TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES

COMPARISON OF HEMATOLOGICAL TOXICITY OF CANCER PATIENTS USING CARBOPLATIN AND CISPLATIN IN NORTHERN CYPRUS

By:

ABDUL'AZEEZ BATURE ADO-KHADEER

MASTERS

A THESIS SUBMITTED TO THE INSTITUTE OF GRADUATE STUDIES

NEAR EAST UNIVERSITY

CLINICAL PHARMACY

2022-NICOSIA

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ASSIST. PROF. DR. NEVZATBİRAND

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APPROVAL PAGE

We declare that we have read **Abdul'Azeez Bature Ado-khadeer's** thesis, "**Comparison of hematological toxicity of cancer patients using carboplatin and cisplatin 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 since in Clinical Pharmacy.

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DECLARATION

I, **Abdul'Azeez Bature Ado-khadeer's**, declare that the thesis hereby submitted to the Near East University for the degree of Master of Clinical Pharmacy, in the School of Pharmacy, has not previously been submitted to this or any other university; that it is my work in design and execution; and that all material contained herein has been duly acknowledged.

Abdul'Azeez Bature Ado-khadeer's

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ABSTRACT

Comparison of Hematological Toxicity of Cancer Patients Using Carboplatin and Cisplatin in Northern Cyprus

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Introduction: Platinum-based chemotherapy agents such as cisplatin and carboplatin are among the drugs included in chemotherapy protocols to treat many cancer types. Also, cisplatin has side effects such as nephrotoxicity, ototoxicity, and neurotoxicity. Carboplatin is used in chemotherapy protocols instead of cisplatin due to toxicities.

Methods: 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. The aim of the study was to assess and compare the hematological toxicity of cancer patients using carboplatin and cisplatin in the Oncology Department of Near East University Hospital in Northern Cyprus.

Results: There were 63 cancer patients who were received cisplatin and carboplatin at Near East University Hospital between January 2018 and May 2021. There were 27 (%42.9) who received Cisplatin, 36 (%57.1) cancer patients who received Carboplatin. There were 16 males (59.3%) and 11 females (40.7%) who have received Cisplatin and 12 males (33.3%), 24 females (66.7%) who have received carboplatin in this study. There was a statically significant difference between baseline and second cycle in grade 1 of Anemia (p=0.0005*) and there was a statically significant difference between the first cycle and second cycle in grade 1 of Anemia (p=0.0001*) in the Cisplatin group. There was a statically significant difference between the baseline and second cycle in grade 2 of Anemia in the Carboplatin group (p=0.015*). There was a statistically significant difference between the carboplatin group and the cisplatin group in grade 2 of the second cycle of Neutropenia (p=0.0008). There was a statistically significant difference between the carboplatin group and the cisplatin group in grade 1 of the first cycle of Anemia (p=0.0002**).

Conclusion: This study has shown that cisplatin has less incidence of hematologic toxicity than carboplatin. Due to the changes in blood counts after chemotherapy in cancer patients, healthcare professionals should monitor their patients regularly between each chemotherapy cycle. We recommend that future studies should be multicenter and include evaluations of more cancer patients.

Keywords: *Cisplatin, Carboplatin, Hematological Toxicity, Northern Cyprus*

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ABBREVIATIONS

HPV:	Human Papillomavirus
VIA:	Visual Inspection of the cervix with acetic acid
AUC:	Area Under the Curve
GFR:	Glomerular Filtration Rate
Cr-EDTA:	Chrome 51-Ethylenediaminetetraacetic Acid
DNA:	Deoxyribonucleic acid
UF:	Ultrafiltration rate
CR:	Complete Response Rate
RR:	Reaction Rate
GOG:	Gynecologic Oncology Group
SWOG:	South West Oncology Group
5-FU:	5-Flurouracil
OS:	Overall Survival
CG:	Cisplatin-Gemcitabine
MVAC:	Methotrexate, Vinblastine, Adriamycin, and Cisplatin
ORR:	Objective Response Rate
PFS:	Progression Free Survival
GCT:	Germ Cell Tumors
EC:	Etoposide and Carboplatin
EOC:	Epithelial Ovarian Cancer
RTOG:	Radiation Therapy Oncology Group
CrCl:	Creatine Clearance
HT:	Hypertension
DM:	Diabetes Mellitus

SCR:	Serum Creatinine
CKD:	Chronic Kidney Disease
PC:	Paclitaxel-Carboplatin
TNM:	Tumor (T), Node (N), Metastasis (M).

1. INTRODUCTION

1.1. Background

- 1.1.1. Definition of Cancer

Cancer, commonly termed as malignant growth, can be described as the common phenomenon of an enormous faction of illnesses that can harm every portion of the body. Dangerous tumors and neoplasms are other terminologies used. Malignancy is defined by the drastic growth of odd cells that develop beyond their normal limits, enabling them to infect neighboring parts of the body and extent to different tissues (Jacques Ferlay, 2010).

- 1.1.2. The problem of Cancer

Metastases are the prominent source of death in people with cancer. Malignant growth is a primary root of death globally, contributing to about 10 million deaths by 2020. The most widely recognized in 2020 (regarding latest instances of malignancy) were: breast (2.26 million cases); lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.09 million cases). In 2020, the most well-known factors responsible for cancer mortality were: lung (1.80 million mortality); colon and rectum (935 000 mortality); liver (830 000 mortality); stomach (769 000 mortality); and breast (685 000 mortality) (J Ferlay et al., 2019).

- 1.1.3. Causes of Cancer

Cancer is characterized by the alteration of healthy cells into cancerous cells in a multi-stage pathway that typically advances from a pre-carcinogenic lesion to a potentially dangerous tumor. These modifications are the product of collaboration among an individual's genomic elements and 3 types of exterior factors, including:

- Cancer-causing bodily factors, like electromagnetic and ionizing radiation;
- Cancer-causing contaminants such as asbestos, cigarette smoke, aflatoxin (a dietary contaminant), and arsenic (a toxin found in drinking water); and

- Cancer-causing organic factors, such as disorders caused by certain infections, bacteria, or parasites (J Ferlay et al., 2019; WHO, 2020).

- 1.1.4. Risks factors of Cancer

- The use of cigarette,
- The use of Alcohol,
- A diet that is unhealthy,
- Not doing physical exercise, and
- Pollution of air are all cancer danger elements

Certain persistent pollutions are tumor danger elements; this is a particular setback in low- and middle-income countries. In 2018, cancer-causing diseases such as H.pylori, human papillomavirus (HPV), hepatitis B and c, and Epstein-Barr infection were accountable for virtually 13% of cancers studied universally. Individually, hepatitis B and C infections, and certain types of HPV, increase the danger of liver and cervical tumor (de Martel, Georges, Bray, Ferlay, & Clifford, 2020). Infection with Human immunodeficiency Virus greatly rises the danger of tumors which may include cervical cancer

- 1.1.5. Symptoms and Signs of Cancer

The variety of tumor, wherever it is detected, and/or wherever the tumor cells have progressed define the symptoms and indicators. Breast cancer, for instance, can cause a lump or nipple discharge, but metastatic breast cancer might cause uneasiness (if it has spread to the bones), sudden weariness (lungs), or seizures (brain). A small percentage of people do not show any signs or symptoms until disease has advanced considerably.

A person should seek medical care if they notice any of the following threatening signs and/or indications of tumor.

1. An alteration in bowel or bladder patterns
2. A throbbing throat that won’t go away

3. An unusual amount of blood or secretion (such as breast discharges or a "sore" that won't heal and leaks stuff)

4. Breast enlargement or tumors in the testicles or other parts of the body

5. Digestive problems or difficulty swallowing (typically prolonged)

6. A noticeable change in size, coloration, form, or hardness of a wart or mole that is visible.

7. Coughing or hoarseness that persists.

Other indications or symptoms that may be present include:

• Inexplicable weight loss or a decreased appetite

- A kind of discomfort in the bones or further fragments of the body which occurs on a regular basis

• Inexplicable low-grade fevers can be prolonged or intermittent.

• Consistent tiredness, nausea, or vomiting

• Recurrent infections that do not respond to standard therapy

• Inexplicable weight loss or appetite reduction

• A particular rhythm of discomfort in the bones or further portions of the body that can be progressive or intermittent, although different from preceding aches.

- Extreme exhaustion, nausea, or vomiting

• Low-grade fevers that are unexplained can be prolonged or intermittent.

• Infections that don't respond to regular treatment (Lacy & Becker, 2013).

- 1.1.6. 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 tumor that starts in the bone, cartilage, fat, muscle, blood vessels, or further connective or supporting tissue. Osteosarcoma, synovial sarcoma, liposarcoma, angiosarcoma, rhabdosarcoma, and fibrosarcoma are all types of sarcoma.

Leukemia: is a cancer that starts in blood-forming tissue like bone marrow and produces a huge number of unusual blood cells to be formed and circulated.

- Lymphoma and myeloma: lymphoma and T-cell lymphoma are cancers that start in immune system cells. (Lacy & Becker, 2013).

Central nervous system cancers: Brain and spinal cord tumors in the membranes of the brain and spinal cord.

- 1.1.7. 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: During this stage, the tumor has affected other organs and parts of the body.. Progressive or disseminated cancer can also be named.

- **1.1.7.1** 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 tumor has transferred to further 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).

- 1.1.8. Prevention of cancer

Currently, between thirty and fifty percent of cancer can be prevented by evading danger elements and exploiting existing proof-based prediction systems. Prompt detection of the disease, and suitable therapy and caution for individuals who have the condition, can aid to reduce the weight of the malignancy. When diagnosed and cured early, numerous tumors develop a elevated opportunity of being cured (de Martel et al., 2020). The risk of cancer can be minimized by:

• Avoiding the use of tobacco

• Keeping a good body mass index (BMI).

• Consuming a nourishment that includes fruits and vegetables.

• partaking in routine physical exercise.

• Refraining from consuming alcohol that is damaging to one's health.

• If you belong to a group for which vaccination is suggested, getting vaccinated against HPV and hepatitis B.

• Protecting yourself from UV rays (which mainly result from contact to the sun and manmade tanning devices).

• Guaranteeing that radiation is used carefully and properly in healthcare system (for diagnostic and therapeutic reasons).

• Reducing ionizing radiation contact in the workplace; and

- Minimizing exposure to indoor and outdoor air pollution, such as radon (a radioactive gas produced by natural uranium decay that can accumulate in constructions such as households, educational facilities, and places of work)

- 1.1.9. Early detection of cancer

Malignant growth death can be decreased if incidents are identified and cured early. There are two segments of early recognition (de Martel et al., 2020; WHO, 2020):

- Early diagnosis when recognized early, tumor growth is certain to react to treatment and can bring about a more noteworthy likelihood of endurance and less morbidity, just as more affordable treatment. Critical enhancements can be made in the existences of malignancy patients by distinguishing disease early and keeping away from delays in care. Early diagnosis comprises of three parts:

- Monitoring the side effects of various types of malignancy and of the significance of looking for clinical counsel in the event that you are concerned.
- Admittance to clinical assessment and indicative administrations; and
- Opportune reference to treatment administrations.

Early finding of suggestive tumors is applicable in all settings and most of diseases. Malignancy programs ought to be intended to diminish delays in, and obstructions to, determination, treatment and care.

- The other segment of early recognition is screening which expects to recognize people with discoveries reminiscent of a particular malignancy or pre-cancer before they have acquired side effects. At the point when anomalies are recognized during screening, further tests to build up (or not) a determination ought to follow, as should reference for treatment if necessary. Screening programs are successful for some however not all disease types and overall are undeniably more intricate and asset serious than early analysis as they require special equipment and committed work force. Patient choice for screening programs depends on age and hazard variables to keep away from exorbitant bogus positive examinations. Instances of screening strategies are:
    - Cervical cancer screening with HPV.
    - The PAP cytology test for malignant growth of the cervical mucosa.

In contexts with robust or fairly solid health frameworks, visual inspection with acetic acid (VIA) for cervical disease and mammography for breast disease evaluation are both recommended. Both screening and early detection programs require quality confirmation.

- 1.1.10. Palliative care

Palliative care is therapy to ease, as opposed to cure, symptoms brought about by malignant growth and to enhance the personal satisfaction of patients and their relatives. Palliative care could make it easier for people to live. It's indeed especially important in areas where there are a large number of patients in advanced stages of malignancy with minute optionof survival. Alleviation from physical, psychosocial, and profound issues within palliative consideration is feasible for over ninety percent of patients with progressive phases of the disease. Successful general wellbeing techniques, involving local area and home-based care, are fundamental to give help with discomfort and palliative care for patients and their relatives. Upgraded admittance to oral morphine is unequivocally prescribed for the therapy of modest to extreme malignant growth torment, endured by more than 80% of individuals with disease in the terminal stage (de Martel et al., 2020)

- 1.1.11. Treatment of cancer

A right disease finding is fundamental for suitable and viable therapy on the grounds that each malignant growth form requires a particular therapy routine. Therapy typically incorporates radiotherapy, chemotherapy, and potential medical surgery. Deciding the objectives of therapy is a significant initial phase. The essential objective is to cure malignant growth and significantly reduce mortality. Improving the patient's personal satisfaction is likewise a significant objective. All of these can be accomplished by help for the patient's physical, psychosocial, and otherworldly prosperity and palliative consideration in life-threatening phases of malignant growth. Probably the utmost widely recognized malignant growth types, for example, breast malignancy, cervical malignant growth, oral malignancy, and colorectal malignancy, have high cure rates when identified early and cured by the finest practices. Certain malignancy forms, like testicular seminoma and various sorts of leukemia and lymphoma in youngsters, additionally do have significant healing rates if fitting therapy is given, in any event, when harmful cells are available in different spaces of the body (WHO, 2020)

1.2. The Platinum-Containing Antineoplastic Agents

Chemotherapy medications work on cells that are effectively separating. Hence, the impact isn't just sustained by the malignant cells but also in typical tissues with an elevated pace of multiplication, for example, gastrointestinal and hematopoietic structures (IARC-WHO, 2020; WHO, 2020).

Cisplatin and carboplatin are the solitary broadly acknowledged and enlisted platinum specialists for clinical use in cancer. Significant contrasts exist in their toxicology and pharmacokinetics; these are applicable to choosing which agent to use in an individual patient. These significant differentiations are audited, alongside a short conversation on the toxicology of 2 new encouraging analogs (Harrap, 1983; Kelland & McKeage, 1994; McKeage, 1995). The significance of Cisplatin and Carboplatin in cancer chemotherapy is unequivocal (A W Prestayko, D'Aoust, Issell, & Crooke, 1979; Z. H. Siddik, Boxall, & Harrap, 1987). Platinum analogs have evolved the cornerstone of treatment for ovarian cancer, lung cancer (both non-small-cell and small-cell), germ cell tumors, head and neck disease, bladder cancer, and, to a lesser extent, breast cancer and gastric cancer. The underlying platinum drug, cisplatin, was presented into clinical practice with a toxic characteristic that included nausea and regurgitation, renal failure, neurotoxicity, and ototoxicity. Carboplatin was the second

therapeutically essential drug to be produced, having a distinct toxicity report that included bone marrow inhibition (particularly thrombocytopenia) and a lower rate of gastrointestinal, hepatotoxicity, and neurotoxicity. Carboplatin is frequently contrasted to cisplatin, however it has the added benefit of having fewer gastrointestinal side effects allowing for patient treatment ease thereby avoiding the need for fluid intake and antiemetic treatment (J. Lokich & N. Anderson, 2000; A W Prestayko et al., 1979). Carbaplatin's therapeutic action was already found in all of the malignancies when cisplatin has been used, with 'practically identical' pharmacological effect reported in germ cell tumors (Horwich, 1990), ovary (Kavanagh & Nicaise, 1989), bladder cancer(Trump, Elson, Madajewicz, & Group, 1990), small cell and non-small-cell lung cancer (Green & Seal, 1990; Smith, 1992), head and neck malignancy (Volling & SCHRODER, 1988) and mesothelioma(Raghavan et al., 1990). Likewise, antitumor action for carboplatin has been set up in resilient severe leukemia (Martinez et al., 1991).

In 1994, Ruckdeschel expressed that "carboplatin (as opposed to cisplatin) is suggested for chemotherapy for palliative or non-corrective expectation" in a non-convention healthcare setting because of its "more positive toxicity profile and lower cost or expense "(Lee & Van Echo, 1990). Then again, Comis has expressed "cisplatin presently (1994) stays the suggested agent of choice for treatment of a few malignancies"(Ruckdeschel, 1994). Cisplatin has already been superseded by carboplatin in clinical settings, and the toxicologic and pharmacological distinctions between the two medications may support this substitution as long as clinical efficacy is not jeopardized. Although the view was not consistent across all preliminary studies, the underlying examinations contrasting cisplatin and carboplatin in ovarian cancer proposed that the treatments were pharmaceutically equal. In several cases, randomized preliminaries contrasting carboplatin and cisplatin in mix regimens in non-small cell lung cancer, bladder malignant development, head and neck cancer, and various cancers have revealed that cisplatin is preferable than carboplatin (J. Lokich & N. Anderson, 2000).

1.3 Pharmaceutical Aspects

- 1.3.1. Cisplatin

Cisplatin [cis-diamminedichloroplatinum(II)] is a square-planar neutral platinum(II) complex subbed by 2 ammonia groups and 2 chloride molecules in the cis-setup. Intravenous formulations containing sodium chloride forestall debasement to receptive and toxic water species or responses with colloid materials inside the medication vehicle (Cheung YW, Cradock JC, Vishnuvajjala BR, 1987). Dosages of 50 to 100 mg/m2 intravenously rehashed each 3 to about a month are utilized in adults. Single portion plans, 2 partitioned dosages one week separated, once daily for five sequential days, and infusion times going from moderate bolus infusions to consistent intravenous administration have been utilized. Simultaneous saline hydration and mannitol diuresis are needed to forestall serious nephrotoxicity (Hayes et al., 1977).

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	• '75-100 mg/m² IV per cycle q3-4Weeks on Day 1 with cyclophosphamide (600 mg/m² IV q4Weeks); administer sequentially'

	(may coadminister systemic Na thiosulfate)	
• 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).

- 1.3.2. Carboplatin

Carboplatin varies from cisplatin by substitution of 2 chloride iotas by an oxygenated bidendate cyclobutane-dicarboxylate bunch. It is more water dissolvable (Harrap et al., 1980) and less responsive than cisplatin (Zahid H Siddik, Newell, Boxall, & Harrap, 1987). Carboplatin is less strong on a mg for every mg premise than cisplatin yet purposes comparative DNA harm at likewise toxic dosages(Richard J Knox, Friedlos, Lydall, & Roberts, 1986). Grown-ups or adults can get dosages of 250 to 400 mg/m2, or portions dependent on renal function, once every four weeks or upon recuperation from hematological harmfulness or toxicity. Carboplatin transformation to cisplatin in sodium chloride containing arrangements is

kept away from by its preparation in dextrose mixture (Cheung YW, Cradock JC, Vishnuvajjala BR, 1987). The medication is generally given intravenously more than 1 hour without hydration. Tumors impervious to cisplatin for the most part display cross protection from carboplatin (Gore et al., 1989). Carboplatin is monetarily accessible as a freeze dried powder in 50-and 150-mg vials containing carboplatin and mannitol. It is modified with sterile water to the last centralization of 10mg/mL. For infusion, additional weakening with 5% dextrose and water or ordinary saline to a centralization of 0.5 or 2mg/mL, in which it is steady for 8 hours at room temperature. Carboplatin is regularly managed by IV infusion for more than 15-30 minutes. Patients with diminished renal capacity (creatinine clearance of <60mL/min) ought to have the portion of carboplatin diminished by the equation portrayed by Egorin et al. (Egorin et al., 1985).

For previously untreated patents:

Dosage(mg/m^2) = (0.091) (Creatine clearance/Body surface area) × [Pretreatment platelet count – Platelet nadir desired / Pretreatment platelet count × 100] +86

For heavily pretreated patients:

Dosage(mg/m^2) = 0.091) (Creatine clearance/Body surface area) × [Pretreatment platelet count – Platelet nadir desired / Pretreatment platelet count × 100] – 17] +86

A formula developed by Calvert and colleagues (Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, n.d.) also takes into account the patient's pretreatment renal function, as follows:

Dosage (mg) = Target AUC (mg / mL × min) H [GFR (mL / min) + 25]

where the dose in mg (not mg/m^2 body surface area) equals target AUC (area under the plasma clearance curve) × GFR (glomerular filtration rate) + 25.

When carboplatin is administered alone, the AUC is anticipated to be 7 in previously untreated people, and 4.5 when used in combination. There will be less toxicity if the AUC is set lower.

1.4. Nephrotoxicity

- 1.4.1 Clinical Features of Cisplatin Nephrotoxicity

Extreme nephrotoxicity was the peak crucial dose-limiting discovery in initial clinical preliminaries of cisplatin provided without hydration and was deadly or needed dialysis support in certain patients (Bitran, Desser, Billings, Kozloff, & Shapiro, 1982; Dentino, Luft, Yum, Williams, & Einhorn, 1978; Rossof, Slayton, & Perlia, 1972). With the utilization of saline hydration and mannitol diuresis, these impacts turned out to be more reasonable in spite of the fact that cisplatin stays a nephrotoxic analogue. Regardless of these actions, irreversible abatements in glomerular filtration rate (GFR) estimated by Cr-EDTA elimination happen over a wide measurement range: 12 to 20% diminishing at 20 mg/m2/day for five sequential days, 0 to 32% with bolus dosages of 50 to 100 mg/m2, and ≥ 35% at 40 mg/m2/day for 5 continuous days (Plowman, McElwain, & Meadows, 1991). Intense renal tubular injury and expanded discharge of urinary tubular enzymes (N-acetyl-glucosaminidase and leucine aminopeptidase), 2-microglobulin and glucose are obvious at 1 to 6 days after treatment yet resolve by 1 to 3 weeks(Jones et al., 1980). Tubular deficiencies in magnesium homeostasis are all the more in long duration (Bell, Woods, & Levi, 1985; Schilsky, Barlock, & Ozols, 1982). Hypomagnesaemia progresses in about 75% of patients, starting 3 to 12 weeks after treatment and continuing for quite a long time to years in 40%. Hypomagnesaemia might be related with unseemly urinary magnesium discharge, potassium and calcium squandering, and manifestations like muscular weakness, quiverness and dazedness (Bell et al., 1985; Schilsky et al., 1982). Long haul survivors of cisplatin-based treatment show persistent shortages in glomerular capacity and higher than anticipated paces of arterial hypertension (Bissett et al., 1990; Hamilton, Bliss, & Horwich, 1989).

- 1.4.2. Nephrotoxicity of Carboplatin

In the absolute first clinical preliminary of carboplatin, sequential estimations of Cr-EDTA clearance, and urinary N-acetyl-j3-glucosaminidase, leucine aminopeptidase and 2-microglobulin, uncovered no critical nephrotoxicity. There was no lessening in GFR appropriate to the medication and just minor transient increase in urinary enzymes demonstrative of mild reversible injury to the renal tubule at higher portions (Calvert et al., 1982). Long duration follow-up investigations of renal capacity after carboplatin treatment show no critical total damage (Mason, Nicholls, & Horwich, 1991). Carboplatin at high portions of 1200 mg/m2 is related with nephrotoxicity in more than half of patients, encountering diminishes in GFR of 25 to 50 percent (Gore, Calvert, & Smith, 1987).

Carboplatin at portions of 2000 mg/m2 given with autologous bone marrow support is related with a 30% decrease in creatinine clearance in most patients (Shea et al., n.d.). The decreased level of nephrotoxicity with carboplatin contrasted with cisplatin may relate with contrasts in renal handling and reactivity with macromolecules (Zahid H Siddik et al., 1987). It doesn't seem to connect with renal platinum absorptions since these are comparative after maximally endured portions, at any rate in rodents (Z H Siddik, Dible, Boxall, & Harrap, 1986).

1.5. Gastrointestinal Toxicity

- 1.5.1 Clinical Features

Nausea and regurgitation are among the most dreaded unfavorable impacts related with cancer chemotherapy (Coates et al., 1983) and cisplatin is the most emetogenic. Cisplatin at dosages of 100 mg/m2 taken without antiemetics or prochlorperazine only causes emesis in many patients with, on average, 11 occurrences in the initial 24 hours, starting at two to three hours after administration (Gralla et al., 1981). Patients may likewise encounter nausea and regurgitation past the principal day of treatment (postponed emesis) or before treatment (expectant emesis), and other gastrointestinal indications like anorexia and loose bowels(diarrhea). The frequency and seriousness of nausea and regurgitation expands ensuing to the first cycle of chemotherapy, regardless of the utilization of antiemetics (Cubeddu & Hoffmann, 1993). Hazard factors for intense emesis are female sex, high cisplatin portion, fast infusion, and treatment with cisplatin in addition to anthracyclines (A Du Bois et al., 1992). Hazard factors for deferred emesis are helpless control of intense emesis in past therapy cycles, female sex, high cisplatin portion and second-line chemotherapy (A Du Bois et al., 1992). Carboplatin is less emetogenic, although some patients experience nausea and vomiting uncontrolled by antiemetic therapy (Harvey et al., 1991).

1.6. Peripheral Neurotoxicity

Neurotoxicity is the most dose-limiting issue related with cisplatin since the counteraction of its renal and intense gastrointestinal adverse impacts (Robert F Ozols et al., 1984). In spite of the fact that cisplatin-actuated neurotoxicity is seldom lethal, it can bring

about extreme and perpetual disability. The most well-known manifestations are peripheral neuropathy and hearing loss. Less regularly, autonomic neuropathy, Lhermitte's sign, seizures, retrobulbar neuritis, encephalitic indications, cerebral herniation, retinopathy, cortical visual impairment, and vestibular instabilities occur (Cersosimo, 1989; Gispen, Hamers, & Neijt, 1990). The announced rate of peripheral neurotoxicity depends on the meaning of neurotoxicity, dosage plan, administration of different neurotoxins(Cersosimo, 1989), and foundation frequency of paraneoplastic neurological conditions(Cavaletti et al., 1991). Subclinical peripheral neurotoxicity happens in >90% of patients accepting combined portions of 300 mg/m2 or more and going through assessment of vibration sensation threshold (Elderson et al., 1989; Lipton et al., 1987). A prospective study of 292 women with ovarian cancer who were cured using conventional amount cisplatin (75 to 100 mg/m2 per course for a median of 5 to 6 courses) found that clinically obvious peripheral neurotoxicity occurred at a significant rate (Van Der Hoop, Van der Burg, Ten Huinink, Van Houwelingen, & Neijt, 1990). Signs and adverse effects were found in 47% of patients and 61 % of long duration survivors (> 5 years) of ovarian malignancy (Van Der Hoop, Van der Burg, Ten Huinink, Van Houwelingen, & Neijt, 1990).

1.7. Ototoxicity

The occurrence of cisplatin-actuated ototoxicity revealed in the literature goes from 11 to 91 % relying upon its definition, the dose plan, and simultaneous treatment(Strauss et al., 1983; Waters, Ahmad, Katsarkas, Stanimir, & McKay, 1991). At combined dosages of 200 mg/m2, 74 to 100% of patients develop elevated recurrence damage on audiograms, 46 to 68% develop tinnitus and 13 to 20% have critical suggestive hearing loss (Aguilar-Markulis NV, Beckley S, Priore R, 1981; Laurell, 1992; Malhotra, 2009; Pathology, 1985). Nonetheless, tinnitus isn't constantly trailed by hearing damage (Aguilar-Markulis NV, Beckley S, Priore R, 1981) and hearing indications are not generally connected with audiometric irregularities (Reddel RR, Kefford RF, Grant JM, Coates AS, Fox RM, 1982). Normally, audiograms show respective and even high recurrence hearing loss with an incidental contribution of speech frequencies (Aguilar-Markulis NV, Beckley S, Priore R, 1981). In the best-case situation, recovery is unexpected and insufficient (Aguilar-Markulis NV, Beckley S, Priore R, 1981; Laurell, 1992; Malhotra, 2009).

1.8. Haematological Toxicity

- 1.8.1 Cisplatin

Cisplatin is toxic to all three blood ancestries. Cisplatin incited leucopenia happens in 0 to half of the patients, however, white blood cell counts underneath 1.5 x 109/L happen in just 5% of patients. The onset of leucopenia occurs between days 6 and 26, and recuperation happens around days 21 to 45 (Von Hoff DD, Schilsky R, Reichert CM, Reddick RL, Rozencweig M, Young RC, 1979). Cisplatin-initiated thrombocytopenia happens in 2 to half of patients and platelet counts under 50 x 109/1, happen in under 10% of patients. The onset of thrombocytopenia occurs between days 10 and 26, with recovery occurring between days 28 and 45. Despite the fact that the etiology of anemia in disease patients is typically complex and complicated, cisplatin can cause it. Anemia is related with cisplatin in 9 to 40% of patients(Von Hoff DD, Schilsky R, Reichert CM, Reddick RL, Rozencweig M, Young RC, 1979). Separated portion and high portion cisplatin schedules are linked to more severe hematological damage, which, coupled with peripheral neurotoxicity, could be dose-limiting (Blumenreich MS, Woodcock TM, Jones M, Richman SP, Gentile PS, Kubota TT, 1985; Robert F Ozols et al., 1984). Diuresis and hydration don't influence the rate or seriousness of cisplatin-initiated myelosuppression(Archie W. Prestayko, Crooke, & Carter, 1980). Because of cisplatin's low hematological toxicity, it can be used with myelosuppressive drugs like etoposide and cyclophosphamide.

- 1.8.2. Carboplatin

Hematological toxicity is carboplatin's dose-limiting toxicity, which is more noticeable than cisplatin's. At ordinary dosages, thrombocytopenia is a more prominent issue than leucopenia. Platelet counts take place between 14 and 28 days, and recovery takes 7 to 10 days. Leucopenia, on the other hand, is less severe. (Calvert et al., 1982; Curt GA, Grygiel JJ, Corden BJ, Ozols RF, Weiss RB, Tell DT, Myers CE, 1983). Anemia needing transfusion assistance occurs in less than 25% of patients with leucopenia and thrombocytopenia, which can lead to infection or bleeding. (Canetta R, Rozencweig M, 1985). Carboplatin dose intermissions rely on platelet recuperation, which ordinarily happens a month after treatment. The carboplatin administration plan (single dose versus day by day x 5) seems to have little impact on the

seriousness of myelosuppression(Calvert et al., 1982; Curt GA, Grygiel JJ, Corden BJ, Ozols RF, Weiss RB, Tell DT, Myers CE, 1983). Renal capacity has a significant impact on the initial carboplatin administration and the severity of carboplatin-induced thrombocytopenia. (Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, n.d.).) The lack of non-hematological toxicity levels in carboplatin has led to its use in high-dose treatment. Myelosuppression is the dose-limiting toxicity at 1200 mg/m2, with >90% of patients experiencing grade IV neutropenia and thrombocytopenia, and a decrease in hemoglobin fixation of 30 to 35 g/L.(Gore et al., 1987). Attempts to speed up platelet recuperation after high portion carboplatin with interleukin 1 alpha(Smith JW 2nd, Longo DL, Alvord WG, Janik JE, Sharfman WH, Gause BL, Curti BD, Creekmore SP, Holmlund JT, Fenton RG, n.d.) and autologous bone marrow transplantation (Shea et al., n.d.) are being scrutinized. Preliminary studies of carboplatin and paclitaxel in combination, prompted by the lack of cross-resistance and covering the neurotoxicity of these two experts, have revealed substantially less thrombocytopenia than expected.(Huizing MT, Giaccone G, van Warmerdam LJ, Rosing H, Bakker PJ, Vermorken JB, Postmus PE, van Zandwijk N, Koolen MG, ten Bokkel Huinink WW, van der Vijgh WJ, Bierhorst FJ, Lai A, Dalesio O, Pinedo HM, Veenhof CH, n.d.).

1.9. Pharmacokinetics

Cisplatin and carboplatin have the same cell-killing system, by attaching to cell DNA and generating cross-links, they act as non-traditional chemotherapeutic drugs. The level of cell extinction is linked to the degree of platinum DNA adduct formation that can be measured. Knox et al. demonstrated that achieving the same degree of DNA attachment is required for similar tumor cytotoxicity (Weed, 1997). Carboplatin does have a higher level on substance stabilisation than cisplatin, which means it has less DNA interaction. As a result, a greater proportion of carboplatin is needed in clinical trials to obtain effective anti-cancer results. Although the range of exploratory tumor framework action is comparable for the two specialists, carboplatin may be eight to ten times weaker than cisplatin in vivo trial anti-tumor frameworks (R J Knox, Friedlos, Lydal, & Roberts, 1986). The percentage of carboplatin remedial prescription vs cisplatin remedial prescription has typically been depicted as 4:1 (400-500 mg/m2 versus 100 mg/m2) centered on scientific findings in ovarian tumor in which these dosages attained comparative equality. When using the Calvert et al. equation, the unfavorable

effects of carboplatin are even more strongly anticipated.(Reed, 1996), Jodrell et al. have also made adjustments in this way..(Calvert et al., 1989) Because 90 percent of a carboplatin portion is expelled by the kidneys, a specific area under the curve (AUC) is founded as an aim for carboplatin plasma fixation identified with creatinine clearance in this equation. A single customized AUC of 5-7 mg/ml x minutes for carboplatin was being established as a starting point for accurate dosage determination. The metabolism and excretion of the two analogs differ significantly. Carbaplatin has no crucial catabolism in vivo, whereas cisplatin is destroyed by the sulfhydryl group. In most cases, 90 percent of a carboplatin infusion is retrieved in the urine, but just 25% of cisplatin is expelled unchanged. As per Reed et al's standard pharmacokinetic design, cisplatin and carboplatin are relatively comparable (R J Knox et al., 1986). In any case, the proximal half-lives of the two drugs are identical at 5.8 and 5.4 days, respectively.

Various clinical studies have used a combination of carboplatin and cisplatin organized in a synchronized manner (Patton et al., 1996; Sengeløv, Nielsen, Kamby, & Von Der Maase, 1995; van der Vijgh, 1991), Because the toxicity profiles of carboplatin and cisplatin differ, and because tumor cell execution is contingent on increasing DNA adduct arrangement, higher all-out platinum portions have been postulated to provide better amounts of cell death in diverse clinical trials. Three studies using a combination of cis- and carboplatin gave carboplatin dosages of 280, 300, and 350 mg/m2, with combined cisplatin doses of 75, 100, and 150 mg/m2. Despite the large proliferation of UF platinum in ovarian malignant development, no significant increase in tumor responses was seen (Patton et al., 1996) and head and neck cancer (Sengeløv et al., 1995). Despite the fascinating if not persuasive rationale for its use, the strategic complexity of these twofold platinum regimens, as well as the lack of a major positive advantage seen, have limited further investigation of the platinum analogue combination.

2.1. Clinical trials

There is a wide spectrum of malignancies for which platinum analogs have become conventional treatment. Ovarian cancer, germ cell tumors, head and neck cancers, both small cell and non-small cell lung cancer, and bladder cancer all require platinum as part of their main line chemotherapy regimen. Furthermore, platinum regimens are often used to treat certain gastrointestinal tumors (particularly, esophageal, gastric, and anal malignancies), though 5-fluorouracil is said to play a larger role. Cisplatin, despite being infrequently used as

a first- or second-line treatment for breast cancer, is also efficient. Randomized preliminaries comparing cis- and carboplatin have accounted for the 5 most collective malignancies for which a platinum specialist is usually supplied as a component of first-line treatment.

- 2.1.2 Ovarian cancer trails

Between 1989 and 1997, 10 randomly selected studies associating cis- and carboplatin for ovarian cancer therapy were accounted for (Adams et al., 1989; Alberts et al., 1992; Belpomme, Bugat, & Rives, 1992; Conte et al., 1991; Edmonson et al., 1989; Mangioni et al., 1989; Piccart et al., 1990; Swenerton et al., 1992; Taylor, Wiltshaw, Gore, Fryatt, & Fisher, 1994; ten Bokkel Huinink et al., 1988). 11 preliminary studies looking at cis and carboplatin were identified In a 1991 meta-analysis of cancer treatment in ovarian cancer, as well as a 1993 general audit with the identical subject (Group, 1991) However, most of the other preliminary studies were still in the early stages of development, and two out of 11 have either been unreported or even had small patient populations. Three out of the ten current preliminary investigations, one of which was updated in 1994, included a single specialized carbo and cisplatin correlation in initially undiagnosed patients. The three single-specialist examinations, which were conducted mostly in patients with persistent disease that was not improving, contained over 400 individuals. The carboplatin fraction was fixed at a 4:1 ratio to the cisplatin fraction in each of the three investigations. In two of the three investigations, the general reaction rate was higher in cisplatin, whereas the general reaction rate was higher in carboplatin in the third study.

The alkylating specialist cyclophosphamide was used in 6 of the 7-combination chemotherapy considers incorporating cis-versus carboplatin, with two preliminary studies adding an anthracycline. In one preliminary, paclitaxel was the acquaintance specialist. The portion of carboplatin in the Mayo Clinic study was 150 mg/m2 (despite the fact that portion elevation was used as part of the plan), whereas it was 300 mg/m2 or higher in 4 reports, one of which used the AUC method. Over the course of the 7 examinations, about 1700 patients were assessed, with the majority of them having a troublesome residual tumor. The pathologic complete reaction rate for cisplatin was better than carboplatin in two studies (Alberts et al., 1992; Conte et al., 1991), but not by a significant margin. With two exceptions, the endurance and reaction rates for cis- and carboplatin were approximately identical in all preliminary studies. The Mayo Clinic experiment indicated that the cisplatin arm had a significant

infection-free endurance advantage, which was closed to new patients after a break review (Belpomme et al., 1992). This preliminary also used a method of portion equivalence according to toxicities for the arms of cis- and carboplatin. The break research found that the cisplatin-containing arm had an average endurance of seveenteen months vs a year for the carboplatin (P = 0.04) in this exploratory study of 103 patients. Overall endurance was higher in the cisplatin group (twenty-seven versus twenty months), however, this was statistically non-significant (P = 0.14). Patients who were still on carboplatin medication at the end of the research received a cisplatin combination treatment. and the endurance pattern in this group of 21 patients was restored to that of patients who had cisplatin as their underlying treatment.

Belpomme et al. accounted for the other preliminary findings in their conceptual framework for the French ARTAC ovarian malignancy trial group, demonstrating a significant helpful contrast between the analogs and preferring cisplatin (Belpomme et al., 1992). The cisplatin-containing arm had a higher pathologic CR and overall reaction rate, with 33 percent Complete Response Rate and seventy-three percent PR compared to fifteen percent and forty-seven percent (P =0.008) for the carboplatin arm, respectively. This material has not yet been accepted for publication.

3 out of 5 preliminary studies about cis-and carboplatin-based combination chemotherapy have astonishingly similar reaction rates (59 percent, 61 percent, 62 percent RR for carboplatin and 57 percent, 52 percent, 66 percent RR for cisplatin), indicating clear analog equivalency (Swenerton et al., 1992) discovered lower total reaction rates (36 and 45 percent) and a higher response rate with cisplatin, but the difference was not significant. An AUC of 5 was achieved in a research utilizing paclitaxel 175 mg/m2 in conjunction with either cisplatin 75 mg/m2 or carboplatin, according to a preliminary report from the Netherlands (Edmonson et al., 1989). These preliminary lack the test configuration deficiencies and challenges of the continuous GOG preliminary (see below) and are accounted for in particular with an interval examination.

Additional way to compare cis- and carboplatin is to examine information from preliminary experiments, after acquiring resistance or chronic condition towards one of the analogues, patients are treated successively with the other platinum specialist. In a large percentage of the randomized preliminaries studied, crossover was permitted. Two studies using carboplatin or cisplatin as a rechallenging or crossover specialist have been published (Gore, Fryatt, Wiltshaw, & Dawson, 1990; Vermorken et al., 1993). In a research undertaken

by the Royal Marsden Hospital, fifteen of forty-three patients (34%) reacted, compared to 9% of rechallenged patients (those who were treated with a comparable platinum treatment after relapse (Vermorken et al., 1993). After receiving cisplatin, ten patients had a complete reaction to carboplatin, with no statistically significant difference in frequency depending upon what specialist was treated initially. Another study included 57 patients, with 24 receiving cisplatin and 33 receiving carboplatin as the treatment (Gore et al., 1990). Cisplatin had a higher reaction rate (25 percent versus 9 percent for carboplatin), and reactions were only seen in patients who had not responded to first-line platinum treatment with cisplatin (three of twelve for cisplatin versus zero of eleven for carboplatin).

- 2.1.3. Non-ovarian cancer trials

Eight research assessing cisplatin and carboplatin in a randomly selected system analysis were conducted in the 4 cancer types for which platinum has long been a fundamental piece of adjuvant chemotherapy. Depending on the kind of tumor or the combination of medicines used, carboplatin doses ranged from 250 mg/m2 to 500 mg/m2, however two exploratory investigations utilized an AUC-guided carboplatin fraction.

- 2.1.4. Head and neck cancer

The issue of cisplatin vs carboplatin in head and neck cancer is the subject of two planned randomized trials (De Andres et al., 1995; Markman, 1996). The Southwest Oncology Group (SWOG) looked at 277 patients who were given 5-fluorouracil (5-FU) as a companion medicine in a 96-hour implantation. As a control arm, single specialist methotrexate was used. The cisplatin group had significantly higher ototoxicity and renal toxicity than the carboplatin group, and hematologic harmfulness was similarly higher in the cisplatin unit. Despite the fact that the cisplatin group had a larger reaction rate (32 percent versus 21 percent), both the cisplatin and carboplatin units, as well as the distinct specialist methotrexate arm, had similar reaction length and median endurance. The second study in head and neck cancer that combined cisplatin and carboplatin also used 5-FU implantation, but this time for 120 hours, and the carboplatin dose was increased by 1/3 to 400 mg/m2. In the SWOG study, cycles for the cisplatin arm were repeated after 21 days, compared to 28 days for the carboplatin arm. The

study was hampered by the small number of patients, with only 95 patients. Individuals with tumours or reoccurring cancer were excluded from a smaller study.

- 2.1.5. Bladder cancer

For patients with privately extensive bladder cancer, there is growing evidence to support the need for neoadjuvant cisplatin-based therapies. 3005 patients from 11 randomized controlled preliminary studies were pooled in a meta-analysis that compares this routine to local treatment alone (Vale, 2005). The latter identified a substantial OS benefit similar to a 5% outright increase in endurance at five years with cisplatin-based therapy. There is little proof to substantiate the usage of carboplatin in peri-employable patients, and there isn't any related adjuvant investigations to discuss any differences in outcomes among cisplatin and carboplatin.

Cisplatin-based treatments (such as cisplatin-gemcitabine (CG) or hgh prescription methotrexate, vinblastine, doxorubicin, and cisplatin (DDMVAC)) address the cornerstone of first-line basic delivery once again in the metastatic set - up. (Sternberg et al., 2001; von der Maase et al., 2000). CG has a better toxicity profile than excellent MVAC, but having the same ORR (49 percent versus 46 percent) (von der Maase et al., 2005). When compared to part thick MVAC, MVAC has been reported to be worse in relations of ORR, PFS, and CR rates (Sternberg et al., 2001);. In any event, no direct link between CG and dosage thick MVAC has been discovered. Considering the latter, Dogliotti et al. presented a new stage II comparative trial contrasting carboplatin-gemcitabine with CG. finding that cisplatin was greater than carboplatin (Dogliotti et al., 2007). Santis et al. compared carboplatin-gemcitabine to an adjusted MVAC treatment for cancer patients who are considered cisplatin resistant (for example, GFR 30ml/min and PS 2) (De Santis et al., 2012) . Additional, minor research looked at the usage of carboplatin-gemcitabine in old or ill-suited patients who couldn't take cisplatin. With a 45.1 percent ORR and a average OS of twenty months, preliminary results demonstrate that this technique is an acceptable option to cisplatin-based management in this patient population (Park et al., 2013).

- 2.1.6. Germ cell tumors

In men with metastatic germ cell tumors (GCT), current cisplatin-based treatment has led to treatment efficacy of over eighty percent (Mead et al., 1997). Treatment-related toxicities of cisplatin-based treatments have been reduced in these patients with a spectacular longstanding prognosis by a variety of efforts. As a result, a slew of random comparative studies have been conducted in an attempt to find some possible non-mediocrity with carboplatin. Horwich et al. (Horwich et al., 1997) led the biggest metastatic GCT study to date, with 598 "serious hazard" non-seminomatous GCT patients. During a period of many days, patients were randomly selected to take one of four regimens of bleomycin, etoposide, and cisplatin (BEP) (n=300) or bleomycin, etoposide, and carboplatin (CEB) (n=298). At one year, the CEB partner had considerably more treatment disappointments than the BEP arm (79 versus 30 treatment disappointments, p 0.001). Furthermore, the CEB arm had considerably more human mortality (27 versus 10, p=0.003) than the BEP arm, implying 90 percent (95 percent CI, 86 percent to 94 percent) versus 97 percent (95 percent CI, 95 percent to 99 percent) long-term endurance rates (Horwich et al., 1997) (Horwich et al., 1997).

In a multicenter, randomized stage III trial, Barjorin et al. compared the efficacy of four etoposide and cisplatin (EP) patterns (n=134) to four etoposide and carboplatin (EC) patterns (n=131) in patients with advanced metastatic GCT as defined by Memorial Sloan Kettering Cancer Center (MSKCC) models (Bosl et al., 1988). Complete response (CR) rates between EC (88%) and EP (100%) showed no significant differences (90 percent). Patients treated with EC showed worse relapse occurrence and endurance after a mean follow-up of 22.4 months, but no detectable change in overall survival (OS) (Horwich et al., 1997). A 4 week by week cycling of EC and the carboplatin dosage strategy are two significant antagonistic aspects that could have influenced results in the EC partner. Bokemeyer et al (Bokemeyer et al., 1996) studied 54 patients with metastatic non-seminomatous germ cell tumors who had "negligible" or "moderate" morbidity, according to Indiana University criteria (Birch et al., 1986). They were given either three patterns of cisplatin, etoposide, and bleomycin (PEB) (n=29) or four patterns of carboplatin, etoposide, and bleomycin (CEB) (n=29) (CEB). Enrollment began in 1992, and following a provisional review of the initial fifty-four patients disclosed that patients in the CEB unit had a greater risk of occurrence, the research was completed. The CEB arm had a higher rate of recurrence (32 percent against 13 percent) and mortality (16 percent versus 3 percent) than the PEB arm, and the higher adverse rate in the CEB arm was significantly significant (Bokemeyer et al., 1996). This basic preliminary implies that carboplatin is inferior to cisplatin, even with the existing proof-based dosage of bleomycin and etoposide.

Because these individuals had a better prognosis than their non-seminomatous counterparts with metastatic seminoma, carboplatin as a solitary treatment in metastatic seminoma, it has been contrasted to cisplatin-based combination therapies (Mead et al., 1997). The purpose was to minimize toxic effects of cisplatin, which had treatment efficacy of 80-95 percent. In two randomized stage III trials, Bokemeyer et al. aggregated and evaluated information from 361 patients (181 cisplatin-based versus 177 carboplatin monotherapy) (Bokemeyer et al., 2004). Patients cured with solitary specific carboplatin had subpar 5-year PFS (seventy-two percent and ninety-two percent; p0.0001) and non-measurably poor OS (89 percent and 94 percent; p=0.090) as equated to patients cured with cisplatin-based mixtures. This is obviously a contrast of a solitary specialist with a mixture of therapies, each of which have been proven to be helpful, and should be viewed with caution.

- 2.1.7. Lung cancer

The mixture of etoposide and cisplatin is now an extensively used systemic therapy regimen in both small cell and non-small carcinoma. Carboplatin is effective in both small cell carcinoma and non-small cell carcinoma when used alone or in combination with other drugs such as ICE (ifosfamide and etoposide) and paclitaxel. In a new significant trial, Skalos et al. presented data in small cell lung cancer patients with moderate or advanced stage cancer who were given etoposide 300 mg/m2 and cisplatin or carboplatin 100 and 300 mg/m2 separately (Horwich et al., 1997). The two arms had similar reaction rates, at 57 percent and 58 percent respectively. The hematologic harmfulness of the cisplatin arm was compared to the carboplatin unit in this study.

In 1990, a multi-institutional preliminary study of cisplatin against carboplatin in non-small cell lung cancer was reported (Samantas et al., 1995). For three days, patients were given etoposide 300 mg/m2, as well as cisplatin 120 mg/m2 on the first day or carboplatin 325 mg/m2 (fixed dose) on the first day. The reaction rates of 200 and two patients were compared, with a pattern favoring cisplatin (reaction degree twenty-seven percent versus sixteen percent), although no substantial differences in endurance were found. On the cisplatin arm, toxicity, notably renal and hematologic, was more noticeable.

- 2.1.8. Gynecological cancer

Unlike the majority of other tumor types investigated, carboplatin are presently the best anticancer agents therapies for epithelial ovarian cancer (EOC) in preventive, postoperative, and supportive care settings (Joly et al., 2017). The cornerstone of this treatment philosophy has been the subject of numerous important study. The most important of which was a stage III Gynecologic Oncology Group (GOG) study (n=792) that compared carboplatin-paclitaxel to the then-standard cisplatin-paclitaxel integration for optimally debulked stage III EOC (R F Ozols et al., 2003). Furthermore, the carboplatin-doublet was tolerated well, with considerably lower levels of renal and gastrointestinal toxicities. Grade 2 thrombocytopenia was frequently related with the carboplatin arm, despite grade 4 leucopenia being extra visible with cisplatin. In a subsequent European research, carboplatin-paclitaxel was shown to provide unsurpassed personal satisfaction and to be indistinguishable from cisplatin-paclitaxel in terms of survival (Greimel et al., 2006). Nonetheless, cisplatin has made a comeback in the adjuvant circle, thanks to the documented impact of intraperitoneal chemotherapy (i.p.) in patients with optimally debulked EOC (Tewari et al., 2015), For instance, the landmark GOG 172 stage III finding contrasting i.p. with i.v. cisplatin revealed a significant increase in average OS (Armstrong et al., 2006). Even after a 68 percent drop-out rate in the intraperitoneal arm, that was linked to elevated levels of evaluation 3/4 toxicity and impaired the standard of living for up to a month and a half after treatment, the benefit was clear. In a review research, intraperitoneal cisplatin and carboplatin treatment as a second-line palliative treatment were shown to be non-inferior and to have comparable toxicity levels (Milczek, Klasa-Mazurkiewicz, Sznurkowski, & Emerich, 2012). In terms of more traditional first-line i.v. treatment for progressive EOC, a 2003 stage III randomized trial equating the use of cisplatin-paclitaxel versus carboplatin-paclitaxel found an equivalent fraction of patients exclusive of disease advancement at two years (40.0 percent versus 37.5 percent) and comparable PFS and OS frequencies (Andreas du Bois et al., 2003). Once again, carboplatin use has been connected to improved tolerability and personal satisfaction.

The GOG 120 assessment founded the use of cisplatin-based chemoradiation as the highest quality level of treatment in patients with locally progressive cervical malignant development (Peters III et al., 2000). Green et al. reported that danger proportions Chemoradiation was found to be beneficial for both PFS and OS, with an ideal survival advantage of 12percent at five years, in a meta-analysis published in 2001, researchers looked at 19 randomized control research studies chemoradiation to RT alone. Despite the fact that cisplatin emerges to be the preferred radiosensitizer in this situation, carboplatin can be used for patients who have experienced severe toxicity with cisplatin or who are thought to be at

elevated possibility of acquiring renal harmfulness (for example, diabetes, hypertension, or age >70 years) (Cetina et al., 2008). There have been no relative findings of cisplatin and carboplatin's radiosensitizing effects. However, response rates were equivalent to those found with cisplatin in a minor Phase I research of twenty-four patients with Stage IIIB cancer who received regular conventional bean radiation with 6 x weekly carboplatin (Duenas-Gonzalez et al., 2003). In the metastatic setting, cisplatin is still considered as the most effective treatment for cervical cancer. The carboplatin-paclitaxel doublet had a superior toxicity profile than the individual components, as well. Patients who were platinum naive, on the other hand, had a much improved overall survival with cisplatin/paclitaxel (Kitagawa et al., 2012).

Cisplatin has been researched more widely in the treatment of endometrial cancer than carboplatin. 11 stage 3 studies and 80 stage 2 studies were included in a recent Cochrane review of chemotherapy for advanced, recurrent, and metastatic cancer (Humber et al., 2007). 7 of the eleven stage 3 findings were designed to see how cisplatin interacted with some cytotoxic medications This same combined effect of cisplatin and doxorubicin achieved an ORR of forty to forty-six percent, while cisplatin-based triple approach routines reached a high ORRs of 57 to 69 percent (Humber et al., 2007). Cisplatin monotherapy was used in 23 of the 80 stage II studies, with ORRs ranging from four percent to 42.3 percent. Just five stage II studies have found the usage of solitary specialist carboplatin, which showed reaction rates of twenty-eight to thirty-three percent as well as improvements close to sixty-one percent when combined with paclitaxel (Humber et al., 2007). The overall favorite for cisplatin in the first line set-up for platinum naive individuals was also examined in these studies (Humber et al., 2007). In the case of metastatic cancer, a stage II finding was being reported in 2011 that compared three treatment arms: cisplatin-docetaxel, carboplatin-docetaxel, and carboplatin-paclitaxel (Nomura et al., 2011).

- 2.1.9. Oesophageal and Gastric Cancer

Simultaneous radioactivity with cisplatin/5-fluorouracil was established as decisive therapy in severely progressive oesophageal cancer in the RTOG 85-01 study in 1999 (Cooper et al., 1999). When compared to radiotherapy (RT) alone, this practice revealed a large median OS advantage (fourteen months versus nine months) as well as five-year endurance degree of twenty-seven percent. In any event, platinum-based chemoradiation's significance in neoadjuvant therapy is debatable. In patients amid possibly resectable cancer, CROSS trial

revealed a mean overall survival improvement with carboplatin/paclitaxel plus radiation therapy instead of medical therapy only, with a rough 30% neurotic CR (Van Hagen et al., 2012). A neoadjuvant stage 3 test with cisplatin/5-fluorouracil, on the other hand, proposed that this methodology stayed negative for stages I/II cancers (Mariette et al., 2014).

Preliminary results for both MAGIC (epirubicin, cisplatin, and 5-fluorouracil) and FNCLCC/FFCD neoadjuvant chemotherapy in gastro-oesophageal cancer have shown that cisplatin-based regimens improve long-term OS significantly over medical treatment alone (34-36 percent versus 19-23 percent) (Cunningham et al., 2006; Ychou et al., 2011). There is currently a shortage of information to assist in the usage of carboplatin-based treatments for this set-up. Cisplatin has established itself as a key specialist in management of metastatic oesophageal squamous cell carcinoma. In a stage III research, Van Custem et al. found ORRs of thirty-seven percent, twenty-five percent, and 25 percent with docetaxel, cisplatin, and 5-FU, respectively. Despite the fact that a more basic stage II research with carboplatin and paclitaxel produced an optimistic forty-three percent objective response rate in fifty-three patients (El-Rayes et al., 2004), cisplatin-based routines continues to be the best choice in a metastatic scenario.

2. METHODOLOGY

Study Setting

A retrospective study was conducted with cancer patients receiving service in the oncology department between January 2018 and May 2021 in the Near East University Hospital.

Study Design

The aim of the study was to assess and compare the hematological toxicity of cancer patients using carboplatin and cisplatin in the Oncology Department of Near East University Hospital in Northern Cyprus. From the cancer patients' file was collected cancer patients' information and their laboratory results from the first (Baseline), second, and third cycles of chemotherapy administration. Patients' Neutrophils, Platelets, Hemoglobin and Lymphocytes levels were evaluated separately and compared these lab results at baseline, first and second cycles for hematological toxicity. The inclusion criteria of the study were patients who were 18 years and more than 18 years and patients who received cisplatin or carboplatin in the chemotherapy. The excluded criteria of the study were patients who had an incomplete laboratory parameter and patients who did not complete their treatments at the Near East University Hospital (NEUH).

Data Collection

The data consisted of health files from patients who were diagnosed with cancer and had undergone chemotherapy at the oncology clinic of Near East University Hospital, Lefkoşa, Northern Cyprus. Information was gathered from the health reports of patients who met the eligibility criteria The excluded criteria of the study were patients who had an incomplete laboratory parameter and patients who did not complete their treatments at the Near East University Hospital (NEUH). Information gathered comprised of kinds of cancer, regimens of chemotherapy, and results of hematological (White Blood Cells, Neutrophils, Lymphocytes, Hemoglobin, and Platelets). Haematological toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. [in detail Anemia grade 1 (haemoglobin; Hb < LLN to 10 g/dL), grade 2 (Hb: 8-10 g/dL), grade 3 (Hb < 8 g/dL), grade 4 (life-threatening consequences); Thrombocytopenia grade 1 (<LLN to

75,000/microL), grade 2 (50,000 to 75,000/microL), grade 3 (25,000 to 50,000/microL), grade 4 (< <25,000/microL); Neutropenia grade 1 (<LLN to 1500/microL), grade 2 (1000 to 1500/microL), grade 3 (500 to 1000/microL), grade 4 (<500/microL); Lymphocytes (total) Grade 1, <LLN to 800/microL, Grade 2, 500 to 800/microL, Grade 3, 200 to 500/microL, Grade 4, <200/microL.].

Statistical Analysis

Statistical package for social sciences (SPSS) version 21.0 for windows was used for the analysis of Data. Percentages were used for categorical data. A P-value of less than 0.05 ($P<0.05$) was considered statistically significant. Categorical variables were evaluated in a Fisher's Exact Test.

Ethical approval

This study was approved by the institutional review board (IRB) of the Near East University (YDU-2020/86-1217).

3. RESULTS

There were 63 cancer patients who were received cisplatin and carboplatin at Near East University Hospital between January 2018 and May 2021. There were 27 (%42.9) who received Cisplatin, 36 (%57.1) cancer patients who received Carboplatin. There were 16 males (59.3%) and 11 females (40.7%) who have received Cisplatin and 12 males (33.3%), 24 females (66.7%) who have received carboplatin in this study. The age of mean was 61.81±11.34 years old, and the body surface area of mean was 1.80±0.17 for patients who were received cisplatin. The age mean was 61.42±13.5 and the body surface area of mean was 1.79±0.20 for patients who received carboplatin. The most common kind of cancer for patients who were given cisplatin was Head and Neck (29.6%) and the most common kind of cancer for patients who were given carboplatin was Lung (33.3). Most patients who received cisplatin didn't have additional Diseases (59.3%). Most patients who received carboplatin had Hypertension disease (Table 1).

Table 1. Demographic Information of Cancer Patients Receiving Cisplatin and Carboplatin Drugs

	Cisplatin	**Carboplatin**
Gender	**N (%)**	**N (%)**
Male	16 (59.3)	12 (33.3)
Female	11 (40.7)	24 (66.7)
Mean	**Mean±SD**	**Mean±SD**
Age	61.81±11.34	61.42±13.53
Body Surface Area (BSA)	1.80±0.17	1.79±0.20
Cancer Type	**N (%)**	**N (%)**
Breast	0 (0)	5 (13.9)
Gynecology	4 (14.8)	10 (27.8)
Genitourinary	3 (11.1)	5 (13.9)
Gastrointestinal	6(22.2)	2 (5.6)
Lung	6(22.2)	12 (33.3)
Head/Neck	8 (29.6)	1 (2.8)
Chronic Diseases	**N (%)**	**N (%)**

No additional Diseases	16 (59.3)	12 (33.3)
Hypertension	10 (37.0)	16 (44.4)
Angina	1 (3.7)	0 (100.0)
Arrythmia	1 (3.7)	0 (100.0)
Chronic Kidney Disease	0 (100.0)	3 (8.3)
Diabetes Mellitus	6 (22.2)	6 (16.7)
Dyslipidemia	1 (3.7)	3 (8.3)
Thyroid Disorders	1 (3.7)	2 (5.6)

The laboratory results during the cycles are shown in Table 3 which were indicated the comparison of the hematological toxicity of the baseline, first cycles and second cycles of patients receiving cisplatin and carboplatin.

According to the hematological toxicities, the number of patients in the cisplatin group who were in grade 1 lymphocytopenia was 4(14.8%) at baseline which increased in the first and second cycles to 6(22.2%) each. There was no statically significant difference between baseline and first cycle ($p>0.05$). In addition, the number of patients in grade 1 neutropenia was 1(3.7%) at baseline which decreased to no cases in both first and second cycles, also in grades 2 and 3 there were no cases at both baseline and first cycle but in the second cycle, there was 1(3.7%) at both cycles respectively. The number of patients in the cisplatin group who were in grade 1 Thrombocytopenia was 1(13.7%) at baseline which they increased in number at both first and second cycles which were 2(7.4%), 5(18.5%) respectively. There was a statically significant difference between baseline and second cycle in grade 1 of Thrombocytopenia ($p=0.001^*$). Also, there was a statically significant difference between the first cycle and second cycle in grade 1 of Thrombocytopenia ($p=0.019^*$). Furthermore, the number of patients in grade 1 Anemia were 2(7.4%) at baseline while at first and second cycles were 1(3.7%), 7(25.9%) respectively. There was a statically significant difference between baseline and second cycle in grade 1 of Anemia ($p=0.0005^*$). Also, there was a statically significant difference between the first cycle and second cycle in grade 1 of Anemia ($p=0.0001^*$) (Table 2).

On the other hand, the number of patients in carboplatin group in grade 1 Lymphocytopenia were 7(19.4%) at baseline while at first and second cycles were 18(50.0%),

8(22.2%) respectively. There was a statically significant difference between baseline and first cycle in grade 1 of Lymphocytopenia (p=0.0001*). Also, there was a statically significant difference between the first cycle and second cycle in grade 1 of Lymphocytopenia (p=0.0001*). In addition, the number of patients in grade 1 neutropenia was 2(5.6%) at both baseline and second cycle respectively, there were no cases in grade 2 at both baseline and first cycle but 7(19.4%) at second. Also, there were no cases in grade 3 at both baseline and second cycles but in the first cycle were 1(2.8%), also there were no cases in grade 4 at baseline but 2(5.6%), 1(2.8%) at both first and second cycles respectively.

The number of cases in grade 1 thrombocytopenia were zero at baseline and at first and second cycles were both 3(8.3%) respectively, there were no cases in grades 2 and 4 but there were 1(2.8%) in grade 3 at baseline and no cases at both first and second cycles. Furthermore, the numbers of patients in grade 1 anemia were 6(16.7%) at baseline which increased in number at first and second cycles to 8(22.2%), 9(25.0%) respectively. Likewise, in grade 2 there were 4(11.1%) at baseline which increased in number at both first and second cycles which were 8(22.2%), 9(25.0%) respectively. There was a statically significant difference between the baseline and second cycle in grade 2 of Anemia (p=0.015*) (Table 2).

Table 2. Comparison of Hematological Toxicity for at Baseline, First and Second Cycles for Cisplatin and Carboplatin

Cancer Medications	Hematological Toxicity	Grade	Baseline N(%)	First Cycle N(%)	P-value (Baseline vs First Cycle)	Second Cycle N(%)	P-value (Baseline vs Second Cycle)	P-value (First Cycle vs Second Cycle
Cisplatin	Lymphocytopenia	Grade 1	4 (14.8)	6 (22.2)	0.274	6 (22.2)	0.274	-
		Grade 2	2 (7.4)	3 (11.1)	0.459	1 (3.7)	0.537	0.1
		Grade 3	0	2 (7.4)	-	4 (14.8)	-	0.112
		Grade 4	0	0	-	0	-	-
	Neutropenia	Grade 1	1 (3.7)	0	-	0	-	-
		Grade 2	0	0	-	1 (3.7)	-	-
		Grade 3	0	0	-	1 (3.7)	-	-
		Grade 4	0	0	-	0	-	-

	Thrombocytopenia	**Grade 1**	1 (3.7)	2 (7.4)	0.537	5 (18.5)	0.001*	0.019*
		Grade 2	0	0	-	0	-	-
		Grade 3	0	0	-	0	-	-
		Grade 4	0	0	-	0	-	-
	Anemia	**Grade 1**	2 (7.4)	1 (3.7)	0.537	7 (25.9)	0.0005**	0.0001**
		Grade 2	3 (11.1)	4 (14.8)	0.529	4 (14.8)	0.528	-
		Grade 3	0	0	-	0	-	-
		Grade 4	0	0	-	0	-	-
Carboplatin	**Lymphocytopenia**	**Grade 1**	7 (19.4)	18 (50.0)	0.0001**	8 (22.2)	0.726	0.0001**
		Grade 2	0	2 (5.6)	-	4 (11.1)	-	0.31
		Grade 3	0	2 (5.6)	-	1 (2.8)	-	0.497
		Grade 4	0	0	-	0	-	-
	Neutropenia	**Grade 1**	2 (5.6)	0	-	2 (5.6)	-	-
		Grade 2	0	0	-	7 (19.4)	-	-
		Grade 3	0	1 (2.8)	-	0	-	-
		Grade 4	0	2 (5.6)	-	1 (2.8)	-	0.497
	Thrombocytopenia	**Grade 1**	0	3 (8.3)	-	3 (8.3)	-	-
		Grade 2	0	0	-	0	-	-
		Grade 3	1 (2.8)	0	-	0	-	-
		Grade 4	0	0	-	0	-	-
	Anemia	**Grade 1**	6 (16.7)	8 (22.2)	0.476	9 (25.0)	0.224	0.739
		Grade 2	4 (11.1)	8 (22.2)	0.05	9 (25.0)	0.015*	0.739
		Grade 3	0	0	-	1 (2.8)	-	-
		Grade 4	0	0	-	0	-	-

The laboratory results during the cycles are shown in Table 3 which were indicated the comparison of neutropenia and lymphocytopenia values of patients receiving cisplatin and carboplatin.

According to the comparison of the hematological toxicities of neutropenia and lymphocytopenia of cisplatin and carboplatin, the number of patients in grade 1 lymphocytopenia was 4(14.8%) at baseline while at first and second cycles were both of 6(22.2%) in the cisplatin group. The number of patients in grade 1 lymphocytopenia was 7(19.4%) at baseline while at first and second cycles were 18(50.0%) and, 8(22.2%) respectively in the carboplatin group. Likewise, the number of patients in grade 2 lymphocytopenia was 2(7.4%) at baseline, while first cycle 3(11.1%) and second cycle 1(3.7%) for in the cisplatin group. The number of patients in grade 2 lymphocytopenia was no patients at baseline but there were 2(5.6%) patients at the first cycle and 4(11.1%) patients at the second cycle in the carboplatin group. Also, the number of patients in grade 3 lymphocytopenia had no patients at baseline but there were 2(5.6%) patients at the first cycle and 1(2.8%) patient at the second cycle in the carboplatin group. There had no patients in grade 4 lymphocytopenia all cycles in the cisplatin group and likewise there were no cases in grade 4 lymphocytopenia in all cycles in the carboplatin group. There was a statistically significant difference between the carboplatin group and the cisplatin group in grade 1 of the first cycle of Lymphocytopenia ($p=0.0001$). Also, there was a statistically significant difference between the carboplatin group and the cisplatin group in grade 3 of the second cycle of Lymphocytopenia ($p=0.005$).

In addition, the number of patients in grade 1 neutropenia was 1(3.7%) at baseline while there had no patients in both first and second cycles in the cisplatin group. The number of patients in grade 1 neutropenia was 2(5.6%) at both baseline and the second cycle respectively in the carboplatin group. Also, the number of patients in grades 2, 3 and 4 neutropenia had no patients at baseline in cisplatin and carboplatin groups. but the number of patients in grades 2 and 3 neutropenia was both 1(3.7%) at second cycle in cisplatin group. On the other hand, the number of patients in grades 2 and 3 neutropenia was 7 (19.4%) and 0 (0.0%) respectively at second cycle in carboplatin group. There was a statistically significant difference between the carboplatin group and the cisplatin group in grade 2 of the second cycle of Neutropenia ($p=0.0008$) (Table 3).

Table 3: Comparison of Neutropenia and Lymphocytopenia Values of Patients Receiving Cisplatin and Carboplatin.

	Hematological Toxicity	Cisplatin	Carboplatin	P-value	Cisplatin	Carboplatin	P-value
		Neutropenia N (%)	Neutropenia N (%)		Lymphocytopenia N (%)	Lymphocytopenia N (%)	
Baseline	**Grade 1**	1 (3.7)	2 (5.6)	0.7475	4 (14.8)	7 (19.4)	0.572
	Grade 2	0 (0.0)	0 (0.0)	-	2 (7.4)	0 (0.0)	-
	Grade 3	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
	Grade 4	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
First Cycle	**Grade 1**	0 (0.0)	0 (0.0)	-	6 (22.2)	18 (50.0)	0.0001**
	Grade 2	0 (0.0)	0 (0.0)	-	3 (11.1)	2 (5.6)	0.31
	Grade 3	0 (0.0)	1 (2.8)	-	2 (7.4)	2 (5.6)	-
	Grade 4	0 (0.0)	2 (5.6)	-	0 (0.0)	0 (0.0)	-
Second Cycle	**Grade 1**	0 (0.0)	2 (5.6)	-	6 (22.2)	8 (22.2)	-
	Grade 2	1 (3.7)	7 (19.4)	0.0008**	1 (3.7)	4 (11.1)	0.104
	Grade 3	1 (3.7)	0 (0.0)	-	4 (14.8)	1 (2.8)	0.005*
	Grade 4	0 (0.0)	1 (2.8)	-	0 (0.0)	0 (0.0)	-

The laboratory results during the cycles are shown in Table 4 which indicated the comparison of anemia and thrombocytopenia values of patients receiving cisplatin and carboplatin.

The number of patients in grade 1 anemia was 2(7.4%) at baseline while in the first and second cycles were 1(3.7%) and 7(25.9%) respectively in the cisplatin group. The numbers of patients in grade 1 anemia were 6(16.7%) at baseline while was an increased number of patients in the first and second cycles to 8(22.2%) and, 9(25.0%) respectively in the carboplatin group. Also, in grade 2 of patients' number were 3(11.1%) at baseline and at the first and second cycles were both 4(14.8%) respectively in the cisplatin group. while in grade 2 of patients' the number was 4(11.1%) at baseline which was increased in the number of patients in both first and second cycles which were 8(22.2%) and, 9(25.0%) respectively in the carboplatin group. There was a statistically significant difference between the carboplatin group and the cisplatin group in grade 1 of the first cycle of Anemia (p=0.0002**).

Moreover, the number of patients with grade 1 thrombocytopenia was 1(3.7%) at baseline while they were an increase in the number of patients in both the first and second cycles which were 2(7.4%) and, 5(18.5%) respectively in cisplatin group. The number of patients in grade 1 thrombocytopenia had no patient at baseline and at first and second cycles were both 3(8.3%) in the carboplatin group. There had no patients in grades respectively 2, 3 and 4 at baseline, first cycle and second cycle in the cisplatin group. Likewise, there were no patients in grades 2 and 4. Also, there were 1(2.8%) number of patients in grade 3 at baseline and no patients at both first and second cycles in the carboplatin group (Table 4).

Table 4. Comparison of Anemia and Thrombocytopenia Values of Patients Receiving Cisplatin and Carboplatin.

	Hematological Toxicity	Cisplatin	Carboplatin	P-value	Cisplatin	Carboplatin	P-value
		Anemia N (%)	Anemia N (%)		Thrombocytopenia N (%)	Thrombocytopenia N (%)	
Baseline	**Grade 1**	2 (7.4)	6 (16.7)	0.04*	1 (3.7)	0 (0.0)	-
	Grade 2	3 (11.1)	4 (11.1)	-	0 (0.0)	0 (0.0)	-
	Grade 3	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (2.8)	-
	Grade 4	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
First Cycle	**Grade 1**	1 (3.7)	8 (22.2)	0.0002**	2 (7.4)	3 (8.3)	-
	Grade 2	4 (14.8)	8 (22.2)	0.274	0 (0.0)	0 (0.0)	-
	Grade 3	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
	Grade 4	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Second Cycle	**Grade 1**	7 (25.9)	9 (25.0)	-	5 (18.5)	3 (8.3)	0.03
	Grade 2	4 (14.8)	9 (25.0)	0.11	0 (0.0)	0 (0.0)	-
	Grade 3	0 (0.0)	1 (2.8)	-	0 (0.0)	0 (0.0)	-
	Grade 4	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-

4. DISCUSSION

Cisplatin has a broad spectrum of efficacy against malignancies, and it has become the cornerstone of testicular and ovarian cancer curative regimens. It also shows promise against lung, head, and neck cancers, as well as esophageal, bladder, cervix, and endometrial malignancies. On the other hand, it has significant toxicity, including severe renal, neurologic, and emetic symptoms. Carboplatin, a cisplatin analog, use to help patients avoid some of cisplatin's side effects. Although carboplatin has replaced cisplatin in some cancer chemotherapy regimens, such as ovarian carcinoma, it is still unknown whether carboplatin has equal potency to cisplatin in all tumour types. (Rosenberg, Van Camp, Grimley, & Thomson, 1967; Rosenberg, Van Camp, & Krigas, 1965).

We saw that the chemotherapy conventions embraced in the guidance being referred to are those normalized and demonstrated by logical writing, and we saw the administrations' concern in adjusting the conventions to the patients in the most ideal manner, into an individualized way, as we could see with chemotherapy conventions altered because of the patient's overall condition, just as the neoplasm staging (Jacques Ferlay, 2010).

Numerous chemotherapeutic specialists are utilized in the therapy of malignant growth, as platinum-based specialists (cisplatin and carboplatin). Despite their strength, these specialists have unintended consequences that may cause patients to reconsider their therapy and personal satisfaction (Cavalcanti & Larrazabal-hadj-idris, 2020)

This review backs up Harrap et al. and Levine et al finding's that cisplatin and carboplatin have differing nephrotoxicity. Nonetheless, the findings show that both cisplatin and carboplatin cause hematological damage in patients, and that this harmfulness is extra fatal with carboplatin in comparison to the parent compound. The carboplatin group's reported hindered recuperation in cell counts when compared to the cisplatin unit is most likely due to this increased relevance (Harrap et al., 1980). A mouse study demonstrated that the temporary characteristics of cisplatin-influenced leucopenia are related to those described in humans (Nowrousian & Schmidt, 1982). Cisplatin, on the other hand, seems to have erythropenic outcomes in humans that differ from what is shown in mice in regards to intensity and progression rate (Nowrousian & Schmidt, 1982), Cisplatin-induced leucopenia, anemia, and thrombocytopenia are all common side effects in patients (A W Prestayko et al., 1979)

Thrombocytopenia, as opposed to cisplatin, is the component of carboplatin that limits toxicity in patients. Anemia in certain patients has remained bothersome enough to necessitate blood transfusions, thus leucopenia is also examined (Calvert et al., 1982; Wiltshaw, Evans, Jones, Baker, & Calvert, 1983). In patients treated with the new platinum specialist, a substantial number of three forms of myelosuppression have been observed. Because red cell transfusions can guard against carboplatin-induced severity, our review found that anemia is the utmost common source of mortality. Thrombocytopenia is the utmost probable source of anemia, which would occur as a consequence of internal hemorrhaging, which would be exacerbated by carboplatin.

A similar report of women with breast cancer that were undertaking chemotherapy also found that anemia, neutropenia, and thrombocytopenia occurred during the treatment period, which was based on the usage of cisplatin (Cavalcanti & Larrazabal-hadj-idris, 2020). The study by Nam et al. (2013) compares the fundamental toxicity rates of cisplatin-related radiotherapy and carboplatin-related radiotherapy for cervical cancer, finding that the carboplatin-related radiotherapy has a greater impact on the progression of thrombocytopenia (Nam et al., 2013). In our study, we found that cisplatin did not present a greater risk of developing thrombocytopenia when compared to carboplatin alone.

Despite the fact that Porras, Nogueda, and Chacón (2018) (Regalado Porras, Chávez Nogueda, & Poitevin Chacón, 2018) found that the combination treatment increases the risk of hematological harm, the current review finds that patients who obtained cisplatin stayed less likely to acquire hematological infections and had lower rates when compared to patients who were given carboplatin only.

In a retrospective report, Ho et al. (Ho, Swindell, & Brammer, 2008) compared the dosage intensity, latencies, and toxic effects of cisplatin was given to patients with nearby progressive HNC on a weekly and three-weekly basis in addition to radiotherapy. The publishers came to the conclusion that three-weekly cisplatin at 100 mg/m2 given concurrently with RT was relatively poorly accepted than weekly cisplatin at 40 mg/m2, and that fewer patients received a combined prescription of over 200 mg/m2, presumably lessening the chemotherapeutic prescription frequency. Built on these findings, an excessive amount of cisplatin may not be acceptable for regular usage.

The Head and Neck Intergroup led a Phase III randomized trial between 1982 and 1987, comparing radiation treatment alone with weekly cisplatin at a dosage of 20 mg/m2 (Quon, H., Leong, T., Haselow, R., Leipzig, B., Cooper, J., & Forastiere, A, 2011). Notwithstanding the point that patients who received the concurrent regimen had a greater response rate, the average endurance time was simply thirteen months and did not vary among the dual treatment units. Adding 20 mg/m2 weekly cisplatin to daily radiation did not significantly increase endurance, however, there was some proof of an outcome. Concurrent CRT with low-dose (4 mg/m2) cisplatin had similar outcomes (Homma et al., 2004). An elevated dosage of cisplatin was thus assumed to be necessary to achieve an acceptable result (Browman, Hodson, Mackenzie, Bestic, & Zuraw, 2001; Marcu, van Doorn, & Olver, 2003).

According to a recent study, the toxicity of chemotherapy is based on the doses administered to patients (Clinical, Guidelines, & Guidelines, 2020). The current investigation found that the doses of chemotherapeutic medications were all appropriate, according to NCCN recommendations, which specify that dosages should be estimated focused on the patient's body surface area, specifically for cisplatin and carboplatin, and mainly on renal function for carboplatin. As a result, the use of chemotherapy in excess of therapeutic doses may not be considered a significant contributor to chemotherapy toxicity in the current study (Clinical et al., 2020).

Many major adverse effects from chemotherapeutic medications are typical during the initial cycle of chemotherapy. Chemotherapy-related hematologic adverse effects can arise at any time during the treatment, with the fifth week or the end of the second cycle being the most common (Syahruddin, Marlina, & Hudoyo, 2012; Usami et al., 2016). Hematologic toxicity intensified as the second treatment cycle progressed, according to the current analysis. Chemotherapy drugs, in addition to eliminating cancer cells, also kill progenitor cells that produce granulocytes, erythrocytes, and platelets in the peripheral blood circulation. These immature cells will be eliminated within 7–14 days after chemotherapy, whereas the maturation of those cells in the bone marrow takes 8–12 days, thus those blood components will revert to their original state on day 28-35 (Syahruddin et al., 2012).

The most prevalent hematologic hazard discovered in this investigation was anemia. Fortunately, it was grade 1 and 2 anemia that had the highest occurrence. The right chemotherapy dose could help to prevent high-grade anemia, as well as leukopenia and thrombocytopenia, because it's generally known that significantly larger doses cause more hematologic side effects (Syahruddin et al., 2012). The current data also revealed that all of the patients received only three treatment cycles. The intensity of the toxicity is said to be linked to the treatment cycle. The severity of toxicity encountered by patients increases as the number of chemotherapy cycles increases (Holmboe, Andersen, Mørkrid, Slørdal, & Hall, 2012)

4.1. Strength and Limitations

This study was unique in that it carried out a comparison of hematological toxicity of cancer patients using carboplatin and cisplatin 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 the 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. Data from several hospitals may need to be collected and analyzed in future studies. More data will allow for more analysis, which could include comparative and correlated approach that is based on the sociodemographic profile of the patients. Electronic health records, on the contrary, should be utilized to aid in the digital era transition. This execution not just helps with investigation, but it also enhances the value of service and collaboration between healthcare providers (O'Malley, Grossman, Cohen, Kemper, & Pham, 2010; Wilke et al., 2011).

5. CONCLUSION

As shown in this study, cisplatin has a lower risk of hematologic toxicity than carboplatin. Due to the changes in blood counts after chemotherapy in cancer patients, healthcare professionals should monitor their patients regularly between each chemotherapy cycle. We recommend that future studies should be multicenter and include evaluations of more cancer patients.

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7. APPENDIXES

7.1. CURRICULUM VITAE

NAME, SURNAME: DATE of BIRTH and PLACE:	ABDUL'AZEEZ BATURE ADO-KHADEER 06/10/1995. KANO, NIGERIA
CURRENT OCCUPATION: STUDENT ADDRESS of CORRESPONDENCE: FAMAGUSTA, REPUBLIC OF NORTHERN CYPRUS TELEPHONE: +905338893922 E-MAIL: abdelazeezkhadeer@gmail.com	

EDUCATION

YEAR	GRADE	UNIVERSITY	FIELD
FEB 2020-PRESENT	MSc	NEAR EAST UNIVERSITY	CLINICAL PHARMACY
SEP 2014-SEP 2019	BSc	EASTERN MEDITERRANEAN UNIVERSITY	PHARMACY

ACADEMIC EXPERIENCE

PERIOD	TITLE	DEPARTMENT	UNIVERSITY

FIELD OF INTERESTS

FIELDS OF INTERESTS	KEY WORDS
CLINICAL PHARMACY SPORTS TEACHING	CLINICAL PHARMACY

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

Computer Knowledge

Program	Use proficiency
Microsoft Word	EXCELLENT
Microsoft Excel	EXCELLENT
SPSS	GOOD