothelial (MS1) cells were exposed to low and high concentrations of cisplatin. Cells treated with low concentration of cisplatin had normal ATP levels, increased caspase-3 activity, and apoptosis. However, cells treated with higher concentration of cisplatin had severe ATP depletion, increased caspase-3 activity, and necrosis. Calpain activity significantly increased with higher concentrations of cisplatin. Both pan-caspase inhibitor and calpain inhibitor were able to reduce cisplatin-induced necrosis. It was demonstrated that, in cisplatin-treated endothelial cells, caspases can also cause necrosis. Furthermore, calpain inhibitors may protect the endothelial cells from necrosis independent of caspase-3.

2.4.3 Rate of Cisplatin- induced nephrotoxicity

According to a research done by Santoso et al (2003). The incidence of renal insufficiency in more recent experience using saline hydration and diuresis, is in the range of 20–30% of patients (Santoso, Lucci Iii, Coleman, Schafer, & Hannigan, 2003). Normally, the onset of renal insufficiency begins several days after the dose of cisplatin, it is evidence by increases in the serum creatinine and blood urea nitrogen concentrations. The urine output is usually preserved (non-oliguric) and the urine may contain glucose and small amounts of protein, indicative of proximal tubular dysfunction.

2.4.4 Prevention method

The most important supportive measures are hydration, replacement of electrolyte losses, and avoidance of other potentially nephrotoxic drugs.

Renal function (GFR) should be routinely assessed before each administration of cisplatin.

Hydration should be started before the treatment and should be maintained for at least 3 days after the treatment.

The adequacy of the hydration may be determined by the measurement of urine output which should be maintained at least at 3-4 L/day.

Magnesium wasting is commonly seen in the course of cisplatin-induced AKI, thus routine assessment of serum magnesium levels may be recommended in all patients receiving cisplatin treatment.

Magnesium should be replaced adequately according to serum magnesium levels.

Determine the risk of AKI (high risk; females, elderly patients, dehydration, patients with CKD and repeated doses of cisplatin.

Adjust cisplatin dose according to patient's renal function

Avoid concomitant nephrotoxic agents (NSAIDs, aminoglycosides, contrast agents, etc.)

Determine renal function within 1 week of treatment

Consider newer, less nephrotoxic platinums such as carboplatin and oxaliplatin

2.5 Mannitol : Mannitol in Prevention of Acute Kidney Injury

Mannitol, chemically 1,2,3,4,5,6-hexanehexol ($C_6H_8(OH)_6$), is a polyol (sugar alcohol) which is widely used in the food and pharmaceutical industries because of its unique functional properties. Mannitol is a six-carbon, linear, simple sugar which is only mildly metabolized by the body and primarily excreted rapidly by the kidneys when given intravenously and poorly absorbed when taken orally. In particular, it is about half as sweet as sucrose and, when taken orally, has a cooling effect which is considered desirable in masking bitter tastes. It is a naturally occurring substance found in marine algae, fresh mushrooms, and in the exudates from trees. It is an isomer of sorbitol, which is usually synthesized by the hydrogenation of specialty glucose syrups. Mannitol is available commercially in a variety of white crystalline powder and granular forms, all of which are soluble in water.

In addition to its use in the food and pharmaceutical industries, mannitol is also widely used in medical practice for a variety of indications, primarily because of its osmotic properties.

Mannitol has four Food and Drug Administration (FDA)-approved uses.

1. Mannitol has approval for the reduction of intracranial pressure and brain mass.

2. Mannitol is approved to reduce intraocular pressure if this is not achievable by other means.

3. Mannitol can promote diuresis for acute renal failure to prevent or treat the oliguric phase before irreversible damage.

4. Mannitol can also promote diuresis to promote the excretion of toxic substances, materials, and metabolites.

For clinical use, it is supplied as sterile solutions of 10% and 20% in a 500 ml bag of water containing 50 and 100 g of mannitol, respectively. Mannitol solutions are acidic (pH 6.3) but proprietary preparations have sodium bicarbonate added for pH adjustment. Mannitol may crystallize if stored at room temperature but can be made soluble again by warming the solution. Because of its low molecular weight (182.72g/mol), mannitol is freely filtered through the renal tubules. However, as it is not reabsorbed, it continues to be osmotically active in the tubules and this accounts for its action as an osmotic diuretic. Mannitol also causes release of renal prostaglandins that lead to renal vasodilation and an increase in tubular urine flow that is believed to protect against renal injury by reducing tubular obstruction.Its mechanism of action is by increasing the osmotic pressure of the glomerular filtrate, thereby inhibiting reabsorption of water and electrolytes. Causes excretion of: Water, Sodium, Potassium, Chloride, Calcium, Phosphorus, Magnesium, Urea, Uric acid.

Mannitol is normally given for oliguria of acute renal failure, mannitol also can be given to increase the excretion of toxic materials, substances, and drugs. Mannitol is ussually poorly reabsorbed once excreted by the tubules and thus it draws extra water with it into the renal collecting ducts. The extra water in the renal collecting ducts can help in increasing the excretion of water-soluble toxic materials, substances, and drugs. Thus mannitol acts as a free-radical scavenger and reduces the harmful effects of free radicals during ischaemia – reperfusion injury. For excretion of toxic materials,

the ca dose of 0.25 g/kg to 2 g/kg with the observation of effects should be considered. If the patient receives more than 200 gm of mannitol without benefit, mannitol use should be discontinued.

2.5.1 Complications of Mannitol

Volume depletion and hypernatremia —Mannitol is freely filtered by the glomerulus and does not undergo tubular reabsorption. Thus, it acts as an osmotic diuretic, increasing urinary losses of both sodium and electrolyte-free water. Lack of replacement of the fluid losses can lead to both volume depletion and hypernatremia that can be severe.

Volume expansion, hyponatremia, hyperkalemia, hypokalemia, and metabolic acidosis — If very high doses of hypertonic mannitol are infused, or if the drug is given to patients with preexisting renal failure, mannitol is retained in the circulation. The ensuing rise in plasma osmolality, similar to that produced by hyperglycemia, results in the osmotic movement of water and potassium out of cells leading to extracellular fluid volume expansion (and possibly pulmonary edema), hyponatremia, metabolic acidosis (by dilution), and hyperkalemia . Water losses from brain cells cause neurologic symptoms.

The rise in the plasma potassium concentration following hypertonic mannitol is due to the movement of potassium out of the cells into the extracellular fluid via two mechanisms

The rise in cell potassium concentration induced by water loss favors passive potassium exit through potassium channels in the cell membrane

The frictional forces between solvent (water) and solute can result in potassium being carried out through the water pores in the cell membrane (a process that is called solvent drag). A similar process can occur with acute hypernatremia and also largely accounts for the hyperkalemia that is commonly seen with marked hyperglycemia in uncontrolled diabetes mellitus

If kidney function is normal, the transient shift of potassium out of cells due to mannitol seldom leads to hyperkalemia.

Contraindication

There are multiple contraindications to giving mannitol, including:

- Established anuria due to renal disease

- Pulmonary edema or severe pulmonary congestion

- Active intracranial bleeding except for during a current craniotomy

- Severe dehydration

- Progressive heart failure

- Known mannitol hypersensitivity

- Renal damage caused by mannitol

- Impaired renal function. If the patient has impaired renal function, a small test dose should be given, and the patient observed for a response. If there is no response, a small test dose is repeatable, but the clinician should administer no more than two test doses.

- Electrolyte abnormalities. As mannitol works, it first increases the intravascular free water content, which can worsen electrolyte abnormalities, including hyponatremia. In the second phase of action, mannitol gets excreted in

the urine with excess free water, potentially causing hypernatremia due to the induced diuresis. Electrolytes should be monitored carefully with mannitol use.

- Mannitol may worsen intracranial hypertension in patients, especially children, with hyperemia, which can be fatal.

- Repeated frequent doses of mannitol can leach into the brain and worsen cerebral edema in the long term. Thus, mannitol is frequently recommended as a bolus spaced apart every 6 to 8 hours and limiting the number of boluses given.

- Mannitol can worsen renal function and precipitate renal failure.

- Mannitol should only be given intravenously and never given intramuscular or subcutaneously.

- Mannitol should not be administered with whole blood.

Monitoring

When mannitol given, monitoring of cardiac function as the fluid shifts can precipitate heart failure. Additional electrolytes, including sodium, potassium, and osmolality, all require monitoring. Mannitol should be stopped if significant electrolyte abnormalities develop or the osmolality reaches 320 mOsm or higher. Finally, urine output also requires monitoring; failure for urine output to increase after administration of mannitol should prompt cessation of mannitol and evaluation for possible renal or genitourinary issues.

2.5.2 Mannitol in prevention of Acute Kidney Injury

To our knowledge, no previous studies exist on the effects of mannitol on renal perfusion, filtration, and oxygenation in patients with AKI. In most animal studies, it has been shown that mannitol increases RBF by renal vasodilation during both normotensive and hypotensive conditions. Data on the effects of mannitol on RBF in

humans, however, are scarce. With the xenon133 washout technique, Castaneda-Zuniga et al. studied the effects of mannitol (20%) infusion on RBF in humans and demonstrated only a minimal increase in RBF. With the same methods as in the present study, Kurnik et al. studied the effect of mannitol (15%) on RBF in patients with moderate chronic renal failure and found that mannitol did not affect RBF. It has been suggested that the mannitol-induced renal vasodilatory response to experimental renal ischemia is mediated directly by increased synthesis of prostacyclin, or indirectly by augmenting plasma levels of ANP because of the plasma volume expansion . Flores et al. showed in an animal study that ischemia-induced endothelial cell swelling can be reversed and prevented by mannitol. They suggested that the failure of blood flow to return to the kidney after transient ischemia, the so-called "no reflow" phenomenon, was due to swollen endothelial cells, and that the no-reflow could be corrected by mannitol. Based on those experimental studies, one could therefore speculate that mannitol might exert its beneficial effect on renal perfusion in patients with AKI by a deswelling effect on injured endothelial cells.

2.6 Acute Kidney Injury

Acute kidney injury (AKI) is defined by a rapid increase in serum creatinine, decrease in urine output, or both. AKI can be classified into pre-renal AKI, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases. Only 'intrinsic' AKI represents true kidney disease, while pre-renal and post-renal AKI can be a consequence of extra-renal diseases leading to the decreased glomerular filtration rate (GFR). When pre- and/or post-renal conditions persist, it will eventually cause renal cellular damage and hence intrinsic renal disease. The current diagnostic approach of AKI is based on an acute decrease of GFR, as reflected by an acute rise in sCr levels and/or a decline in urine output (UO) over a given time interval.

Table 1: RIFLE criteria for classification and staging AKI and the modifications proposed by the AKIN network

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum Creatinine criteria	Urine output criteria
Risk	1.5fold increase in sCr or >25% decrease in GFR	UO < 0.5mL/kg/h for 6h	Stage 1	Absolute increase in sCr ≥ 0.3 mg/dL (≥26.5 μmol/L) or ≥ 1.5 to 2.0 fold from baseline	UO< 0.5mL/kg/h for 6h
Injury	2.0 fold increase in sCr or >50% decrease in GFR	UO < 0.5mL/kg/h for 12h	Stage 2	Increase in sCR> 2.0 to 3.0 fold from baseline	UO< 0.5mL/kg/h for 12h
Failure	3.0 fold increase in sCr or >75% decrease in GFR or sCr>4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3mL/kg/h for 24h or anuria for 12 h	Stage 3	Increase in sCr > 3fold from baseline or increase of sCr to ≥4.0 mg/dL (≥ 354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)	UO< 0.3mL/kg/h for 24h or anuria for 12h
Loss	Complete loss of kidney function for > 4 weeks				
ESKD	End stage kidney disease for > 3 months				

Kidneys are prone to the drug toxicity because of their role in the metabolism and excretion of toxic agents. The kidney receives about 25% of cardiac output, and the renal tubules and proximal segment has the capacity of drug uptakes through endocytosis or transporter proteins. The high delivery and uptake results in high intracellular concentration of different substances that undergoes extensive metabolism, further resulting in toxic metabolites and reactive oxygen species (ROS). Several chemotherapy agents are associated with renal toxicities including tubulointerstitial damage, glomerular disease, electrolyte abnormalities, hypertension, and proteinuria. A Danish study with 37,257 cancer patients had 17.5% of AKI incidence, per the definitions of the Rifle classification (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease. Chertow et al. found that an increase of serum creatinine (SCr) of 40.3 mg/dl (426.5 mmol/l) was independently associated

with mortality. Similarly, Lassnigg et al. 3 saw, in a cohort of patients who underwent cardiac surgery, that either an increase of SCr X0.5 mg/dl (X44.2 mmol/l) or a decrease 40.3 mg/dl (426.5 mmol/l) was associated with worse survival.

Cisplatin triggers ROS production thus inhibiting antioxidant enzymes, that leads to oxidative stress injury. Subsequently leading to increase in renal expression of tumor necrosis factor a and increased tubular cell apoptosis and production of ROS . Cisplatin is excreted and concentrated in the kidneys entering renal tubular cells via organic cation transporter 2, which is kidney specific. Renal toxicity is manifested by decrease in renal blood flow and subsequent decline in GFR within 3 hours of cisplatin administration. These changes is due to increased vascular resistance secondary to tubulo-glomerular feedback and increased sodium chloride delivery to macula densa. The decline in GFR is normally dose dependent. For instance, in a group of patients who received four cycles of 100 mg/m2, the 51Cr-EDTA–measured GFR declined by 11.7%, whereas in patients who received three cycles of 200 mg/m2 , the mean decline was 35.7%. This effect was noted to be lasting, as GFR was still 30% below baseline at 2 years. Acute tubular toxicity of cisplatin may cause mitochondrial dysfunction, decreased ATPase activity, impaired solute transport, and altered cation balance, thus causing sodium and water reabsorption to decrease, while salt and water excretion is increased, leading to polyuria. Cisplatin also causes dose-dependent renal magnesium wasting. Tubulointerstitial injury is a predominant finding on pathologic examination of human kidneys affected by cisplatin toxicity. Both proximal and distal tubules will be affected, and in patients with AKI, normally there is an acute tubular necrosis. Long-term cisplatin exposure may also cause cyst formation and interstitial fibrosis. Patients with cisplatin toxicity typically present with progressive azotemia in the setting of bland urinalysis and minimal proteinuria. Although renal function may

improve in most patients, a subgroup of patients developed permanent renal impairment. Hypomagnesemia is common and may be present in 42%−100% of patients depending on total cisplatin dose and length of exposure. Hypomagnesemia and renal magnesium wasting may persist for up to 6 years after initial dose. Renal salt wasting syndrome has been reported in up to 10% of patients, manifesting as hyponatremia and severe orthostatic hypotension in the setting of high urinary sodium concentration. This syndrome may present 2–4 months after initiation of cisplatin therapy. Rare cases of thrombotic microangiopathy have been reported in patients who were also receiving bleomycin with cisplatin . Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been documented in patients receiving vigorous hydration but is less common now as cisplatin-associated nausea is treated with new-generation antiemetics, diminishing the stimulus for antidiuretic hormone secretion.

Vigorous hydration has been proven to reduce the incidence of AKI in patients receiving cisplatin. Both mannitol and loop diuretics have also been used to ameliorate toxicity; however, randomized studies have not shown a clear benefit.

2.6.1 Treatment of Cisplatin Nephrotoxicity.

There is no specific treatment for cisplatin-induced renal dysfunction or injury. These patients need careful attention to hydration and electrolyte treatment. They frequently need magnesium and potassium replacement. Cisplatin and magnesium affect the same sodium and water channels in the outer medulla. Cisplatin induces magnesium depletion, and magnesium deficiency itself may enhance cisplatin nephrotoxicity.

Cisplatin treatment often produces extensive gastrointestinal side effects, which might lead to more magnesium depletion through anorexia and diarrhea. Eventually, patients

with such side effects might be rendered more susceptible to the nephrotoxicity of cisplatin. Therefore, magnesium repletion may attenuate cisplatin-induced nephrotoxicity. In a small study, 17 patients with germ cell tumor who were receiving cisplatin in a dosage of 20 mg/m2 per day for 5 days in four series were randomly assigned into a group receiving continuous Mg supplementation and a group receiving supplementation only at serum levels below 0.45 mmol/L. Although there were no differences in serum creatinine or creatinine clearance, there was significantly less tubular damage measured by urine N-acetyl-B-D-glucosaminidase excretion in the patients receiving continuous supplementation. There was 2.4-fold higher concentration of urine N- acetyl-B-D-glucosaminidase in the nonsupplemented group compared with that in the Mg-supplemented group. In addition, these patients should avoid, to the extent possible, other nephrotoxic agents, including intravenous radiographic contrast and nephrotoxic antibiotics.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

This was a randomized double blinded control trial. All patients had biopsy-proven cancer of uterine cervix. All patients tumors were staged by criteria of the International Federation of Gynecology and Oncology and had locally advanced disease who consented for the study. Eligible patients were scheduled for concurrent chemoradiation. They randomly assigned into 2 arm of treatment (control / intervention). Their baseline, weekly and end kidney function levels were recorded. Throughout the whole study, the principal investigator along with the health provider were not aware of which group the patients were being randomized into. At the end of the study, the results are documented and analyzed.

3.2 Study Setting

Patients were interviewed and recruited mainly at Chandaria Chronic Disease and cancer center and Eldoret Hospital, while all the patients recruited to this study received their radiotherapy treatment at Eldoret Hospital.

The study was carried out in Chandaria Chronic Disease and Chronic Center at Moi Teaching and Referral Hospital (MTRH). MTRH is situated in Eldoret, in Uasin Gishu County, Kenya. It is the second largest teaching and referral hospital in Kenya. Being the main referral hospital in Western Kenya, it has a catchment population of 13 to 15 million people which comprises about 40 percent of the Kenyan population. The chemotherapy department is staffed by Consultants, Medical officers, nurses and clinical officers. The hospital has a routine reference laboratory that was used for the kidney function analysis. Currently Radiation therapy is unavailable in MTRH, all

oncology patients requiring radiation therapy are referred either to private hospitals (Eldoret Hospital) or to Nairobi (http://www.mtrh.go.ke/)

Eldoret Hospital Ltd is one of the largest private hospitals in Eldoret, The hospital has a team of qualified staff, professional medical doctors and surgeons. Services include a 24hr Casualty, Pharmacy and Laboratory facility, a fully equipped Major and Minor Theatre, a Radiology and Cardiology department, all manned by trained staff and professional doctors and surgeons. Eldoret Hospital is the only hospital that offers Radiation therapy in Rift Valley region, hence most the patients requiring radiation therapy seen in Rift valley are referred to Eldoret Hospital.

At the time of the study, radiation therapy services were not available in MTRH however it is available currently.

3.3 Study population

Study population adult women who consented with newly diagnosed and histologically confirmed disease eligible for concurrent chemoradiation.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

All women clinically and histologically diagnosed with Cervical Cancer stage 1B to 2B.

Who consented to participate in the study.

Without renal derangement.

3.4.2 Exclusion criteria.

With known renal failure due to the nephrotoxic effect of Cisplatin that may cause more damage to the kidney.

Chronic illness that may cause renal failure

Pregnancy and breast feeding because Cisplatin will affect the fetus or may adversely affect the normal microbiome and chemical makeup of breast milk.

3.4.3 Criteria for Termination of study

Patients could withdraw from the study at any time upon their request or the request of their legally acceptable representative. The PI could also withdraw a patient from the study treatment and/or follow-up procedures if the patient experienced a serious or intolerable adverse event or develops, during the course of the study, symptoms or conditions listed in the exclusion criteria. That said, when a patient withdraws or is withdrawn from the study, the reasons for withdrawal was recorded by the PI or a research assistants. All patients completed the study.

In accordance with recommendations by the Pharmacy and poisons board (PPB) of Kenya regarding the conduct of clinical trials, (Pharmacy and Poisons Board, 2016) we constituted a data and safety monitoring board (DSMB). The team had 4 members comprising a biostatistician, a pharmacist, a consultant oncologist and a clinical pharmacologist. Upon 50% of recruitment, the team met and the recommendation to continue the study. The DSMB members were not involved in the conduct of the trial nor had any other possible conflicts of interest.

3.5 Sample size determination

The primary aim of the study was to determine the effect of Mannitol on the rate of averted acute kidney injury among cervical cancer stage 1B to 2B patients receiving Mannitol plus the standard of care compared to those receiving the standard of care alone in Eldoret. Literature show that cisplatin-induced nephrotoxicity ranges between $20 - 30\%$ implying that between $70 - 80\%$ of the patients fail to experience cisplatin induced nephrotoxicity (Santoso et al, 2003).

We determined the sample size such that with 80% power, 5% type I error rate, an intra class correlation coefficient of 0.25. We hypothesize that our study will reduce the loss to follow up (or improve completion of treatment cycles) by half, to 20% (or 80%) respectively. Hence we account for the 20% loss to follow up in our sample size computation. The three measurement points we used to detect a 15% increase in the rate of averted cisplatin-induced nephrotoxicity from 70% (worst case of nephrotoxicity) to 85%. Unpublished data from MTRH (Chandaria Cancer and Chronic Disease Center) show that the rate of loss to follow up from care among breast cancer patients receiving care is 41.5%. The required sample size was calculated using the following formula (Hedeker, Gibbons, & Waternaux, 1999).

$$n = \left(\frac{Z_{1-\alpha/2}\sqrt{(P_1+P_2)\times(1-P_1+1-P_2)\big/2} + Z_{1-\beta}\sqrt{P_1\times(1-P_1)+P_2\times(1-P_2)}}{(P_1-P_2)} \right)^2 \times \frac{1+(m-1)\rho}{m}$$

$$= \left(\frac{1.96\sqrt{(0.70+0.85)\times(1-0.70+1-0.85)\big/2} + 0.84\sqrt{0.70\times(1-0.70)+0.85\times(1-0.85)}}{(0.70-0.85)} \right)^2 \times \frac{1+(3-1)\times0.25}{3}$$

$$= \quad 50$$

Where

Z is the quantile of the standard normal distribution corresponding c x 100% percentile, c = (1 − a/2) or (1-b), a is the type I error rate equal to 0.05, and b is the type II error rate (equal to 0.2) such that the power = 1-b.

P1 is the rate of averted Acute kidney injury in the standard of care arm, and P2 is the rate of averted Acute kidney injury in the Mannitol plus standard of care arm.

m is the number of time points, and is the intra-class correlation of the outcomes between the time points.

Power analysis showed that the sample size of 50 required in order to determine the effect of Mannitol on the rate of averted Acute kidney injury will have a sufficient power (97.2%) to demonstrate a 20% loss to follow up rate.

Number Needed to Treat

Number Needed to Treat (NNT) represents the number of patients over a given time period that one would need to treat to achieve one additional study endpoint.

Intervention - (a = 1 , b = 24)   Control - (c = 2 , d = 23)

NNT = 25

(a : no. of patients with AKI in the intervention group, b ; no. of patients without AKI in the intervention group , c: no. of patient with AKI in the control group , d: no. of without AKI in the control group.)

On average, 25 patients would have to receive experimental treatment (instead of control treatment) for one additional patient to NOT have the study outcome.

3.6 Enrollment of participants

After the Institutional Research and Ethics Committee (IREC) approved the study, data collection began. Patients attending Gyn-oncology clinic at MTRH were approached, informed about the nature and purpose of the study and their consent was obtained. Patients with diagnosis of cervical cancer who met the eligibility criteria were enrolled for the study. The relevant clinical data was entered into the data collection form.

Hospital permission were given to conduct data collection for patients who were enrolled in Eldoret Hospital.

3.7 Randomisation procedure

We used simple randomisation. The process involved recruitment of participants and ensuring that half of the participants are randomly allocated to the treatment arm and the other half to the control arm. We initially approached 102 patients with locally advanced cervical cancer, 90 patients accepted to participate in this study, 12 patients declined. From 90 patients, 3 patients were excluded, 35 declined consent, 1 was lost to follow up and 1 died, we were left with 50 patients who were eligible and consented for this study. For our study, a total of 50 subjects was recruited and randomly allocated into either intervention or control by picking SNOSE's prepared prior to the study by an individual not involved in the study.

An online block randomisation tool was used to help effect this. (https://www.sealedenvelope.com/simplerandomiser/v1/lists). Patient and the care givers were unaware of the arm the patient belongs to, similiar infusion bottles was labelled with specific SNOSE code that only the pharmacist was aware about.

3.8 Study Procedure

Patients are identified during Gyno-oncology clinic at MTRH by research assistant and oncology nurses, the patients with histological and clinical diagnosis of locally advanced Cervical cancer who were naive to radiotherapy were taken aside to a private room, the nature of the study, pros and cons of the study, follow up of the patient from enrolment up to 5 weeks of chemoradiation and 1 week post chemoradiation along with the procedure was explained thoroughly. Consent was taken from Patients who fit the eligibility criteria to participate in the study. Consented patients are randomly assigned to the intervention and control group using randomization software.

The 50 consented patients were subjected to a blood test to determine the baseline serum creatinine level, 2cc of venous blood was withdrawn by trained laboratory technician using aseptic technique. It was put in vaccutainers and within 30 minutes it was taken to the laboratory for analysis. The blood sample was analyzed using the standard urea and electrolyte analysis machine that is available at MTRH routine lab (Roche- Cobas Intergra 400 plus)

Patients with normal serum creatinine (up to 80mmol/L) level were then assigned in 2 groups: 1st group of patient were given standard of care chemoradiation regime with 200mls of Mannitol and 2nd group were given standard of care Chemoradiation along with 200mls of normal saline as placebo.Mannitol or normal saline for the control arm were given 30mins prior to cisplatin administration along with pre chemotherapy hydration regimen .

This study implemented a double blind design in which patients were randomly assigned into placebo or intervention arms. Randomization took place after consent was obtained from the study participants. A computer program (randomize sampler) was

used to allocate the patients in one of the two arms until the required sample size was reached. Allocation concealment was done by sequentially numbered opaque envelope. The principal investigator was blinded for allocation sequence. Pharmacist prepared the infusions and the oncology nurses administered the infusion to both arm of the patients without disclosing the content. Health care providers were unaware of the intervention drug. All individuals involved in the study were kept unaware of what arm the participants had been assigned to. In both arm, patients and care givers were unaware of the study group they belong to, as similar bottles were labelled with assigned computer generated SNOSE codes that either contains Mannitol or N/saline. The principal investigator or research assistant documented the weekly kidney function results of the patient in the data collection form. Kidney function test was carried out for 5 cycles of chemotherapy and 1 week post chemoradiation was documented in a table.

Baseline serum creatinine level on day of initiation, serum creatinine on weekly basis and final serum creatinine level on completion of 5rd chemotherapy cycle and 1 week post chemoradiation was collected and measured. Results of serum creatinine was tabulated and compared. The rate of averted acute kidney in both arm was determined along with the time of chemoradiation completion.

The same study procedure was applied to private patients at Eldoret Hospital. 38 patients out of the 50 participants received their chemotherapy in Chandaria Cancer center, 12 received their chemotherapy in Eldoret hospital. All the patients from this study had their radiotherapy done in Eldoret Hospital.

3.9 Study Variables

3.9.1 Independent variables

The independent variables included the age, marital status, education level, and occupation, stage of the disease, HIV-status, Drug history, co-morbid illness, drug reactions and allergies, surgical history, parity

3.9.2 Dependent variables / outcomes

The dependent variables included creatinine, and urea measured at baseline and weekly up to week 6.   We also measured the duration of completion of the treatment.

3.10 Data collection and entry

Baseline socio-demographic (age, education level, marital status among others) and clinical (serum creatinine) characteristics was collected using interviewer–administered questionnaires. The outcomes (serum creatinine) at enrolment, weekly up and at completion of the chemotherapy on week 5 and 1 week post chemoradiation was processed at the lab and captured using appropriate data form. The collected data was stripped of the identifying information to ensure that the patient confidentiality is maintained. The data was then entered into an electronic database created using Microsoft Access. The entered data was reviewed and verified for accuracy. After entry the database was backed up using removable disc drives that was stored in separate safe location to cushion against data loss. All the databases was encrypted with password to prevent unauthorized access. The password was accessible to the principal investigator alone. After data entry was completed the hard copies of the questionnaires were kept in a cabinet under a lock and the key retained by the principal investigator.

3.9.1 Data analysis and presentation

Continuous variables such as the mean and the corresponding standard deviation was used to summarize continuous variables such as age, weight, height, and body mass index among others if the Gaussian assumptions hold. If the Gaussian assumptions was violated, the median and the corresponding inter quartile range (IQR) was used to summarize the continuous variables. Gaussian assumptions was assessed using the Shapiro-Wilks test. Categorical variables such as the severity of the disease, level of education, marital status among others was summarized using frequencies and the corresponding percentages.

Clinical and the socio-demographic characteristics was compared by the treatment group (intervention vs control). Pearson's Chi Square test was used to compared categorical variables while independent samples t-test (if Gaussian assumptions hold) or two sample Wilcoxon rank-sum test (if Gaussian assumptions will be violated) was used to compare continuous variables between the treatment arm.

Kaplan- Meier survival curve was-used to describe the mean profile Creatinine levels in both Arms.Adverse effects were summarized for each of the two treatment arms (Mannitol plus the standard of care and the standard of care arm alone) using frequencies and the corresponding percentages.

Results were presented using tables and graphs.Data analysis was done using STATA version 13 Special Edition (College Station, Texas 77845 USA)

3.10 Ethical considerations

IREC approval of the study was sought before the study commenced

Written approval to conduct the research was sought from Eldoret hospital management

Informed consent was obtained from all participants before their enrollment into the study

Education and counseling services was provided freely to all participants, including those who withdrew from the study

Confidentiality was maintained strictly by obtaining consent in a private room, storing the questionnaires and lab results in locked data cabinets, databases was pass worded with password known only by the research assistant and principal investigator.

CHAPTER FOUR: RESULTS

4.1 Enrolment flow chart
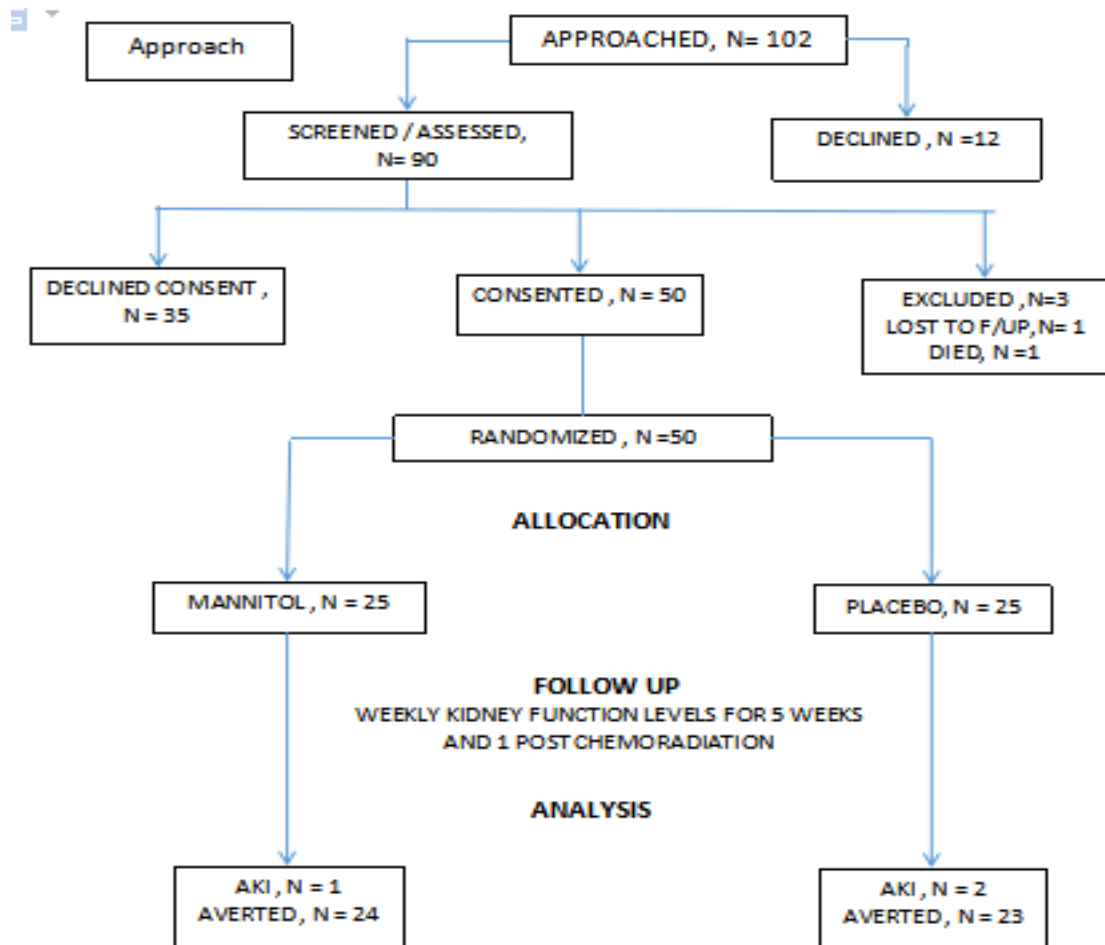
Figure 4: Enrolment flow chart

There were a total of 50 participants included in the Analysis per protocol 25 in the Mannitol arm and 25 in the standard of care. The overall mean age was 51.7 years (std=11.8). The mean for those in the intervention arm was 50.6 years (SD=10.4) while for those in the control arm was 52.8 years (SD=13.2). Majority of the participants were married (72%) in the intervention arm and 68% in the control arm. In both arms majority of the women had between 1 and 3 children 48% in the control and 40% in the intervention arm. In terms of occupation 52% of those in the control arm were employed while 44% in the intervention arm were employed. Majority of the

participants in both arms had primary level education 48% and 68% in control and intervention arm respectively. Medical cover uptake was 64% in the control arm and 60% in the intervention arm. We observed that there was a balance in the demographic characteristics between the two arms since the p-values were >0.05 for all the variables.

4.2 Socio-demographic characteristics of the participants

Table 2: Socio-demographic characteristics of the participants

	Control (N=25)	Intervention (N=25)	Total (N=50)
Age (yrs)			
Count	25	25	50
Mean (sd)	52.8 (13.2)	50.6 (10.4)	51.7 (11.8
Marital status			
Married	17 (68.0%)	18 (72.0%)	35 (70.0%)
Single	8 (32.0%)	7 (28.0%)	15 (30.0%)
Parity			
Nulliparous	0 (0.0%)	1 (4.0%)	1 (2.0%)
1-3 Children	12 (48.0%)	10 (40.0%)	22 (44.0%)
4-6 children	6 (24.0%)	11 (44.0%)	17 (34.0%)
Over 6 children	7 (28.0%)	3 (12.0%)	10 (20.0%)
Education level			
Primary	12 (48.0%)	17 (68.0%)	29 (58.0%)
Secondary	8 (32.0%)	6 (24.0%)	14 (28.0%)
Tertiary	4 (16.0%)	1 (4.0%)	5 (10.0%)
University	1 (4.0%)	1 (4.0%)	2 (4.0%)
MEDICAL COVERAGE			
No	9 (36.0%)	10 (40.0%)	19 (38.0%)
Yes	16 (64.0%)	15 (60.0%)	31 (62.0%)

T-test

Fisher's Exact Test for Count Data

4.3 Clinical characteristics of the participants

Table 4 shows the clinical characteristics of the participants by arm. Almost all the women reported not to have a chronic illness, 72% reported no known allergies in the control arm and 68% in the intervention arm. In both arms 56% were HIV positive and none had any HPV vaccination. Contraceptive use in the control arm was 60% while in the intervention was 64% with the injectables being the most commonly used contraceptive in both arms. Less than half reported to have had a transfusion 48% in the control and 36% in the intervention. (Table 4) We observed that there was no statistically significant difference in the clinical characteristics at presentation between the two arms since the p-values were >0.05 for all the variables.

Table 3: Clinical Characteristics of the participants by arm

	Control (N=25)	Intervention (N=25)	Total (N=50)
Known allergy			
No	18 (72.0%)	17 (68.0%)	35 (70.0%)
Yes	7 (28.0%)	8 (32.0%)	15 (30.0%)
HPV vaccination			
No	25 (100.0%)	25 (100.0%)	50 (100.0%)
Cervical cancer screening			
Yes	1 (4.0%)	2 (8.0%)	3 (6.0%)
No	24 (96.0%)	23 (92.0%)	47 (94.0%)
Contraceptive Use			
No	10 (40.0%)	9 (36.0%)	19 (38.0%)
Yes	15 (60.0%)	16 (64.0%)	31 (62.0%)
Contraceptive Type			
Oral	5 (20.0%)	5 (20.0%)	10 (20.0%)
Injectables	7 (28.0%)	11 (44.0%)	18 (36.0%)
IUD	3 (12.0%)	0 (0.0%)	3 (6.0%)
None	10 (40.0%)	9 (36.0%)	19 (38.0%)
Transfusion			
No	13 (52.0%)	16 (64.0%)	29 (58.0%)
Yes	12 (48.0%)	9 (36.0%)	21 (42.0%)
Weight			
Mean (sd)	64.72(11.18)	64.12 (13.01)	64.42 (12.01)
Height			
Mean (sd)	161.71 (4.84)	160.44 (5.28)	161.06 (5.06)
BSA			
Mean (sd)	1.77 (0.16)	1.72 (0.18)	1.74 (0.17)

Fisher's Exact Test for Count Data

T-test

Objective 2 : To determine the effect of Mannitol on the rate of averted acute kidney injury among cervical cancer patients stage 1B to 2B receiving Mannitol with concurrent chemoradiation in MTRH and Eldoret Hospital.

Table 4 : Rate of Averted AKI

AVERTED	INTERVENTION	CONTROL
YES	24	23
NO	1	2
TOTAL	25	25

Intervention = $\dfrac{24}{25}$ Control = $\dfrac{23}{25}$

           = 0.96   = 0.92

Risk ratio : 0.04   Risk ratio : 0.08

Risk Difference = 0.04

Difference in Confidential interval (95%) = - 0.13 , 0.12

There were 23 without kidney injury in the control arm and 24 in the intervention arm. The 95% confidence interval of the difference was (-0.13, 0.12), since 0 is contained in the interval we fail to reject the null hypothesis and conclude that we have no enough evidence to conclude that the proportion with averted acute kidney injuries differed between the two arms.

4.5 Objective 3: Compared time of chemotherapy completion by arm:

KM plot

From the Kaplan Meier plot (Figure 4) we observed that the participants in the two arms completed the treatment.

The log rank p-value comparing the time to completion between the two groups=0.06 indicating that we do not have enough evidence at 95% level of significance to conclude the time to completion differs between the two groups.
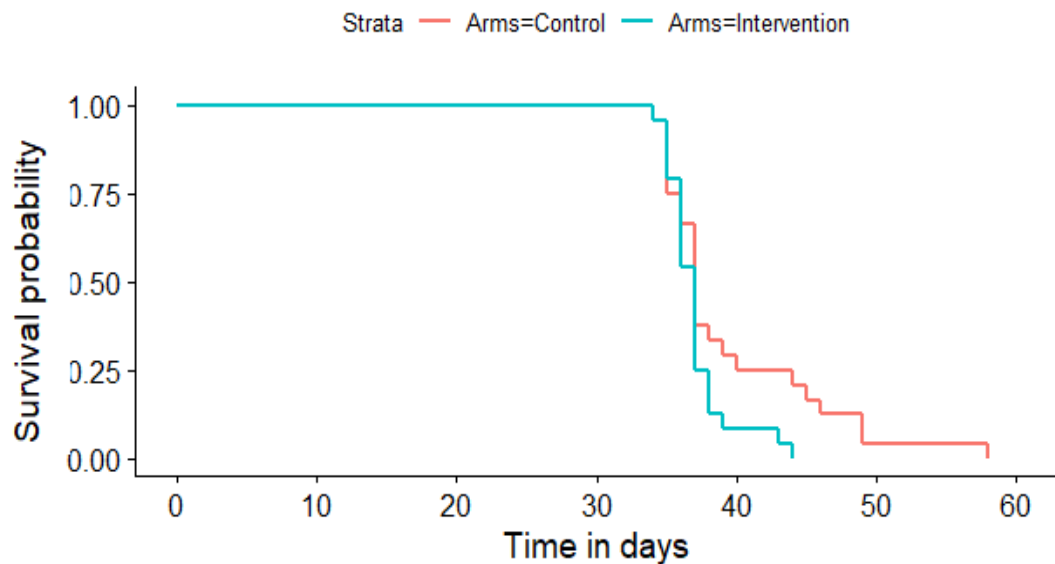

Figure 5: Time to treatment completion by arm

CHAPTER FIVE

5.0 DISCUSSION

The goal of drug therapy is to achieve defined therapeutic outcomes and improve the patient's quality of life while minimizing patient risk. However, inappropriate use of drugs during disease management may lead to drug therapy problems.

This study was undertaken to evaluate the rate of averted cisplatin induced acute kidney injury among cervical cancer patients by measuring biochemical parameters including serum creatinine and urea levels.

Based on our objectives, from our study, There was a statistically significant difference in the change P-value=0.007 with the intervention having a lower change compared to the control arm. A study done by Martina Perše et al, 2018, found that repeated administration of cisplatin results in time related increase of many parameters. However, the time course of the disease depends on the dosage, frequency of cisplatin injection, and cumulative dose of cisplatin. For instance, cisplatin treatment in rats (1mg/kg daily for 14 days) resulted in functional renal damage from day 5 onwards. Creatinine increased 2-3-fold from day 5 on, while BUN showed 3-fold on day 5 up to 6-fold by day 14 gradual increase.

A similiar review done by Katherine P. Morgan et. al, 2012 concluded that although mannitol plus hydration is used to decrease cisplatin-induced nephrotoxicity, there are no compelling data that the addition of mannitol is more nephroprotective than the use of hydration alone.

However a study done by Robert. Philips Jr. et al , 2016 , they compared the use of hydration with mannitol versus rehydration only and found that in total of 313 patients (95 treated with mannitol and 218 without) that were evaluated. The average increase in serum creatinine (mg/dL) was lower in patients who received mannitol versus those

who did not (0.30 vs. 0.47; 95% confidence interval for difference, 0.03 to 0.31; P = 0.02). Grade 2 or higher nephrotoxicity occurred less frequently in patients who received mannitol versus those who did not (8% vs. 17%; P = 0.04). Hayes et al. showed that prehydration and posthydration with mannitol resulted in a reduced risk of nephrotoxicity. Al-Sarraf et al. performed a prospective phase II RCT in patients with receiving cisplatin 100 mg/m2 . Patients were randomized to receive hydration (n = 33) or hydration with mannitol (n = 34). After the first cycle, patients who received mannitol experienced lower rates of nephrotoxicity when compared with hydration alone (15% versus 30%; no p value reported); however, in subsequent cycles, the nephroprotective effect of mannitol was not maintained (32% versus 39% experienced nephrotoxicity; no p value reported). Morgan et al. performed a retrospective study in patients receiving either 30 or 100 mg/m2 of cisplatin (n = 143). Among patients who did not receive mannitol (n = 85), there was a 2.6-fold increased risk of nephrotoxicity when compared with patients who received mannitol . In patients who received the higher dose of cisplatin but no mannitol, there was an 11.5-fold increased risk of nephrotoxicity (p< .0001) . McKibbin et al. performed a retrospective study on patients receiving 100 mg/m2 of cisplatin with concurrent radiation (n = 139). Patients who received mannitol were at 84% lower risk for grade 3 SCr increase. Conversely, Leu and Baribeault performed a retrospective study in patients receiving 40 mg/m2 of cisplatin. Patients received either mannitol with prehydration (n 5 46) or hydration alone . No differences in average CrCl decrease, incidence of nephrotoxicity were observed between the two arms.

When we compared the time chemoradiation completion rate in both arms we found that all participants managed to complete the chemoradiation. However in the control

group, some patients took slightly longer to complete but the difference was statistically insignificant.

5.1 Study Limitation

Findings from this study can not be generalized to another facility without using the same chemotherapy protocol.

There was selection biasness when it came to patient's affordability power to fund their chemoradiation treatment.

5.2 Strengths

- It is a pioneer study done in this region

- It was a Randomized Double Blind Control Trial in 2 centers

CHAPTER SIX

6.0 CONCLUSION AND RECOMENDATION

6.1 Conclusion

The average age in the control group was 52.8 and 50.6 in the intervention group. Majority of the patients were married and received primary education. We fail to reject the null hypothesis and conclude that we have no enough evidence to conclude that the proportion with averted acute kidney injuries differed between the two arms.

We do not have enough evidence at 95% level of significance to conclude the time to completion differs between the two groups.

Mannitol has no role in the rate of chemotherapy completion and there was no significant differences in both arms.

6.2 Recommendation

Further studies should be done to evaluate the effectiveness of Mannitol in preventing of CIN and AKI.

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APPENDICES

APPENDIX 1: BUDGET

Items	Quantity	Unit Price (Kshs)	Total (Kshs)
Stationery & Equipment			
Printing Papers	5 reams	500.00	2,500.00
Black Cartridges	2	2,000.00	4,000.00
Writing Pens	1 packet	500.00	500.00
Flash Discs	1	2,000.00	2,000.00
Box Files	2	200.00	400.00
Document Wallets	2	50.00	100.00
Sub total			9,500.00
Research Proposal Development			
Printing drafts & final proposal	10 copies	500.00	5,000.00
Photocopies of final proposal	6 copies	100.00	600.00
Binding of copies of Proposal	5 copies	100.00	500.00
Sub total			6,100.00
Personnel			
Biostastician	1	40000	40000
Research assistant	1	10,000	10000
Sub total			60000
Mannitol	200 x 6 x 25 = 92,400		
Thesis Development			
Printing of drafts and final thesis	10 copies	800.00	8,000.00
Photocopy of final thesis	6 copies	200.00	1,200.00
Binding of thesis	6 copies	300.00	1,800.00
Sub total			11,000.00
Total			179000
Miscellaneous Expenditure (10% of Total)			17900
Grand Total			196900

APPENDIX 2: CONSENT FORM

My name is Dr. Wong Li Ping and I am currently pursuing my Masters Degree at Moi University. A requirement of this course is to do a dissertation. I chose to study the effectiveness of Mannitol as a renal protective agent in patients with Cervical Cancer stage 1B to 2B in Moi Teaching and Referral Hospital. I will ask you some questions about your socio-demographic characteristics. You are free to respond or choose not to respond to some of the questions that you may find inconvenient to you.

Your participation in the study will in no way change the treatment plan that your doctors deem is fit for you, or in any other way prejudice either of you. This study will not put you at any risk; no immediate benefit will accrue to you.

Information gathered will be treated with utmost confidentiality; your identity will be protected (your name will not be used and you will be identified with a number, only known to me and my immediate assistant). The information obtained will be used to improve services in MTRH, to form protocols and may be published in medical journals and/or presented in scientific symposia (both local and international).

The Moi University Ethics and Research Committee has approved this study

For any question or clarification, please do not hesitate to contact me on 0721913962 or contact the chairperson of IREC, MOI TEACHING AND REFERAL HOSPITAL P.O BOX 3-30100 ELDORET

May I proceed with the questions? Yes/ No.

Respondent's signature…………………………… Date ………………

Fomu ya Ridhaa

Jina langu ni Dr. Wong li ping, kwa sasa najiendeleza masomo ya shahada ya uzamili kwenye chuo kikuu cha moi. Vigezo vya masomo haya nikufanya utafiti. Nimechagua kufanya utafiti juu ya ufanisi wa Mannitol,kama nephroprotector kukinga Cisplastin nephrotoxicity katika wagonjwa wenye Cervical Cancer stage 1B,katika hospital ya Moi teaching and Referral hospital. Nitakuuliza maswali kutokana na tabia ya mfumo na hali ya maisha,makazi na vinginevyo. Uko huru kujibu ama kutojibu maswali mengineo usiotaka kuelezea.

Uhusika wako katika utafiti huu,hauta badilisha kamwe mfumo wa matibabu ambao daktari wako amekuwekea,wala hauta mshtumi yeyote kati yenu. Utafiti huu hauta kuhatarisha maisha kwa aina yoyote wala kukunufaisha kwa njia yoyote.

Taarifa zote zitawekwa kwa uangalifu na utambulisho wako utalindwa(majina yako hayatatumika,utatambulika kwa nabari,inayojulikana kwangu na msaidizi wangu). Taarifa zote zitakazo kusanywa,zitatumika kuboresha huduma za afya kwenye hospitali ya MTRH,kufuma protocols,na zinazewa chapishwa katika majarida ya afya,na/ama kuwasilishwa kwenye maonyesho ya kisayansi.(kote nchini ama duniani) Kamati ya maadili na utafiti ya chuo kikuu cha Moi kimepitisha kufanywa kwa utafiti huu

Kwa maswali au maelezo zaidi,usisite kuwasiliana nami kupitia nambari ya simu 0721913962, ama kuwasiliana na mwenyekiti wa IREC, MOI TEACHING AND REFERRAL HOSPITAL P.O BOX 3-30100 ELDORET.

Je,naweza endelea na maswali!? Ndio/La

Sahihi ya muhojiwa................ Tarehe.............

Appendix 3: Data Collection Form
Title :   Effectiveness of Mannitol in Prevention of Acute Kidney Injury Among

Patients with Cervical Cancer stage 1B- 2B receiving Chemoradiation in Moi

Teaching and Referral Hospital.

Research number :

Date of Enrollment :

Personal Details

Inpatient no :

Date of Birth :

Home Address :

Contact no :

Marital Status : Married ( ) Single ( ) Divorced ( ) Widowed ( )

Others (please state) …........

Education level : Primary School ( ) Secondary school ( ) College ( )

University ( ) Others (please state) ….…

Occupation : ………

Parity : Nulliparous ( )   1-3 children ( )   4-6 children ( )

More than 6 children ( )

Last Delivery (year)

History of Chronic / Co- Morbid Illness ; YES ( ) NO ( )

If yes, please state :

Drug history (type and frequency)

Known Drug reaction/ Allergy :

History of Surgery : YES ( ) NO ( )

If yes, please state :

History of Blood Transfusion : YES ( ) NO ( )

Risk Factors

Sero status : POSITIVE ( ) NEGATIVE ( )

Date of Diagnosis :

Date of ARVs started :

History of Sexual Transmitted Disease : YES ( ) NO ( )

If yes, please state (diagnosis, date and treatment)

HPV Vaccination : YES ( ) NO ( )

If yes, please state date and type :

Have you ever done Cervical Cancer Screening in the past 5 years :

YES ( ) NO ( )

History of Smoking : YES ( ) NO ( )

If yes,

(I) How many sticks or packets per day ? …..................

(II) For how long have you been smoking (years) ? …..................

History of Oral Contraceptive use: YES ( ) NO ( )

Physical (on first day of enrollment)

Weight : ….. (kg) Height : ...... (cm) BSA: .....

BP :   mmHg   Pulse :   B/min   RR: /min

General Condition :

State of Hydration :

History of Chemotherapy : YES ( ) NO ( )

History of Radiotherapy : YES ( ) NO ( )

Pain Medications currently on :

Date of Chemotherapy initiation:

Date of Radiotherapy initiation :

Kidney Function Test (U/E/Cs)

W	1	2	3	4	5	6	7	8
U								
Cr								
k								

Week

Appendix 4: Staging of Cervical Cancer

FIGO staging of cancer of the cervix uteri (2018) - Revised

Stage	Description
1	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm*
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension

IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic LN
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic LNs, irrespective of tumor size and extent (with r and p notations)
IIIC1	Pelvic LN metastasis only
IIIC2	Para-aortic LN metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (a bullous edema, as such, does not permit a case to be allotted to stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Appendix 5: Protocol
Standard of Care Chemotherapy Regimen

Preload

1L normal saline over 30 mins

Dexamethasone 12g IV Stat

Ondansetrone 8mg Iv stat

Chemotherapy

Cisplatin 40mg / m2 with or without KCL or MgSo4- when necessary

Postload

1L normal Saline over 30mins

Ondansentrone 4mg BD P.O X 5/7

weekly x 4-6cycle

Treatment recommendations for stage IB to 2B

Stage IB to IIB:

Primary surgery consists of radical hysterectomy plus bilateral pelvic lymph node dissection with or without para-aortic lymph node sampling (for tumors < 2 cm)

In general, surgery is the most appropriate option for patients with stage IB1 or IIA1 disease, whereas concurrent chemoradiation is most appropriate for those with stage IB2 to IIB2 disease.

If lymph nodes are positive, then a hysterectomy is not recommended; instead, the patient should receive chemoradiation.

Patients with stage IB to 2B may also be given pelvic radiotherapy and brachytherapy with (or without) concurrent cisplatin-based chemotherapy . The addition of concurrent cisplatin-containing chemotherapy has been shown to improve survival .

Cisplatin 40 mg/m 2 IV once weekly plus radiation therapy, 1.8-2 Gy daily per fraction, for six cycles
 or
Cisplatin 40-75 mg/m 2 IV on day 1 plus 5-flurouracil (5-FU) 1000 mg/m 2continuous IV infusion over 24 h on days 1-4 (total dose 4000 mg/m 2 each cycle) every 3 wk plus radiation therapy, 1.8-2.0 Gy daily, for a total of three to four cycles.

Appendix 6: IREC Approval

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3
Reference: IREC/2018/50
Approval Number: 0003154

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
20th November, 2018

Dr. Wong Li Ping,
Moi University,
School of Medicine,
P. O Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE

2 0 NOV 2018

APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Wong,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Mannitol Effectiveness in Preventing Cisplatin Induced Nephrotoxicity in Patients with Stage 1B, 2A and 2B Cervical Cancer at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: *FAN: IREC 3154* on 20th November, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 19th November, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc   CEO   -   MTRH   Dean   -   SOP   Dean   -   SOM
       Principal - CHS   Dean   -   SON   Dean   -   SOD

Appendix 7: MTRH Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

22nd November, 2018

Dr. Wong Li Ping,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC)
to conduct your research proposal titled:-

"Mannitol Effectiveness in Preventing Cisplatin Induced Nephrotoxicity in Patients with Stage 1B, 2A and 2B Cervical Cancer at Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc   -   Senior Director, (CS)

      -    Director of Nursing Services (DNS)

      -    HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: www.mtrh.go.ke
TO BE THE LEADING MULTI-SPECIALTY HOSPITAL FOR HEALTHCARE, TRAINING AND RESEARCH IN AFRICA