TURKISH REPUBLIC OF NORTH CYPRUS

NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES

COMPARISON OF MAGNESIUM AND MANNITOL PRELOADING ON CISPLATIN-INDUCED NEPHROTOXICITY IN NORTHERN CYPRUS

By:

RANIA AL-ZAGHIR

MASTERS

A THESIS SUBMITTED TO THE INSTITUTE OF GRADUATE STUDIES

NEAR EAST UNIVERSITY

CLINICAL PHARMACY

2021-NICOSIA

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ADVISOR

ASSIST. PROF. DR. NEVZATBİRAND

2021-NICOSIA

APPROVAL PAGE

We certify that we have read the thesis submitted by Rania Al-zaghir titled "**Comparison of Magnesium and Mannitol preloading on Cisplatin-induced Nephrotoxicity in Northern Cyprus"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Health Sciences.

Thesis Committee:

Head of the committee: **Prof. Dr. Bilgen Başgut**

Committee member: **Assoc. Prof. Dr. Abdikarim Abdi**

Supervisor: **Assist. Prof. Dr. Nevzad Birand**

Head of the Department: **Assist. Prof. Dr. Nevzad Birand**

Approved by: **Prof. Dr. Hüsnü Can BAŞER**

Director of Health Sciences Institute
Near East University

DECLARATION

Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from planning of the thesis until writing thereof, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list and had no behavior of breeching patent rights and copyright infringement during the study and writing of this thesis.

Rania Al-zaghir

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ABBREVIATIONS

ACEI: Angiotensin-converting enzyme inhibitor

AKI: Acute kidney injury

ARB: Angiotensin receptor blockers

BUN: Blood Urea Nitrogen

CDDP: Cis-Diamminedichloroplatinum (cisplatin)

CIN: Cisplatin-induced nephrotoxicity

CKD: Chronic kidney disease

CrCl: Creatinine clearance

eGFR: Estimated glomerular filtration rate

Elspar: Enzyme L-Asparaginase

K: Potassium

LH-RH: Luteinizing hormone–releasing hormone

Mg: Magnesium

NSAIDs: Nonsteroidal anti-inflammatory drugs

PTECs: Proximal tubular epithelial cells

QOL: Quality of life

RAS: Renin-angiotensin system

rMate1: Multi-drug and toxin extrusion protein

rOct2: Renal organic cation transporter 2

RST: Rosuvastatin

Scr: Serum creatinine

SIM: Simvastatin

TNM: Tumor (T), Node (N), Metastasis (M).

ABSTRACT

Introduction; Cisplatin is a chemotherapy drug that is used to treat a variety of cancers. However, nephrotoxicity is a primary dose-limiting issue for cisplatin, which can lead to the chemotherapy being stopped. As a result, numerous medications have been utilized to protect the kidney from nephrotoxicity caused by cisplatin. One of these agents is mannitol, which can be administered before cisplatin to minimize nephrotoxicity, and another is magnesium sulfate, which has been shown to protect against cisplatin-induced nephrotoxicity.

Aim: The study's goal was to evaluate and compare the magnesium-potassium and mannitol preloading in reducing cisplatin-induced nephrotoxicity in oncology department of "Near East University Hospital" (NEUH) in "Northern Cyprus".

Methods: A retrospective study will be conducted with cancer patients receiving service in the oncology department between January 2018 and November 2020 in the Near East University Hospital.

Result: Between the January 2018 and December 2020, 15 of the 27 cancer sufferers received 20% Mannitol, 8 received the Mg-K regimen, while 4 received hydration with normal saline only. In our analysis, Subjects who received %20 Mannitol (n = 15) were compared to subjects who received Mg-K (n = 8), and Subjects who received hydration with normal saline (n = 4). Measured of GFR, among the 3 groups in first cycle (*P. value: 0.175*) and second cycles (*P. value: 0.441),* while CrCl in first cycle (*P. value: 0.766*) and in second cycle (*P. value: 0.853*), and Scr in first cycle (*P. value: 0.595*) and in second cycle (*P. value: 0.328*). When we compared the mean of GFR, CrCl and Scr among the 3 groups at baseline, first and second cycles, we observed improvement in Mg-K group and worsen in mannitol group.

Conclusion: In conclusion, our study has shown that the effect of mannitol and magnesium-potassium as protective agents against cisplatin-induced nephrotoxicity is the same when they administered during chemotherapy.

1. INTRODUCTION

1.1. Background

1.1.1. Definition of Cancer

A metaphor used to describe illnesses in which aberrant cells divide uncontrollably and can infect neighboring tissues in any area of the body. Cancer cells, tumor cells, and malignant cells are all names for these aberrant cells. Many malignancies and the aberrant cells that make up cancer tissue are further distinguished by the name of the tissue from which the abnormal cells originated (for example; lung cancer, breast cancer and colorectal cancer). When injured or unrepaired cells remain alive, they evolve into cancer cells and undergo uncontrolled division and development, resulting in a mass of cancer cells. Cancer cells frequently migrate from this initial clump of cells, moving through the blood and lymph systems and settling in other organs where they can continue the uncontrolled division cycle. Metastatic spread or metastasis refers to the process through which cancer cells leave one location and develop in another. For example, if breast cancer cells travel to a bone, the patient has bone metastatic breast cancer (Lacy & Becker, 2013).

1.1.2. Risk Factors of Cancer

Everything which could lead a normal body cell to grow abnormally, which has the potential to create cancer. Some cancer causes remain unknown, whilst others have lifestyle or environmental triggers or may be caused by more than one recognized cause. Furthermore, some of them may be impacted by a person's genetic composition during development. Many patients acquire cancer as a result of a combination of these risk factors:

1. Genetic factors

2. Radiation exposure.

3. Chemical compounds

4 .Dietary factors: Meat, calorie equilibrium, cholesterol, protein, alcohol, and nitrates

5. Estrogens

6. Viruses

7. Age

8. Stress

(Lacy & Becker, 2013).

1.1.3. Symptom and Sign of Cancer

Cancer symptoms and signs vary depending on the type of cancer, where it is situated, and/or where the cancer cells have spread. Breast cancer, for example, may manifest as a lump in the breast or nipple discharge, but metastatic breast cancer may manifest as discomfort (if it has gone to the bones), acute tiredness (lungs), or convulsions (brain). A few people exhibit no indications or symptoms until the cancer has progressed significantly.

A person should seek medical care if they notice any of the following warning signs and/or symptoms of cancer.

1. An alteration in bowel or bladder patterns

2. A painful throat that does not go away

3. An unusual amount of blood or discharge (for example, nipple secretions or a "sore" that will not heal that oozes material)

4. Breast thickening or lumps in the testicles or elsewhere

5. Difficulty swallowing or indigestion (typically chronic)

6. A noticeable change in the size, color, form, or thickness of a wart or mole

7. A persistent cough or hoarseness

Other indications or symptoms that may be present include:

• Unexplained weight loss or lack of appetite

• A new form of pain in the bones or other regions of the body that may occur on a regular basis

• Unexplained low-grade fevers may be either persistent or come and go,

• Persistent fatigue, nausea, or vomiting,

• Recurring infections which will not clear with usual treatment,

• Unexplained loss of weight or loss of appetite,

• A distinct pattern of pain in the bones or other regions of the body that may be gradually increasing or intermittent, but differs from prior aches,

• Severe tiredness, nausea, or vomiting,

• Unexplained low-grade fevers can be chronic or intermittent.

• Recurrent infections that do not respond to standard therapy (Lacy & Becker, 2013).

1.1.4. Cancer's types

Carcinoma: cancer which starts with or covers internal organs of the skin or tissues, epithelium, basal, melanoma, papilloma, adenoma or squama cell carcinoma, lung, column, pancreatic, ovarian, etc. Carcinoma. Carcinoma.

Sarcoma: is a kind of cancer that originates in bone, cartilage, fat, muscle, blood vessels, or other connective or supporting tissue. It includes osteosarcoma, synovial sarcoma, liposarcoma, angiosarcoma, rhabdosarcoma, and fibrosarcoma.

Leukaemia: is a cancer that begins in blood-forming tissue, such as bone marrow, and induces a high number of abnormal blood cells to be generated and enter the circulation.

Lymphoma and myeloma: lymphoma and T-cell lymphoma, cancer beginning on cells of the immune system.

Central nervous system cancers: brain and spinal cord tumors in the tissues of the brain and the spinal cord (Lacy & Becker, 2013).

1.1.5. Cancer Stage Grouping

Stage 0: This phase describes on-site cancer, that implies "in-situ." Arena 0 cancer remains in the location it began and has not spread to neighboring fabrics. The entire tumor is generally removed with surgery at this stage of malignancy.

Stage I: Such phase is generally a tiny tumor or cancer that has not deeply transformed into close tissue. Also the lymph nodes or other areas of the body have not been expanded. Early stage cancer is often termed.

Stage II and Stage III: These two phases often imply bigger malignancies or tumors which have developed further into neighboring tissue. They can be transmitted to other regions of the body but not to lymph nodes.

Stage IV: The cancer has spread to other organs and areas of the body during this stage. Progressive or disseminated cancer can also be named.

1.1.5.1. TNM descriptions

Tumor (T): The letter "T" plus The number (0-4), includes how large a tumor has expanded into adjacent tissues, defines the size and locations of a tumor. The size of the tumor is measured by cm (cm).

Node: Node (N). Lymph nodes express by the letter "N" plus a number (0 to 3).

Metastasizing (M). The letter "M" shows if the cancer has migrated to other regions of the body known as remote metastases. The M0 is marked if the cancer did not spread. If the cancer has developed, M1 is evaluated

(*https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/stage-cancer, Accession date: 03February 2021).*

1.1.6. Types of Cancer Treatment

The sort of therapy the person gets depends on the type and progress of cancer. Most patients are treated in conjunction with chemotherapy and/or radiation therapy, for example.

- Chemotherapy
- Immunotherapy
- Radiotherapy
- Hormone therapy
- Cell transplant
- Precision medicine
- Targeted therapy
- Operation

(Lacy & Becker, 2013)

1.2. Types of Chemotherapy Drugs

The methods of chemical treatment, its chemical structures and interaction with other medicines can be grouped together. Some medicines function in several ways and may belong to more than one category.

1.2.1. Alkylating Agents

Alkylating chemicals prevent the reproduction of cells by destroying their DNA (Meschino, 2016). It replaces alkyl groups into hydrogen atoms in DNA, leading to cross-links in the DNA chain, resulting in cytotoxic, mutagenic and carcinogens (Khalife, Muhammad, Kenj, & Salamoon, 2015). These medicines act throughout all stages of the cell cycle and treat several cancers including lung, breast, ovary, leukemia, lymphoma, Hodgkin, multiple myeloma and sarcoma. These cancerous medicines also cure many different types of cancer. It can harm bone marrow cells and cause leukemia as gain the threat is "dose-dependent," which means that the danger is modest at low doses, but rises as the overall amount of the medicine consumed increases. The risk of Leukemia is greatest after 5 to 10 years of therapy following receipt of alkylating medications (Meschino, 2016).

In general, alkylating agents are divided into six groups well:

1. *'The Nitrogen Mustards* [Mechlorethamine, Cyclophosphamide, Ifosfamide, Melphalan and Chlorambucil']
2. *'Ethylenamine and Methylenamine derivatives* [Altretamine, Thiotepa']
3. *'Alkyl sulfonate's* ['Busulfan']
4. *'Nitrosoureas'* ['Carmustine', 'Lomustine']
5. *'Triazenes'* ['Dacarbazine, Procarbazine, Temozolomide']
6. *'The platinum-containing Antineoplastic Agents'* [Cisplatin, Carboplatin, Oxaliplatin] (Khalife et al., 2015)

1.2.2. Antimetabolites

By replacing the usual building components of RNA and DNA, antimetabolites interfere with DNA and RNA. The DNA can't copy itself whenever this occurs and a cell can't reproduce. Leukaemias, breast, ovary and intestinal tract malignancies, and other kinds of cancer are often used to treat (Meschino, 2016).

Antimetabolites include:

A. "Folate antagonist

1. Methotrexate (Folex, Mexate)

B. Purine analogues

1. Thioguanine (6-TG, 6-thioguanine)

2. Mercaptopurine (6-MP, Purinethol)

3. Fludarabine (Fludara)

4. Pentostatin (deoxycoformycin, Nipent)

5. Cladribine (2-chloro-deoxyadenosine, Leustatin)

C. Pyrimidine analogues

1. Cytarabine (cytosine arabinoside, Cytosar-U, ara-C)

2. Fluorouracil" (5-FU, 5-fluorouracil)

1.2.3. Anti-Tumor Antibiotics

The antibiotics administered for infection aren't like these medicines. They aim to prevent growth and multiplication by altering the DNA of cancer cells.

Anthracyclines are antibiotics of tumors which interfere with copying enzymes that are part of the cell cycle of DNA. So, they can't copy themselves and a cell can't replicate them. They are used extensively for a number of malignancies (Meschino, 2016).

Anthracyclines include examples:

i. Daunorubicin

ii. Doxorubicin (Adriamycin)

iii. Doxorubicin liposomal

iv. Epirubicin

v. Idarubicin

vi. Valrubicin

A fundamental hazard in these medicines is that if administered at large doses, they might irreversibly harm the heart. This is why these medicines have often been given lifetime dosage restrictions (also known as cumulative dose*).*

Anti-tumor drugs which do not comprise anthracyclines:

i. Bleomycin

ii. Dactinomycin

iii. Mitomycin-C

iv. Mitoxantrone (also acts as a topoisomerase II inhibitor)

v. Plicamycin (Mithracin)

1.2.4. Topoisomerase Inhibitors

These medicines are also known as alkaloids for plants. They interfere with enzymes known as topoisomerase that help to separate DNA strands to copy. The treatment of a few more lung, ovarian, gastrointestinal, colorectal, and pancreas cancer with topoisomerase inhibitors has been achieved (Meschino, 2016).

Inhibitors of topoisomerase are classified by what sort of enzyme they influence:

Inhibitors of Topoisomerase I (also known as camptothecins):

i. Irinotecan

ii. Irinotecan Liposomal

iii. Topotecan

Inhibitors of Topoisomerase II (also known as epipodophyllotoxins) contain:

i. Etoposide (VP-16)

ii. Mitoxantrone (also acts as an anti-tumor antibiotic)

iii. Teniposide

iv. Topoisomerase

The risk of second cancer can be raised by Topoisomerase II inhibitors (Meschino, 2016).

1.2.5. Mitotic Inhibitors

Also known as plant alkaloids. They are naturally occurring substances, such as plants. They function by preventing cells from being split into new cells, but by preventing enzymes from generating proteins necessary for the reproductive cells, they can harm cells at all phases.

The taxanes and vinca alkaloids are samples of mitotic inhibitors.

i. *Taxanes include: "*Cabazitaxel, Docetaxel, Nab-paclitaxel, Paclitaxel"

ii. *Vinca alkaloids include:* "Vinblastine, Vincristine, Vincristine Liposomal, Vinorelbine"

They treat several kinds of cancer, including breast, pulmonary, myeloma, lymphoma, and leukemia. Certain medication may induce nerve damage that can restrict the amount can provide (Meschino, 2016).

1.2.6. Enzymes

Elspar (L-asparaginases) is enzyme produced from Escherichia coli and Erwinia carotovora bacteria. The hydrolysis of L-asparagine to aspartic acid and ammonia is catalyzed by L-asparaginases. This enzyme can also hydrolyse L-glutamine, and the plasma content of both the amino acid substrates decreases to zero during treatment. L-Asparaginase-sensitive tumor cells are weak in the enzyme asparagine synthetase, hence asparagine synthesis cannot be made. Depletion of asparagine and glutamine limits the production of protein in cells that lack asparagine synthetase, leading to suppression of nucleic acid and cell mortality. In addition to treating specific forms of lymphoma, L-Asparaginase is primarily indicated in the treatment of acute lymphoblastic leukemia and certain types of lymphoma. It does not play a role in the

treatment of non-lymphocytic leukemia or other kinds of cancer (Meschino, 2016; Westfall, 2011).

1.2.7. Hormonal Agents

A. Glucocorticoids

Sometimes simply referred to as steroids, have been used in the treatment of many kinds of cancer and in other diseases, it is natural hormones and hormonal medicines. These medicines are considered chemical medicines when used as components of cancer treatment.

Examples of corticosteroids include:

i. Prednisone

ii. Methylprednisolone

iii. Dexamethasone

Steroids are also frequently used to reduce chemo-induced nausea and vomiting. They are used to avoid severe allergic responses before some kinds of chemo.

B. Estrogens, antiestrogens

1. Tamoxifen citrate (Nolvadex)

2. Estramustine phosphate sodium (Emcyt)

C. Androgens, antiandrogens

1. Flutamide (Eulexin)

D. Progestins

E. Luteinizing hormone–releasing hormone (LH-RH) antagonists

1. Buserelin (Suprefact)

2. Leuprolide (Lupron)

F. Octreotide acetate (Sandostatin) (Meschino, 2016; Westfall, 2011)

Other chemotherapy drugs:

1. Miscellaneous Agents *include:*

i. Hydroxyurea (Hydrea)

ii. Procarbazine (N-methylhydrazine, Matulane, Natulan)

iii. Mitotane (o,p´-DDD, Lysodren)

iv. Hexamethylmelamine (HMM)

2. Monoclonal Antibodies

3. Immunomodulating Agents *include:*

A. Levamisole (Ergamisol)

B. Interferons

i. Interferon alfa-2a (Roferon-A)

ii. Interferon alfa-2b (Intron A)

C. Interleukins: aldesleukin (interleukin-2, IL-2, Proleukin)

4. Cellular Growth Factors *include:*

A. Filgrastim (G-CSF; Neupogen)

B. Sargramostim (GM-CSF, Leukine, Prokine)

(Meschino, 2016; Westfall, 2011)

1.3. The Platinum-Containing Antineoplastic Agents

The platinum-based drugs which are platinum coordinate complexes are often categorized as alkylating agents but do not alkylate DNA. They cause covalent DNA adduct in a different way (Khalife et al., 2015).

Their usage is nevertheless restricted by their severe, dosage limiting adverse effects (Oun, Moussa & Wheate, 2018) as well as innate or acquired therapeutic resistance (Dilruba & Kalayda, 2016).

In the treatment of human neoplasms, cisplatin, carboplatin and oxaliplatin are frequently utilized. There has been considerable work in developing novel platinum cancer clusters, but no clinical application has so far achieved internationally. Only regional approval has been obtained for Nedaplatin, Lobaplatin and Heptaplatin.

Clinical studies are underway on many novel platinum complexes and platinum solutions. In addition, multiple categories of unique platinum medicines were synthesized, examined and appraise to overcome toxic side effects and tumor prescription drugs like as sterically impaired complexes, platinum monofunctions, biologically active ligand complexes, trans-configured and polynuclear platinum complexes, platinum (IV) drugs, and platinum-based therapeutics (Dilruba & Kalayda, 2016).

Conversely, cisplatin, which is platinum (II) with 2 ammonia groups, is quite well accepted in clinical oncology since the discovery of the bio-active platinum complexes 30 years ago (M.J., 1995).

1.3.1. Cisplatin

1.3.1.1. Definition of Cisplatin

Cisplatin (CDDP,cis-Diamminedichloroplatinum,cis-dichlorodiammineplatinum (II), cis-Platinum II, DDP), A first platinum counterpart (Matsuoka & Ando, 2017), is a powerful antineoplastic medication that is comparable to bifunctional alkylating drugs (Agency, 2010; Casanova et al., 2020). Cisplatin was originally synthesized in 1844 by M. Peyronie. Alfred Werner had first defined his chemical structure in 1893. Yet, the substance was not scientifically researched until the 1960s. It was the first FDA-approved cancer platinum compound in 1978. (Dasari & Bernard Tchounwou, 2014).

Cisplatin having in the treating of ovarian, lung, head and neck, testicular, and bladder malignancies in humans. It has been shown to be effective in the treatment of germ cell tumors, sarcomas, carcinomas, and lymphomas (Aldossary, 2019). It also possesses antibacterial, immunosuppressive, and radiosensitizing effects. (McEvoy, 2006).

1.3.1.2. Mechanism of Action

It binds to DNA covalently and impairs DNA function (Chabner & Longo, 2011). The chloride ligands are replenished by water molecules when cisplatin reaches the cells (Agency, 2010; Go & Adjei, 1999). The creation of positively charged platinum complexes reacts with the nucleophilic sites on DNA as a result of this reaction (McEvoy, 2006). These platinum nanoparticles form cisplatin-DNA adducts by covalently binding to DNA bases via intra-strand and inter-strand cross-links, inhibiting DNA, RNA, and protein production (Chabner & Longo, 2011). This activity is not dependent on the cell cycle phase. (Matysiak & Gustaw-Rothenberg, 2009).

1.3.1.3. Side Effects

Nausea, nephrotoxicity, cardiotoxicity, hepatotoxicity, and neurotoxicity are only a few of the drug's severe side effects (Aldossary, 2019). In general, the risk of such adverse effects is attributed to the dose and interval of cisplatin, and it can be reduced by adequate hydration, which is considered the most important strategy for preventing cisplatin-induced nephrotoxicity, though the selection of hydration alone or hydration plus mannitol to secure nephrotoxicity is debatable. (Agency, 2010)(Ruggiero, Rizzo, Trombatore, Maurizi, & Riccardi, 2016).

Direct Coombs ̕positive haemolytic anemia that sometimes result because red blood cells have been found to be susceptible to cisplatin. (Perry, 2008).

Hypomagnesemia, hypocalcemia, and hypokalemia are the most common *electrolyte disorders*. Some individuals taking cisplatin combination regimens have developed hypophosphatemia and hyponatremia (McEvoy, 2006). Damage to the renal tubules is the cause of these side effects. Cisplatin causes a significant rise in magnesium and calcium excretion in the urine, as well as increased excretion of potassium, zinc, copper, and amino acids. (Agency, 2010).

Cisplatin treatment has *emetogenic effects*, which may be serotonin-mediated (Murry, 1997). Acute nausea and vomiting can develop within 1-6 hours (typically 2-3 hours) following cisplatin treatment (McEvoy, 2006). Selective 5-HT3-receptor inhibitors protect against nausea and vomiting caused by cisplatin and carboplatin (M.J., 1995). In addition, newer-generation antiemetic drugs like aprepitant and palonosetron considerably reduce nausea and vomiting, allowing for improved oral intake management. (Horinouchi et al., 2013).

Peripheral neuropathies and sensory effects (e.g., parenthesis of the upper and lower extremities) are the most common nervous system consequences (McEvoy, 2006). Motor problems (particularly gait) are common, as are decreased or absent deep tendon reflexes and leg weakness. Peripheral neuropathy is a progressive condition that is typically treatable, however recovery might be delayed (O'Dwyer, Stevenson, & Johnson, 2000). It's worth mentioning that older individuals could be more susceptible to cisplatin-induced neuropathies (Agency, 2010). Peripheral neurotoxicity is the most common dose-limiting issue with cisplatin. (M.J., 1995).

Otic effects embrace tinnitus, with or without clinical hearing loss, and intermittent deafness are among the symptoms (McEvoy, 2006). Ototoxicity is caused by injury to the inner ear and is cumulative and permanent (O'Dwyer et al., 2000). Audiograms can help detect early indications of hearing loss before they become serious. (M.J., 1995).

Sensitivity reactions comprises face edema, flushing, wheezing or breathing problems, tachycardia, and hypotension are examples of anaphylactic responses (FDA, 2010; Perry, 2008). Diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, anxiety, and a sense of chest tightness can all develop within minutes after receiving cisplatin intravenously. Anaphylactic responses to cisplatin

are more common after many cycles of the drug (e.g., at least 5 doses), although they can even happen after the first dosage (McEvoy, 2006).

When prescribing cisplatin, *nephrotoxicity* is a serious issue and limits the clinical application of it (Q. Li et al., 2013). It is affecting 30%of cisplatin recipient patients (Holditch, Brown, Lombardi, Nguyen, & Edelstein, 2019). During the first 24 hours after cisplatin treatment, more than half of the cisplatin given is eliminated in the urine. However, the concentration of platinum in renal cells is many times higher than in plasma and other organs (Yoshida et al., 2014), and it is approximately five times higher in renal proximal tubular epithelial cells (PTECs) than in the blood (Pabla & Dong, 2008). PTECs (proximal tubular epithelial cells) in the kidney absorb molecules from the primary urine and are mostly exposed to xenobiotics discharged in the urine (Fliedl et al., 2014). In humans, the reduction in glomerular filtration rate produces a rise in serum creatinine within 6 to 7 days after cisplatin infusion. For three weeks, the serum creatinine levels remain high. (Santoso, Lucci, Coleman, Schafer, & Hannigan, 2003).

Renal manifestations of cisplatin treatment:

- Acute kidney injury (20–30%)
- Hypomagnesemia (40–100%)
- Fanconi-like syndrome
- Distal renal tubular acidosis
- Hypocalcemia
- Renal salt wasting
- Renal concentrating defect
- Hyperuricemia
- Transient proteinuria
- Erythropoietin deficiency

- Thrombotic microangiopathy
- Chronic renal failure

Acute kidney damage (AKI) is the most severe and one of the most common presentations, occurring in 20–30% of patients (Miller, Tadagavadi, Ramesh, & Reeves, 2010). A reduction in kidney function manifested by a 0.3 mg/dL increase in blood creatinine or a 0.5 mL/kg/h decrease in urine output is clinically classified as AKI. (Holditch et al., 2019).

Mechanism of Cisplatin-induced Nephrotoxicity;

DNA damage response, activation of apoptotic and other cell death pathways, activation of inflammation, autophagy, and other processes are all implicated in cisplatin nephrotoxicity. However, the mechanism of cisplatin nephrotoxicity is not completely understood. (Xiang, Guo, Tang, Cai, & Dong, 2019).

CDDP accumulates in the kidneys during glomerular filtration and tubular secretion (Pabla & Dong, 2008). Renal tubules experience a variety of acute morphologic transformations when it is secreted by kidney tubular epithelial cells, including vacuolation, loss of polarity, loss of transmembrane channels, mitochondrial malfunction, G1 cell-cycle arrest, and death (Xiang et al., 2019). Cisplatin damages mitochondrial DNA more than nuclear DNA at the cellular level, since mitochondria possess the treated promptly found in nuclear DNA. Renal mitochondrial dysfunction and a decrease in adenosine triphosphate synthesis occur from these damage. The cellular sodium-potassium pump is impaired, which decreases proximal tubular salt and water ingestion. Because the third module of the proximal tubule has the highest concentration of renal mitochondria, a drop in renal mitochondria results in a lower proximal tubule oxidative metabolism rate. Excess salt and water in the proximal tubule increase renal vascular resistance, lowering renal blood flow and glomerular filtration rate (Santoso et al., 2003). After cisplatin contact, tubular dysfunction causes acute kidney damage (AKI) that can progress to

chronic kidney disease with tubulointerstitium degeneration and impairment of renal function. (Xiang et al., 2019).

Furthermore, even non-toxic CDDP serum concentrations can reach toxic levels in the kidneys, causing renal failure due to severe damage to the S3 section of the acute tubules (Bolisetty, Traylor, Joseph, Zarjou, & Agarwal, 2016; Yao, Panichpisal, Kurtzman, & Nugent, 2007).

Risk Factors of Cisplatin-induced Nephrotoxicity:

Hypoalbuminemia, history of cisplatin usage, periodicity of cisplatin dosage, and hydration without magnesium are all major risk factors for CIN, according to a recent research (Yamamoto et al., 2017). Also regarded potential indicators for the formation of nephrotoxicity include advanced age, female gender, and present smoking. (Muraki et al., 2012).

It is worth noting that geriatric sufferers may be more susceptible to nephrotoxicity (Agency, 2010), The high incidence of cisplatin-induced nephrotoxicity in elderly patients may be linked to renal hypoperfusion; increased comorbidities, such as chronic kidney disease (CKD), coronary heart disease, and diabetes mellitus; and enhanced utilization combination drugs [particularly nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blocker (ACEI/ARB)]. (Duan, Cai, Li, & Chen, 2020).

Gender influences CDDP-induced nephrotoxicity. Female gender appears to be associated with a reduced incidence of nephrotoxicity following CDDP treatment. CDDP therapy in women is suggested when the serum level of the sex hormone estrogen is not high in the corpus because estrogen may enhance the risk of kidney damage following CDDP medication. (Nematbakhsh et al., 2017).

Because NSAID co-administration is an important risk factor for cisplatin-induced nephrotoxicity (CIN), it was suggested that NSAIDs should not be used in conjunction with cisplatin-containing chemotherapy regimens (Saito, Kobayashi, et al., 2017). This was because a comparatively weak efficiency designation and the regular utilization NSAIDs were significantly associated with CIN (Kidera et al.,

2014), As a result, other medicines such acetaminophen, tramadol, or oxycodone may be used. (Saito, Kobayashi, et al., 2017).

Biomarkers of Cisplatin-stimulated Nephrotoxicity:

Established diagnostics for CDDP-induced AKI diagnosis, such as Blood Urea Nitrogen (BUN) and Serum Creatinine, are still employed, although they are neither precise nor effective. (Shin et al., 2014).

Numerous proteins (clotted-1, beta- 2 micro globalulin, lipocaline neutrophil gelatinase-related, calbindin, trefoil factor 3 monocyte chemical protein), were shown promising to detect cisplatin-induced acute human kidney damage (George, Joy, & Aleksunes, 2018). Age, sex, and patient comorbidities are all considerations to consider. (Holditch et al., 2019).

The capacity to early anticipate and diagnose nephrotoxicity in clinics and sub clinics can lead to an improvement in the long-term results of cisplatin chemotherapy patients. Subclinical cisplatin-induced kidney damage risk were evaluated utilizing new Urine Biomarkers for peak plasma concentrations and urinary platinum and pharmaco-kinetic parameters (Ibrahim et al., 2019). This made it useful for the early diagnosis of the AKI caused by Cisplatin chemistry to be monitored for urine indicators (Bunel et al., 2017).

In addition, magnesium waste is the basic characteristics of nephrotoxicity in patients undergoing weekly cisplatin transfusions (40 mg/m2) with whole pelvic radiation and has no influence on the incidence of hypomagnesemia or its treatment response when choosing diuretic (mannitol versus furosemide) hydration (Mach et al., 2017).

- The medication has some resilience, along with an increase in DNA repair, decrease in intracellular accumulation and cytosolic deactivation of cisplatin.

- Other platinum-containing anti-cancer medicines including certain carboplatin and oxaliplatin in conjunction with cisplatin were utilized for cancer chemotherapy due to varied adverse effects and drug resistance

(Aldossary, 2019). In addition, cisplatin combination therapy with other medicines has proved very important for overcoming drug resistance and reducing morbidity (Dasari & Bernard Tchounwou, 2014).

1.3.1.4. Cisplatin Doses Used in the Chemotherapy Treatment

The dose of cisplatin is dependent upon the main disease, the predicted reaction, and the usage of cisplatin in the treatment of monotherapy or in combination chemotherapy. The medications for adults and children are appropriate.

For Mono-therapy, the following two dosage regimens are recommended:

- *"Single-dose of 50 to 120 mg/m^2 body surface every 3 to 4 weeks.*
- *15 to 20 mg/m^2/day for five days, every 3 to 4 weeks.*

If cisplatin is used in combination therapy, the dose of cisplatin must be reduced:

- *A typical dose is 20 mg/m^2 or more once every 3 to 4 weeks.*

For treatment of cervical cancer cisplatin is used in combination with radiotherapy:

- *A typical dose is 40 mg/m2 weekly for 6 weeks".*

(https://www.medicines.org.uk/emc/product/6111/smpc, Accession date: 11February 2021)

Table 1. Doses of Cisplatin in Adult and Geriatric According to the Type of Cancer

TYPE OF CANCER	***ADULT***	***GERIATRIC***
Testicular tumors Metastatic	*Repeated in combination with bleomycin and etoposide for 5 days every 3 weeks)*	*Up to 20 mg/m2/day IV every 5 days/cycle, in conjunction with other authorized chemotherapeutic drugs.*
Advanced Bladder Cancer	*50-70 mg/m² IV cycle q3-4Weeks, depending on prior radiation therapy or chemotherapy* *Heavily pretreated patients: 50 mg/m²/cycle initially; repeat q4Weeks*	*50 -70 mg/m² IV cycle q3-4Weeks, depending on prior radiation therapy or chemotherapy; for heavily pretreated patients, give 50 mg/m²/cycle initially; repeat q4Weeks*
Metastatic Ovarian Carcinoma	*'75-100 mg/m² IV per cycle q4Weeks with cyclophosphamide (600 mg/m² IV q4Weeks); administer sequentially'* *Off-label: '90-270 mg/m² intraperitoneal; retain for 4 hr before draining; repeat q3Week's (may coadminister systemic Na thiosulfate)*	*'75-100 mg/m² IV per cycle q3-4Weeks on Day 1 with cyclophosphamide (600 mg/m² IV q4Weeks); administer sequentially'*
Dosing Considerations	*'Pretreatment hydration: 1-2 L fluid infused for 8-12 hr before dose* *May use concomitant amifostine to decrease nephrotoxicity* *Do not repeat course until SCr <1.5 mg/dL [<133 micromoles/L] or BUN <25 mg/dL [<8.93 mmol/L] or WBC >4000/mm³ AND platelets >100 k/mm³'*	*'Pretreatment hydration: 1-2 L fluid infused for 8-12 hr before dose* *May use concomitant amifostine to decrease nephrotoxicity* *Do not repeat course until SCr <1.5 mg/dL [<133 micromoles/L] or BUN <25 mg/dL [<8.93 mmol/L] or WBC >4000/mm³ AND platelets >100 k/mm³'*

- *Cancers (Off-label):*

Cervical cancer, endometrial, prostate, esophagus, renal; non-small cell lung cancer; squamous cell cancer of head and neck; bone marrow transplantations; osteogenic sarcomas;

100 mg/m² IV q 4 Weeks when used with cyclophosphamide

100 mg/m² IV q 4 Weeks as single agent

Renal Impairment:

CrCl 10-50 mL/min: Decrease dose by 25%
CrCl <10 mL/min: Administer 50% of dose

Hemodialysis:

Partially cleared by hemodialysis
Post hemodialysis: Administer 50% of dose
Continuous ambulatory peritoneal dialysis: Administer 50% of dose
Continuous renal replacement therapy (CRRT): Administer 75% of dose (https://reference.medscape.com/drug/platinol-aq-cisplatin-342108, Accession date: 16 February 2021).

To summarize, platinum based multimodal chemotherapy provides advantages as compared to optimal treatment in terms of symptom and survival (de Castria, da Silva, Gois, & Riera, 2013). While platinum hypersensitivity development may restrict treatment choices (Boccaccio & Boccaccio, 2019). The choice of the platinum element must consider the predicted tolerability and comorbidity of the individual (de Castria et al., 2013).

Cancer patients can have some 40 adverse effects along with the usage of platinum-based medicines (Oun et al., 2018). When taken in conjunction with third generation medication, cisplatin produced greater or more nausea, vomiting, or both, and Grade III/IV anemia, neutropenia, alopecia and kidney damage (de Castria et al.,

2013). In addition, cisplatin has nephrotoxicity as the dose-limiting effect (Oun et al., 2018). A new approach has been devised to reduce this dose-limiting toxicity by reducing the danger and cisplatin-induced nephrotoxicity (Ruggiero et al., 2016).

In addition, platinum-based chemotherapy is still commonly associated with hypomagnesemia (W. Liu et al., 2019). Initially, hypomagnesemia was reported in 1979 as cisplatin-induced electrolyte abnormalities (Kimura et al., 2018). This may result in individuals requiring dosage decrease of between 25% and 100% in their platinum medicines (Oun et al., 2018).

We would like to point out that there were risk factors that found in producing platinum-induced nephrotoxicity the platinum type, baseline serum creatinine (Scr), vinorelbine coadministration and treatment rounds included (H. E. Liu et al., 2014).

platinum (II) complexes also have resistance mechanisms which result Diminishing blood flow from tumors, extracellular conditions, reduced platinum uptake, enhanced efflux, intracellular glutathione detoxification, etc., decreased bonding, repair of DNA, decline in mistreatment, faulty apoptosis, antiapoptotic factors, numerous mentation effects, or presence of non-cycling quiet cells; a reduction in tumor cellular flow (Stewart, 2007).

Due to side consequences and host immunity that are generated during continued treatments, platinum (II) complexes are limited in the clinical use, and not merely changes in primary platinum (II) complex targets, such as improved DNA repair mechanisms, but rather because of numerous other molecular targets, such as membrane lipids. Platinum (II) complexes immediately interact with lipids and lead to membrane-phase behavior alterations which are depending on the composition of lipid plasma membrane and other environmental variables. These relationships, however, are complicated and unintelligible. (Martinho, Santos, Florindo, & Silva, 2019).

Cancer patients who take platinum (II) complexes, Requiring thorough monitoring and, according to the drug to their biochemistries, renal and hepatic function, and earing test. Additional medicines that are not based on chemical therapy for the treatment of side effects, including antiemetic, antimicrobial and

myeloid growth factors, mannitol, propafenone, normal saline hyperhydration, magnesium supplements, monoclonal cytokine antibodies blocker, and antioxidant, are widely used in patients. (Oun et al., 2018).

1.4. Protective Agents

Numerous compounds were tried to investigate whether the nephrotoxicity of platinum medications might be improved or increased. Antioxidants (e.g., melatonin, vitamin E, selenium, etc.), metabolic interfering agents for cisplatin (e.g. procaine HCL), modulators of nitric oxide (e.g. zinc histidine complex), cytoprotective and antifouling agents (e.g. amifostine and erythropoietin), and diuretic (e.g. Furosemide and Mannitol) have been shown to improve experimental cisplatin nephrotoxicity. Only a handful of the agents were human-tested. Nitric oxide synthase inhibitors, spironolactone, gemcitabine and other medications have been found to enhance cisplatin nephrotoxicity. In order to prevent nephrotoxicity of cisplatin, it should avoid combination with such substances (Ali & Al Moundhri, 2006).

In clinical practice, the hydration (intravenous isotonic saline) is now carried out to avoid or reduce CIN, with magnesium supplement or forced diuresis (mannitol and/or furosemide) (Matsuoka & Ando, 2017; Volarevic et al., 2019).

Using hydration is necessary to avoid nephrotoxicity produced by cisplatin in all patients (Crona et al., 2017). The Old Hydration Protocol included regular mannitol and furosemide with normal saline, while the New Protocol included regular magnesium and mannitol with saline lacking furosemide (Muraki et al., 2012).

Furthermore, a heavy proportion hydration of 2500–5000 ml has consistently been implemented in routine clinical operations to reduce the risk of renal toxicity, however this high-volume hydration method may impair patient quality of life (QOL), since long time for the infusion is needed (Ninomiya et al., 2016), while low hydration volume and short term with oral fluid appeared secure, especially in outpatient settings, even in intermediate- to high-dose cisplatin (Crona et al., 2017; Matsuoka & Ando, 2017).

In addition, the short hydration Patients with a lung cancer who were taking cisplatin (>75 mg/m2) are safe without severe renal toxicity (pre-and post-hydration with a potassium chloride content (10 mEq) in 500 ml of fluid for a period of 60 minutes and mannitol (20%) 200 ml, immediately before administration as forced diuresis given over 30 min., magnesium sulfate (8 mEq) pre-hydration) (Horinouchi et al., 2013).

Due to its circulatory maintenance of water and hemodynamic, it may be more suited for elderly to treat short period and low volume hydration. As comparatively low regimens have been more popular, the systematic diuretic therapy of older individuals was not advised. If large dosages of cisplatin (100 mg/m2) were required it was suggested to use a less nephrotoxic platinum (Duan et al., 2020).

A recent study in rats has demonstrated that Simvastatin (SIM) and Rosuvastatin (RST) have the anti-inflammatory and anti-apoptotic characteristics, as a result it protected kidney against cisplatin-induced nephrotoxicity (Mostafa, Saleh, & Mansour, 2018). Capsaicin was also shown to counteract against cisplatin-inducing nephrotoxicity in rats (dietary antioxidants), and lipid peroxidation (Shimeda et al., 2005).

Specific attention is needed to protect the kidney from CDDP-induced nephrotoxicity whenever antioxidants is used in gender, due to there is no preventative function for CIN of same antioxidants in women unlike in men.. (Nematbakhsh et al., 2017).

It should be noted that the frequency of cisplatin nephrotoxicity is related with lower blood pressure and usage of Renin-angiotensin (RAS) inhibitors, whereas lower blood pressure is influenced by nephrotoxicity in patients who cannot consume solid meals. Disconnected antihypertensive medications, which may be useful for people with reduced blood pressure, including RAS inhibitors before cisplatin chemical treatment must be explored. (Komaki et al., 2017).

In the conclusion, magnesium supplementation (8–16 mEq) might reduce the nephrotoxicity of cisplatin and mannitol could be recommended for cisplatin-heavy doses and/or for pre-existing patients with hypertension. (Crona et al., 2017).

1.4.1. Mannitol

Mannitol is a diuretic used to force urine production, it causes diuresis osmotic, which lowers urine's cisplatin concentration. A method to decrease kidney toxicity is considered the lower cisplatin concentration (Santoso et al., 2003).

Controlled diuresis with a low volume hydration technique for preventing cisplatin-associated nephrotoxicity was recently launched using mannitol or furosemide for particular types of malignancies; but there was no clear determination as to which substance should be utilized (G. Makimoto et al., 2018).

Moreover, Mannitol is often combined with cisplatin to protect the kidneys from irreversible damage which is a complication of cisplatin by promoting osmotic diuresis and execration of water (Hägerström et al., 2019; Ruggiero et al., 2016).

Conversely, treatment with mannitol produces excessive diuresis and resultant dehydration in patients with CDDP treatment, which indicates that safe and effective renoprotective medicine must be used as an additional treatment for high dosage patients who have had CDDP (Volarevic et al., 2019).

1.4.2. Magnesium

For a number of biological functions, magnesium is an essential cofactor for several enzymes. The kidney is strictly controlled for magnesium homeostasis. Glomeruli are filtered two-thirds of the total serum magnesium. Reabsorption is mostly carried out in the thick ascending limb of the Henle Loop (70%), with 15% in the proximal tubules, and 10% in the distal tubules. Renal tubes typically suffer from cisplatin damage to magnesium, which results in renal magnesium wasting and hypomagnesemia (F. Li, Livingston, & Dong, 2017).

Magnesium (Mg) deficits are happened by almost all patients receiving cisplatin to make AKI worse based on biochemical indicators (the urea of the blood and the plasma, creatinine), renal histology and the marker of renal oxidative stress, inflammation and apoptosis (Kumar et al., 2017). Hence, this worsening of the nephrotoxicity by magnesium loss in individuals with significant gastrointestinal side

effects after cisplatin medication should be addressed (Kimura et al., 2018). Instead, cisplatin-caused renal damage was prevented by the Mg supplementation. There is therefore a considerable improvement in the cytotoxicity of Mg shortage or inhibition of Mg absorption, whereas Mg supplementation was protected against cytotoxicity. However, no cisplatin-mediated death of CT26 tumorcells in vitro affected either Mg shortage or inhibition of Mg uptake (Kumar et al., 2017).

In addition, Cisplatin-induced nephrotoxicity (CIN) was found to have ameliorated in a clinical study for Mg premedication. The mechanism behind the protection from nephrotoxicity is not fully understood, however, as Mg co-administration reduced the amount of platinum accumulation, either in vitro or in vivo by arranging t renal transporters, renal organic cation transporter 2(rOct2) and multi-drug and toxin extrusion protein 1(rMate1) (A. Makimoto et al., 2019; Saito, Okamoto, Kobayashi, Narumi, Yamada, et al., 2017). It must be noted that the body of clinical evidence showing that this medicament is more effective in individuals with adult cancer (A. Makimoto et al., 2019).

Now check additionally whether the magnesium supplement may preserve the kidneys and enhance the therapeutic benefits (F. Li et al., 2017).

Multiple investigations have shown that cisplatin-induced nephrotoxicity caused by preventive effects of magnesium supplementation has been shown to be inhibitorious to nephrotoxicity in patients with head and neck cancer (Kimura et al., 2018).

A contemporary studies have found that (8 mEq) of magnesium a substantial reduction in nephrotoxicity (Yoshida et al., 2014), and administration of (1 g) magnesium i.v. appears to be the best cisplatin Nephrotoxicity Prevention Strategy (Casanova et al., 2020). Magnesium (20 mEq) supplemental with Short-hydration program were deemed safe and practical in cisplatin-based high-dose patients (Hase et al., 2020). In addition, the (15 mEq) magnesium dosage was reported to have nephroprotective properties in cisplatin alone treatment of cervical cancer patients. (Yamamoto et al., 2015).

Consequently, even after several rounds of therapy with CDDP, Mg co-administration greatly lowered and protected against cisplatin renal damage (Kidera et al., 2014) as in the case of a single dose CDDP model. However, between single and repeated administrations the precise underlying mechanism was varied (Saito, Okamoto, Kobayashi, Narumi, Furugen, et al., 2017).

2. METHODOLOGY

Study Setting

A retrospective study was conducted with cancer patients receiving service in the oncology department between January 2018 and November 2020 in the Near East University Hospital.

Study Design

The study aimed to analyze and comparison the impact on cisplatin-induced Nephrotoxicity reduction of Magnesium/Potassium and Mannitol preloading in the Oncology Department of Near East University Hospital in Northern Cyprus. Patients who were 18 years and more than 18 years and patients who received cisplatin in the chemotherapy have included in the study. We have excluded patients who had an incomplete laboratory parameters, patients who did not complete their treatments in the Near East University hospital and patients who were died during treatment.

Data Collections

All data was accumulated from cancer patients' file. Baseline clinical demographics as including gender, age, body surface area, cancer types, comorbidities, doses of cisplatin and the type of protective agents were recorded. We would like to point out that the choice of protective agents for patients was according to the physician's' decision. Laboratory parameters as including complete blood counts (CBC), serum creatinine, and ALT liver enzyme at each cycle were recorded for baseline, first and the second cycle of the treatment from electronic system in Near East University Hospital. Other tests including blood electrolytes, blood urea nitrogen (BUN) and liver albumin were excluded due to missing information of most patients. The IDMS-traceable MDRD Study Equation was used to compute eGFR, while the formula Cockcroft-Gault was used for CrCl for each patient. For patients taking cisplatin, two distinct applications are used to avoid the associated nephrotoxicity of it in oncology Department of the Near East University Hospital.

These are either Magnesium and Potassium Agents or Mannitol Agent to be administered with patients receiving cisplatin treatment. Patients who are given mannitol, 20% mannitol (50-100 ml) over 60 min was given pre-chemotherapy hydration. Two potassium chloride and magnesium sulfate ampules have been administered to other patients during cisplatin therapy. It is worth noting that there was an exception for a few patients who were not given a protective agents, and physician was satisfied with giving them hydration with normal saline only. In this research, the patients were separated into three different groups, the preloading group of mannitol, the preloading group of magnesium-potassium, and the group using hydration normal saline. The main endpoint was the rate of elevated SCr level than before chemotherapy as well as reduced eGFR, CrCl. Diverse metrics for kidney function measurement such as CBC in the groups were compared as the secondary endpoint. In general, both serum creatinine and creatinine clearance are used to determine nephrotoxicity.

Data Calculations

The dataset was collected and analysed using Microsoft Excel 2016 and the Software 26.0 Social Science Statistics Package (SPSS). In order to summarize and compare patient groups receiving either mannitol or Mg-K as well as hydration with NaCl group, descriptive statistics were utilized. To assess the statistical importance of findings with continuous variables, Kruskal-Wallis Test was employed. Categorical variables were evaluated in a Chi-Square Test.

Ethical Approval

The institutional review board has been granted ethical approval for this project (IRB) of Near East University (YDU-2020/86-1217).

3. RESULTS

Between January 2018 and December 2020, the 27 patients' altogether, 15 received Mannitol in percent 20, 8 received Mg-K in their prescription, while 4 only received sodium chloride as a hydration without another nephroprotective agents. There were 16 male *(59.3%)* and 11 female *(40.7%)* who involved in our study with mean of age (*61.63, ±11.41)* years old, and BSA (*1.803, ±0.17) kg/m2* with different types of cancer: Gynecology *(18.5%),* Genitourinary *(11.1%),* Gastrointestinal *(18.5%),* Lung *(22.2%),* and Head/Neck *(29.6%).* Most patients do not have additional Diseases *(66.7%),* while some of them have Hypertension *(33.3%),* Diabetes Mellitus *(18.5%),* and Angina, Arrhythmia, Dyslipidemia and Thyroid Disorders each of them *(3.7%).*Demographics of patients are summarized in *Table 2*.

Table 2. Demographic Information of Patients (N=27)

Gender	***N(27)***	***%***
Male	*16*	*59.3*
Female	*11*	*40.7*
Mean	***Mn***	***SD***
Age in years	*61.63*	*±11.41*
Body Surface Area(BSA)	*1.803*	*±0.17*
Cancer Type	***N(27)***	***%***
Breast	*0*	*0*
Gynecology	*5*	*18.5*
Genitourinary	*3*	*11.1*
Gastrointestinal	*5*	*18.5*
Lung	*6*	*22.2*
Head/Neck	*8*	*29.6*
Chronic Diseases	***N(27)***	***%***
No additional Diseases	*18*	*66.7*
Hypertension	*9*	*33.3*
Angina	*1*	*3.7*
Arrhythmia	*1*	*3.7*
Chronic Kidney Disease	*0*	*0*
Diabetes Mellitus	*5*	*18.5*
Dyslipidemia	*1*	*3.7*
Thyroid Disorders	*1*	*3.7*
Nephroprotective Agents	***N(27)***	***%***
None	*4*	*14.8*
%20 Mannitol	*15*	*55.6*
Magnesium-Potassium	*8*	*29.6*

No significant variations among GFR, Cr Cl, SCR, laboratory results, HT and DM medical histories were identified between the groups.

The investigated serum creatinine levels, an estimated glomerular filtration rate, and creatinine clearance separately were tested before cisplatin given at baseline, first and second cycles. Subjects receiving 20 percent of mannitol (n = 15) were compared with those receiving Mg-K (n = 8), and those receiving Hydration with NaCl only (n = 4). After analyzed, measured GFR, among the 3 groups in first (*P-value: 0.175*) and second cycles (*P.-value: 0.441)* appeared statistically non-significant different like in baseline (*P.-value: 0.410),* same as CrCl in baseline (*P.-value: 0.828),* in first cycle (*P.-value: 0.766*) and in second cycle (*P. value: 0.853*), and Scr in baseline (*P.-value: 0.515),* in first cycle (*P. value: 0.595*) and in second cycle (*P. value: 0.328*). The measurement of GFR in mannitol group at first (*Mean 87.8, ±SD 14.6*) and second cycles (*Mean 88.73, ±SD 16.87*) appeared statistically non-significantly lower than in baseline (*Mean 92.80, ±SD 11.359*) (they were in grade 1 at baseline then became grade 2 at first and second cycles) same as in Hydration with NaCl group (*Mean 86, ±SD 10*) at baseline, (*Mean 83.75, ±SD 11.24*) at first cycle, and (*Mean 86.25, ±SD 11.0*) at second cycle (they were in grade 2 with different reading), while the measurement of GFR in Mg-K group at first (*Mean 96.12, ±SD 6.75*) and second cycles (*Mean 95.75, ±SD 8.14*) appeared statistically non-significantly higher than in baseline (*Mean 91.50, ±SD 16*)(they were in grade 1 with different reading). Also The measurement of CrCl in mannitol group at first(*Mean 95.37, ±SD 27.61*) and second cycles(*Mean 96.86, ±SD 30.48*) appeared non-significantly lower than in baseline(*Mean 100.01, ±SD 25.53*) same as in Hydration with NaCl group(*Mean 88.38, ±SD 17.14*) at baseline, (*Mean 86.46, ±SD 17.92*) at first cycle, and (*Mean 89.47, ±SD 18.22*) at second cycle, while the measurement of CrCl in Mg-K group at first(*Mean 92.20, ±SD 20.17*) and second cycles(*Mean 91.85, ±SD 21.18*) appeared non-significantly higher than in baseline(*Mean 89.98, ±SD 28.29*). On the other hand, the measurement of Scr in mannitol group at first(*Mean 0.84, ±SD 0.17*) and second cycles(*Mean 0.83, ±SD 0.18*) appeared non-significantly higher than in baseline(*Mean 0.79, ±SD 0.12*) same as in Hydration with NaCl group (*Mean 0.80, ±SD 0.13*) at baseline, (*Mean 0.82, ±SD 0.15*) at first cycle, and (*Mean 0.80, ±SD 0.14*) at second cycle, while the

measurement of Scr in Mg-K group at first (*Mean 0.731, ±SD 0.09*) and second cycles (*Mean 0.73, ±SD 0.11*) appeared non-significantly lower than in baseline (*Mean 0.78, ±SD 0.18*). *(Table 3)*

Table 3. Comparison of Outcomes across All Cycles with Nephroprotective Agents

Cisplatin	Nephroprotective Agents	N (%)	Baseline (Mean±SD)	P-value	First Cycle (Mean±SD)	P-value	Second Cycle (Mean±SD)	P-value
GFR	%20 Mannitol	15(55.6%)	92.80±11.359	**0.410**	87.8±14.6	**0.175**	88.73±16.87	**0.441**
	Mg-K	8(29.6%)	91.50±16		96.12±6.75		95.75±8.14	
	Hydration with NaCl	4(14.8%)	86±10		83.75±11.24		86.25±11.0	
CrCl	%20 Mannitol	15(55.6%)	100.01±25.53	**0.828**	95.37±27.61	**0.766**	96.86±30.48	**0.853**
	Mg-K	8(29.6%)	89.98±28.29		92.20±20.17		91.85±21.18	
	Hydration with NaCl	4(14.8%)	88.38±17.14		86.46±17.92		89.47±18.22	
Creatinine	%20 Mannitol	15(55.6%)	0.79±0.12	**0.515**	0.84±0.17	**0.595**	0.83±0.18	**0.328**
	Mg-K	8(29.6%)	0.78±0.18		0.731±0.09		0.73±0.11	
	Hydration with NaCl	4(14.8%)	0.80±0.13		0.82±0.15		0.80±0.14	

According to GFR the number of patients in mannitol group who were in stage 1 CKD were *11(64.7%)* at baseline, while they decreased in number at first and second cycles (*9(52.9%), 10(52.6%)* respectively), also they were *4(44.4%)* in stage 2 CKD at baseline, and increased at first and second cycles (*6(60%), 5(62.5%)* respectively), which indicated there were decreased in the health state of patients, but statistically non-significant. The patients in the Mg-K group on either side who were in stage 1 CKD were *5(29.4%)* at baseline, while they increased in number at first and second cycles (*7(41.2%), 7(36.8%)* respectively), also they were *2(22.2%)* in stage 2 CKD at baseline, and decreased at first and second cycles (*1(10%), 1(12.5%)* respectively), and in stage 3a was *1(100%)* at baseline then there was no case at first and second cycle which means an improvement in the health state of patients, but statistically non-significant. In addition, Hydration with NaCl patients were *1(5.9%)* in stage 1 at baseline then still *1(5.9%)* at first cycle but they increased *2(10.5%)* at second cycle,

while they were *3(33.3%)* in stage 2 at baseline, *3(30%)* at first cycle and *2(25%)* at second cycle which statistically was not different between them. However there were statistically different between the stages of baseline with first cycle, and baseline with second cycle (*P. value: 0.002*). *(Table 4)*

Table 4. Stages of CKD among Protective Agent at Baseline, First and Second Cycles

Stages	Nephroprotective Agents	Baseline	First Cycle	P-value	Second Cycle	P-value
Stages 1	%20 Mannitol	11(64.7%)	9 (52.9%)	**0.101**	10 (52.6%)	**0.364**
	Mg-K	5(29.4%)	7(41.2%)		7 (36.8%)	
	Hydration with NaCl	1(5.9%)	1(5.9%)		2 (10.5%)	
Stages 2	%20 Mannitol	4(44.4%)	6(60%)	**0.002***	5(62.5%)	**0.002***
	Mg-K	2(22.2%)	1(10%)		1(12.5%)	
	Hydration with NaCl	3(33.3%)	3(30%)		2(25%)	
Stages 3a	%20 Mannitol	0(0%)	0	-	0	-
	Mg-K	1(100%)	0		0	
	Hydration with NaCl	0(0%)	0		0	
Stages 3b	-	0	0	-	0	-
Stages 4	-	0	0		0	
Stages 5	-	0	0		0	
Total	-	27(100%)	27(100%)	-	27(100%)	-

The laboratory results of patients during the cycles are shown in (*Table 5*) which indicated the hematological toxicity associated with cisplatin administration and it was statistically non-significant among protective agents' groups.

Table 5. Laboratory Results of Patients at Baseline, First and Second Cycles

Lab Results	Laboratory Results of Patients					
	Nephroprotective Agents	**Baseline (Mean±SD)**	**First Cycle (Mean±SD)**	**P-value among First Cycle**	**Second Cycle (Mean±SD)**	**P-value among Second Cycle**
GFR	%20 Mannitol	92.80±11.359	87.8±14.6	**0.175**	88.73±16.87	**0.441**
	Mg-K	91.50±16	96.12±6.75		95.75±8.14	
	Hydration with NaCl	86±10	83.75±11.24		86.25±11.0	
Creatinine	%20 Mannitol	100.01±25.53	95.37±27.61	**0.766**	96.86±30.48	**0.853**
	Mg-K	89.98±28.29	92.20±20.17		91.85±21.18	
	Hydration with NaCl	88.38±17.14	86.46±17.92		89.47±18.22	
ALT	%20 Mannitol	22.47±11.128	27.27±19.901	**0.667**	22.93±13.33	**0.596**
	Mg-K	26.88±22.274	18.88±4.97		18.63±9.24	
	Hydration with NaCl	18.25±0.957	22±4.24		33.5±28.48	
WBC	%20 Mannitol	7.013±1.87	6.43±2.31	**0.943**	5.727±1.72	**0.137**
	Mg-K	9.93±3.13	12.06±17.66		12.05±12.42	
	Hydration with NaCl	10.53±5.48	7.43±3.91		4.48±0.974	
NEU	%20 Mannitol	4.53±1.63	4.298±2.20	**0.844**	3.74±1.66	**0.080**
	Mg-K	6.38±2.73	8.56±14.77		9.49±11.33	
	Hydration with NaCl	8.30±5.83	5.58±4.22		2.44±0.78	
LYMP	%20 Mannitol	1.179±0.66	1.42±0.59	**0.722**	1.29±0.64	**0.861**
	Mg-K	2.36±1.34	1.97±1.49		1.48±0.83	
	Hydration with NaCl	1.6±0.78	1.38±0.896		1.46±0.76	
RBC	%20 Mannitol	4.38±0.646	4.31±0.712	**0.973**	4.11±0.687	**0.582**
	Mg-K	4.54±0.59	4.195±0.61		4.03±0.709	
	Hydration with NaCl	4.198±0.968	4.1±0.796		3.73±0.947	
HGB	%20 Mannitol	12.25±1.76	12.13±1.92	**0.736**	11.59±1.78	**0.867**

	Mg-K	12.96±1.77	12.38±2.15		11.8±1.91	
	Hydration with NaCl	12.95±2.56	12.58±1.49		11.43±2.14	
PLT	%20 Mannitol	275.8±91.97	295.8±165.56	**0.259**	213.8±80.23	**0.073**
	Mg-K	311.5±124.43	368.75±120.8		410.63±233.46	
	Hydration with NaCl	357.5±119.64	328±21.25		215±62.17	

Additionally, we found patients who took mannitol, 2 of them had diabetic mellitus (13.3%), and 6 of them had hypertension (40.0%), while patients who took Mg-K, 3 of them had diabetic mellitus (37.5%), and 3 of them had hypertension (37.5%), and there were no comorbidity with Hydration with NaCl group. (*Table 6*)

Table 6. Patients with Comorbidities among Protective Agents' Groups

		Comorbidities	
	Nephroprotective Agents	**Diabetes Mellitus (N, %)**	**Hypertension (N, %)**
Cisplatin	%20 Mannitol	2 (13.3%)	6 (40.0%)
	Mg-K	3 (37.5%)	3 (37.5%)
	Hydration with NaCl	0 (0.0%)	0 (0.0%)

4. DISCUSSION

Cisplatin is an effective anti-tumor agent. Although it is beneficial, its nephrotoxicity limits the dosage of cisplatin which may be given. Even in individuals undergoing cisplatin can still develop renal dysfunction when the normal hydrating treatment is administered to avoid cisplatin-induced nephrotoxicity. This fundamental finding is important as cisplatin continues to be a typical chemotherapy with dose-limiting nephrotoxicity. There are currently no techniques for treating or preventing cisplatin-AKI effectively(Aoyama et al., 2020).

We have proven that a mannitol-containing regimen and a magnesium-potassium-containing regimen with cisplatin infusion to guard against nephrotoxicity by cisplatin has been compared in our study. Several studies have shown agents which can augment or ameliorate against cisplatin induced nephrotoxicity such as diuresis (mannitol or frusemide) and element (magnesium supplement)(Ali & Al Moundhri, 2006). Our findings show the association of mannitol hydration with greater nephrotoxicity than magnesıum-potassium hydration. In our study there were 3 groups who treated with cisplatin infusion according to protective agents that were taken, one of them was mannitol group, and the other one was magnesium-potassium group, while the last one was group who took normal saline as a hydration without protective agent.

We had possibilities as an index of renal impairment, which were serum creatinine and computed creatinine clearance as well as glomerular filtration rate. The highest cost-efficiency of our assessment was creatinine clearance. Blood creatinine is recognized to be increased only in late renal impairment and is shown to be a poor measure of glomerular filtration rate, albeit easy to acquire, and Serum creatinine generally does not become anomalous until its glomerular filtration rate is lowered by 50 percent. Many earlier trials on the nephrotoxicity of cisplatin were criticized for utilizing serum creatinine as endpoints of the research, as a result we measured creatinine clearance and GFR too to analyze the outcomes of the study (Santoso, Lucci, Coleman, Schafer, & Hannigan, 2003).

Despite in results did not differ significantly between the 3 groups in improvement or worsen the health state of patients by their GFR, Scr and CrCl, Our study showed by comparing the means of GFR, Scr and CrCl at baseline, first and second cycles that is using mannitol diuresis with hydration worsen cisplatin nephrotoxicity, which, this is against conventional clinical practice. However, *Santoso et al.* conducted a randomized study in which hydration was linked with the lowest cisplatin nephrotoxicity (saline, salin + mannitol, or saline + furosemide) and their results agreed with our results related to mannitol hydration in terms of nephrotoxicity, although their sample size was small(Santoso et al., 2003).

On the other side, *Muraki et al.* have revealed the nephroprotective the consequence hydration of furosemide-free mannitol and magnesium considered as an emerging protocol for cisplatin and pemetrexed chemotherapy in patients with advanced NSCLC, and its results showed that the nephrotoxicity of cisplatin and pemetrexed could be prevented without affecting the treatment outcomes, Without impairing the results of the process, this might be attributed to the inclusion of magnesium in a new protocol better than the previous hydration Protocol (saline, mannitol and furosemide) (Muraki et al., 2012). While *Horinouchi et al.* found that, immediate before cisplatin mannitol, before and after hydration used 10 mEq of potassium chloride in 500 ml of fluid over a 60-min, and magnesium sulphate (8 mEq) before hydration were used safely without serious renal toxicity, this is called short hydration (Horinouchi et al., 2013).

In addition, when we compared the mean of GFR, Scr and CrCl in Mg-K group, there were an improvement in health state especially in CrCl which showed CKD converted from grade 2 at baseline to grade 1 at first and second cycles, although it was statistically non-significant, however *Yoshida et al.* supported that by reporting a magnesium supplementation as a nephroprotective agent against cisplatin-induced renal failure (Yoshida et al., 2014). In assessing the impact of 15 mEq magnesium provided for prehydration in patients with cervical cancer who undergo cisplatin-alone treatment (40 mg/m^2/week), Yamamoto et al. also agreed on the effectiveness of magnesium in providing for nephroprotective properties against Cisplatin-induced nephrotoxicity. (Yamamoto et al., 2015).

Ahead to mannitol, Ruggiero et al. investigated the actual capacity of mannitol to prevent cisplatin nephrotoxicity and stated that it was always controversial whether to choose hydration alone, or hydration plus mannitol to prevent nephrotoxicity, but recommended that mannitol with pre- and post-Hydration be used in high doses of cisplatin to assure dieresis (Ruggiero, Rizzo, Trombatore, Maurizi, & Riccardi, 2016).

A study was done by *Ninomiya et al.* that emphasized to us the important of magnesium and considered it as key agent in the prevention of renal toxicity in cisplatin-related patients with advanced lung cancer, that were 75 years or older with adequate renal function, during evaluation to the safety and efficacy of short-term and low-volume hydration (Ninomiya et al., 2016). Perhaps the importance of magnesium as *Saito, Okamoto, et al.* found, was that it regulated of renal carriers' expression, rOct2 and rMate1, thereby decreased cumulation of cisplatin and therefore its toxicity (Saito, Okamoto, et al., 2017). A study examined the results of many researches on several synthetic and herbal supplements of antioxidants, and concluded that the pairing of Mg supplements and potassium was effective in attenuating renal function against a range of failure models for the kidney (Nematbakhsh et al., 2017). This was consonant with the way of giving our patients magnesium with potassium together as pre-hydration of cisplatin infusion. Also *Kumar et al.* examined the consequences of magnesium deficiency on cisplatin induced nephrotoxicity and killing tumor in CT26 colon tumor-bearing immunocompetent mice and found that nephrotoxicity due to cisplatin was deteriorated by Mg deficiency while cisplatin-induced kidney injury was blocked by the supplement of Mg, but did not influence the therapeutic value of cisplatin (Kumar et al., 2017).

Among 1,407 identified studies, hydration was considered an essential method to avoid CIN for all patients, short-duration, low-volume hydration with magnesium supplement and mannitol induced diuresis were the best strategy to protect against the toxicity of cisplatin especially in outpatients (Crona et al., 2017). As the matter is still being spoken, *Saito, Kobayashi, et al*. retrospectively investigated a group of patients (58) who suffered from head and neck cancer when they were given cisplatin, docetaxel, and 5-fluorouracil chemotherapies, and intravenous magnesium

pretreatment. they found that magnesium protected kidney against CIN without affecting the other adverse effects or magnesium level in blood(Saito, Kobayashi, et al., 2017).

The magnesium wasting was the primary feature of nephrotoxicity as stated by *Mach et al.* when they retrospective evaluated the selection of diuretic either mannitol or furosemide with premedication hydration, which has had no significant influence on the adverse effect severity, 133 women were included in this study who were given weekly doses of cisplatin (40 mg/ m2) with concomitant whole pelvic radiation. (Mach et al., 2017). *Kimura et al.* demonstrated through their study a nephrotoxicity in patients had cancer in their head and neck was avoided by receiving intravenous hydration with magnesium supplementation (Kimura et al., 2018).

Another comprehensive analysis was carried out to assess and discover substances that might give protection against cisplatin-induced nephrotoxicity with efficient anti-tumor activity and lower adverse effects, and was found that the administration of 1 g of magnesium intravenous was suitable as protective agent against CIN (Casanova et al., 2020). *Hase et al.* stated that for patients with lung cancer who had cisplatin-based chemotherapy a brief hydration program of 20 mEq magnesium supplementation was possible and safe.(Hase et al., 2020).

A recent study of *Aoyama et al.* those 26 gastric cancer patients retroactively was assessed. It was feasible to prevent nephrotoxicity due to cisplatin by suitable hydration when utilizing conventional vs short hydration, but there was still no consensus on the standard hydration technique to be employed. However, it did not seem necessary to have large or long-term hydration. They also noted that after the injection of cisplatin, preventive treatment of magnesium can avoid hypomagnesemia and therefore reduce nephrotoxicity and allow short hydration(Aoyama et al., 2020).

It is worth noting, our result showed that there was no significant difference between protective agents to protect the kidney against cisplatin toxicity, regardless of the means of GFR, CrCl and Scr. Despite results of CKD stages have shown differences between our groups especially in stage 2 of first and second cycles in

Table 4, these results may appear due to old ages and the health state of our patients (comorbidities).

4.1. Strength and Limitations

This study was unique in that it carried out a comparison of the effect of mannitol and magnesium-potassium as protective agents against cisplatin nephrotoxicity in the oncology department in Northern Cyprus.

There were several limitations in this study. These limitations were due to frequent incomplete data in cancer patients' files and absence of frequent laboratory data such as blood electrolyte tests and blood urea nitrogen. These limitations caused our sample size to be small due to insufficient documentation and the lack of many laboratory tests, particularly blood electrolytes and BUN.

5. CONCLUSION

In conclusion, our study has shown that the effect of mannitol and magnesium-potassium as protective agents against cisplatin-induced nephrotoxicity is the same when they administered during chemotherapy. This study was carried out in a single center. We suggest that future studies should be multi-center and include more cancer patients' assessment.

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7. APPENDIXES

7.1. CURRICULUM VITAE

Name: RANIA	**Surname:** AL-ZAGHIR
Place of Birth: ADEN- YEMEN	**Date of Birth:** 11/09/1986
Nationality: YEMENI	**Tel:**+905**428824869**
E-mail: pharmacist-ran@hotmail.com	

Educational Level

Name of the Institution where he/she was graduated	**Graduation year**
Masters: MSc inclinical pharmacy- NEU	CURRENT OCCUPATION
Undergraduate: BSc -Aden University	2005-2010

Job Experience

Duty	**Institution**	**Duration (Year - Year)**
1 Pharmacist	Hospital	9 years

Foreign Languages	**Reading comprehension**	**Speaking***	**Writing***
ENGHLISH	EXCELLENT	VERY GOOD	GOOD
TURKISH	GOOD	GOOD	GOOD

Computer Knowledge

Program	**Use proficiency**
Microsoft Word	EXCELLENT
Microsoft Excel	EXCELLENT
SPSS	EXCELLENT