A PROSPECTIVE STUDY ON UNINTENDED CONSEQUENCES OF ANTI-CANCER DRUG REGIMEN: CISPLATIN

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***Abstract*- Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Chemotherapy works to stop tumor growth and cell division, which prevents invasion and metastasis. However, because chemotherapy also has an impact on normal cells, this leads to hazardous side effects This prospective study aims to investigate the unintended consequences associated with the administration of the anti-cancer drug regimen Cisplatin. Cisplatin, a platinum based chemotherapeutic agent, is widely used in the treatment of various malignancies. While it's efficacy in targeting cancer cells is well-documented, there is a growing concern about its potential adverse effects on healthy tissues and organs. This study will enroll a diverse cohort of cancer patients undergoing cisplatin treatment and will closely monitor and analyze the occurrence of unintended consequences such as nephrotoxicity, ototoxicity, neurotoxicity, and other systemic effects.**

***Index Terms*: Cancer, types of cancers, Chemotherapy, Radiotherapy, Cisplatin and its combinational therapy, adverse effects, Nephrotoxicity.**

I. INTRODUCTION

Cancer is a condition when a few of the body's cells grow out of control and spread to other bodily regions. In the millions of cells that make up the human body, cancer can develop practically anywhere.

Human cells often divide (via a process known as cell growth and multiplication) to create new cells as the body requires them. New cells replace old ones when they die as a result of aging or damage. Sometimes, this systematic process fails, causing damaged or aberrant cells to proliferate when they shouldn't.

Tumors, which are tissue masses, could develop from these cells. Tumors can be malignant or not (benign) cancerous tumors can metastasize (also known as spread) to distant regions of the body to create new tumors. Malignant tumors are another name for cancerous growths.[1]

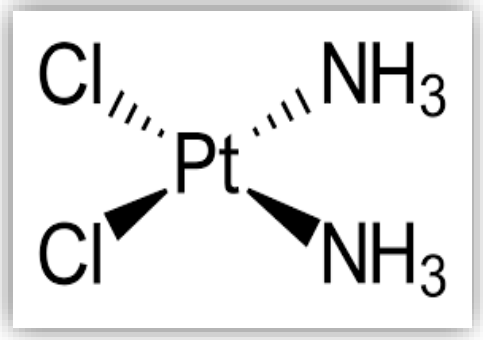
ANTICANCER DRUG

CISPLATIN

CLASS: Platinum-based drug

CHEMICAL FORMULA: Cl2H6N2Pt

STRUCTURE:



➢ Cisplatin is a potent chemotherapeutic drug used in the treatment of various cancers, including testicular, ovarian, bladder, head and neck, lung, oesophageal, neuroblastoma, cervical, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, melanoma, and mesothelioma. Its mechanism of action involves the formation of DNA adducts, leading to DNA damage and apoptosis, ultimately eliminating cancer cells.

➢ Cisplatin, a platinum-based chemotherapy drug, is administered based on individualized factors such as cancer type, patient condition, and treatment plan. Dosage is often calculated using the patient's body surface area (BSA) or weight, typically ranging from 20 mg/m² to 100 mg/m² or more. Treatment is structured in cycles, with each cycle lasting 21 days and may involve multiple sessions. The frequency of cycles and total number vary, determined by the oncologist based on the specific cancer diagnosis and overall health. Cisplatin is commonly used in combination with other chemotherapy drugs. Close adherence to healthcare provider recommendations and attendance at scheduled sessions is crucial. Monitoring blood counts, kidney function, and hearing is essential to manage potential side effects. Cisplatin is administered intravenously in a clinical setting, the duration and frequency tailored to the patient's condition and cancer type. It proves effective in treating a range of cancers, including sarcomas, carcinomas, lymphomas, and germ cell tumours.[2]

➢ Despite its efficacy, cisplatin is associated with a range of side effects. Common side effects include nausea, vomiting, bone marrow suppression, peripheral neuropathy, and hair loss. ***Nephrotoxicity is a significant concern***, resulting in acute kidney injury. Ototoxicity, affecting hearing, and other less common side effects, such as stomatitis, increased blood bilirubin, hepatic enzymes, and cardiac issues, may also occur. Rare side effects, occurring in less than 0.1% of cases, include convulsions, leukoencephalopathy, motor deficits, gait disturbances, and others.

➢ The pharmacokinetics of cisplatin involve rapid absorption when administered intravenously, extensive tissue distribution, minimal metabolism, and renal elimination. Monitoring blood counts, kidney function, and hearing is essential during cisplatin treatment to manage potential side effects.

➢ Cisplatin has contraindications, including allergies, severe kidney impairment, pre-existing hearing loss, blood disorders, pregnancy, and neurological disorders. Caution should be exercised or avoided in individuals with these conditions.

➢ In summary, while cisplatin is a valuable tool in cancer treatment, its side effects and contraindications necessitate careful consideration and monitoring during therapy.[3]

SIDE EFFECTS

COMMON SIDE EFECTS

- **Ototoxicity:**
  - Cisplatin treatment may lead to tinnitus, or ringing and buzzing in the ears.
  - Ototoxicity, which harms the inner ear and hearing system, can result in hearing loss.
- **Chemotherapy-Induced Nausea and Vomiting (CINV):**
  - Nausea and vomiting are common side effects of cisplatin.
  - CINV can significantly impact a person's quality of life during chemotherapy.
- **Blood Cell Suppression:**
  - Cisplatin can lower counts of red blood cells, causing anemia with symptoms like weakness and breathlessness.
  - Neutropenia, a decrease in vital infection-fighting white blood cells (neutrophils), increases the risk of infections.
  - Thrombocytopenia, a reduction in platelet count, raises the risk of bleeding or bruising.
- **Peripheral Neuropathy:**
  - Cisplatin treatment can cause numbness and tingling in the hands and feet.
  - Peripheral neuropathy results from damage to the nerves responsible for transmitting signals from the central nervous system.
- **Electrolyte Abnormalities:**
  - Cisplatin chemotherapy may lead to imbalances, such as elevated levels of potassium and magnesium (hypermagnesemia).
- **Hair Loss:**
  - Temporary hair loss is a common side effect of cisplatin due to its impact on rapidly dividing cells, including hair follicles.
- **Gastrointestinal and Urinary Effects:**
  - Dark or tarry stools may indicate gastrointestinal bleeding, although it's not frequent.
  - Haematuria, or blood in the urine, is a rare side effect of cisplatin.
- **Respiratory Issues:**
  - While uncommon, cisplatin has a slight chance of causing lung damage, potentially leading to symptoms like difficulty in breathing.
- **Loss of Balance:**

- Cisplatin can damage the inner ear, resulting in ototoxicity and potential balance issues, such as vertigo and dizziness.

- **Skin-related Side Effects:**
- Pinpoint red spots on the skin, known as petechiae, are not frequently reported but can occur as a response to cisplatin.[4]

LESS COMMON SIDE EFFECTS

- **Nephrotoxicity:**
- Cisplatin is a known nephrotoxic substance with the potential to harm the kidneys.
- Nephrotoxicity is a serious adverse effect characterized by reduced urine production (oliguria), elevated serum creatinine, increased blood urea nitrogen (BUN), and fluid retention (oedema).

- **Ototoxicity:**
- Cisplatin-induced ototoxicity can occur during or after therapy, varying in severity.
- The mechanism involves factors like reactive oxygen species, inflammation, and damage to inner ear sensory cells and neurons.

- **Stomatitis:**
- Stomatitis, or mouth sores and inflammation, is a possible side effect of cisplatin treatment.

- **Increased Blood Bilirubin and Hepatic Enzymes:**
- Cisplatin may cause elevated blood bilirubin levels and rare liver damage, though this is uncommon.
- Other factors, like concurrent liver disorders or metastases, could contribute to increased bilirubin levels.

- **Cardiac Arrest:**
- Indirectly, cisplatin may lead to cardiac problems, especially with electrolyte imbalances, renal damage, or dehydration.
- Severe cases could contribute to cardiac arrhythmias or cardiac arrest.[5]

RARE SIDE EFFECTS (LESS THAN 0.1%):

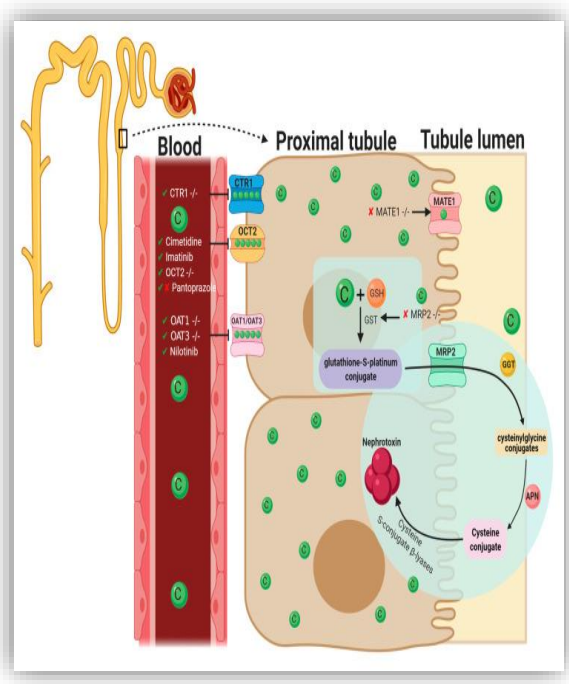
- **Convulsions:**
- Seizures, uncommonly associated with cisplatin, despite its potential neurological effects.

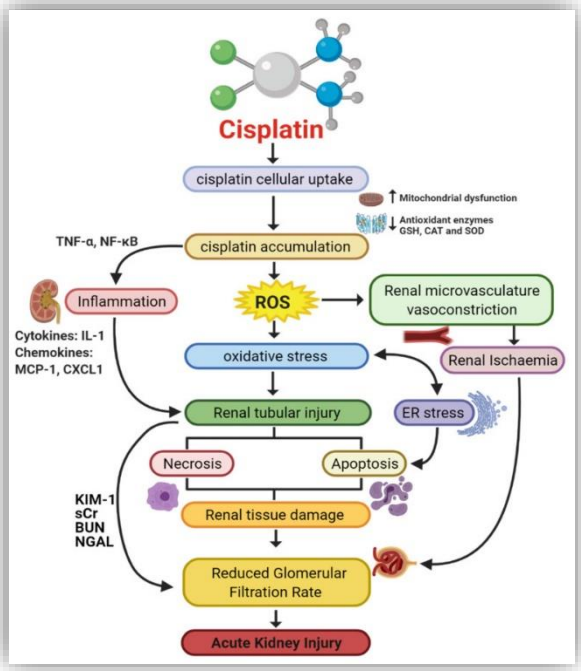
- **Leukoencephalopathy:**
- A rare neurological side effect involving damage to the brain's white matter.
- Manifests as cognitive alterations, including memory, attention, concentration, and problem-solving issues.

- **Motor Deficits:**
- Altered fine motor skills, weakness, clumsiness, and coordination issues are potential motor deficits associated with cisplatin.

- **Gait Disturbances:**
- Changes in walking style, balance problems, and shaky movements can occur as a result of cisplatin-induced gait disturbances.[6]

It's crucial for healthcare providers and patients to be aware of these potential side effects, especially the rare ones, and monitor for any signs during cisplatin treatment. Regular communication and monitoring are essential for effective management and minimizing the impact on the patient's well-being.





II. AIMS AND OBJECTIVE

AIM:

- A prospective study was designed to analyse the adverse drug reactions of cisplatin-based chemotherapy.

OBJECTIVES:

- To examine various adverse effects associated with cisplatin treatment, including short term and long-term effects on various organ systems.
- To evaluate the impact of cisplatin on patient quality of life and assess the relationship between cisplatin exposure and patient outcome.
- To raise awareness of adverse effects of cisplatin among healthcare providers, patients and general public.

NEED FOR STUDY:

- A comprehensive and up-to-date study of the recently reported adverse effects of cisplatin i.e. AKI acute kidney injury (abnormal renal function tests) is necessary to provide a more complete understanding of the drug cisplatin
- The use of cisplatin is increasing, and its long-term consequences are not fully understood. A study is necessary to ensure the patients receive the best possible care and to inform future treatment decisions.
- To report the detected frequency of rare adverse reactions.
- Therefore, results of the study can inform clinical practice and contribute to the development of safer chemotherapy options, ultimately improving patient outcomes and quality of life.

➢ **Study site:** in patients willing to participate in the study from the **Department of Oncology** unit at **Malla Reddy Hospital and Research Institute.**
➢ **Study period:** 6 months
➢ **Study size:** 100 patients
➢ **Study design:** Prospective observational study

STUDY CRITERIA:

INCLUSION CRITERIA:

- Participants diagnosed with a cancer that is treatable with cisplatin chemotherapy.
- Participants who have received cisplatin treatment within the past 5 years.
- Participants who are willing and able to provide informed consent.
- Participants who are willing and able to complete study-related assessments, including questionnaires, interviews, and physical exams.

EXCLUSION CRITERIA:

- Participants who have received less than two cycles of Cisplatin chemotherapy.
- Participants with a history of severe allergic reactions to cisplatin or other chemotherapy drugs.
- Participants who are unable or unwilling to comply with study requirements, including scheduled appointments and assessments.

STUDY PROCEDURE:

- **Recruitment of study participants:** Cancer patients with the cisplatin drug regimen. All Patients with this drug therapy are included in the study. The data will be collected in the data collection form after getting consent from the patient.
- **Patient selection**: Patients meeting inclusion criteria for the evaluation and detection of unintended consequences of the chemotherapeutic drug regimen i.e. CISPLATIN
- **Data collection:** Collect the data on the participant's demographic information, medical history, current health status, dosage, duration, and frequency of cisplatin treatment. Collecting the data on the basis of a questionnaire form.
- **Statistical analysis of the data:** The collected data is analyzed to examine the side effects of cisplatin and occurrence of AKI (Nephrotoxicity). Chi-square analyses were conducted to ascertain relationships between different Age groups and side effects of cisplatin, specially focused on nephrotoxicity. Descriptive statistics and frequency tables provided. A significance level of $p < 0.05$ was utilized to determine statistical significance throughout the analysis.
- **Reporting of results:** The study will provide a up to date knowledge regarding the adverse effects AKI that is found by using cisplatin. The results of the study is noted in scientific paper, including a discussion of findings for future research and clinical practice.

III. RESULTS

STATISTICAL ANALYSIS:

In this study, we conducted a comprehensive statistical analysis using SPSS 2.0 software and the latest version of Microsoft excel to investigate the relationship between various factors

- Chi-square analyses were conducted to ascertain relationships between different Age groups and side effects of cisplatin, specially focused on nephrotoxicity.
- Descriptive statistics and frequency tables provided
- A significance level of $p < 0.05$ was utilized to determine statistical significance throughout the analysis.
- The findings from this rigorous statistical analysis provide valuable insights into the relationships and differences observed within the dataset, enhancing our understanding of the research questions under investigation

TABLE 1.: Stage-wise distribution of subjects

STAGES OF CANCER	FREQUENCY(n=100)	PERCENTAGE
STAGE I	0	0%
STAGE II	13	13%
STAGE III	61	61%
STAGE IV	26	26%

TABLE 2: Distribution of number of cycles of chemotherapy

NO. OF CYCLES OF CHEMOTHERAPY	SUBJECTS(n=100)	PERCENTAGE
I CYCLE	0	0%
II CYCLES	3	3%
III CYCLES	24	24%
IV CYCLES	41	41%
V CYCLES	23	23%
VI CYCLES	7	7%
VII CYCLES	2	2%

TABLE 3: Distribution of Cisplatin and Cisplatin with other combinations in different subjects

CISPLATIN AND CISPLATIN WITH COMBINATIONS	FREQUENCY(n=100)	PERCENTAGE
CISPLATIN	93	93%
CISPLATIN+GEMCITABINE	4	4%
CISPLATIN+CEPECITABINE	2	2%
CISPLATIN+PACLITAXEL	1	1%

FIGURE 1. Distribution of Cisplatin and Cisplatin with other combinations in different subjects

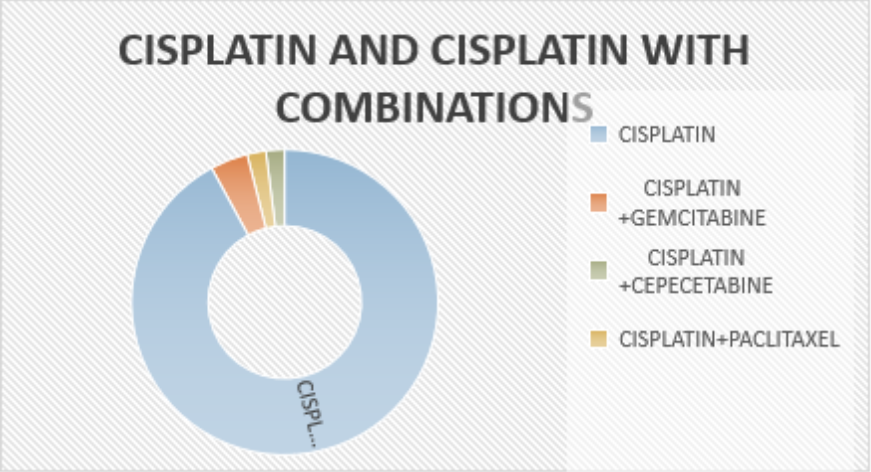


FIGURE 2 Distribution of adverse effects of Cisplatin

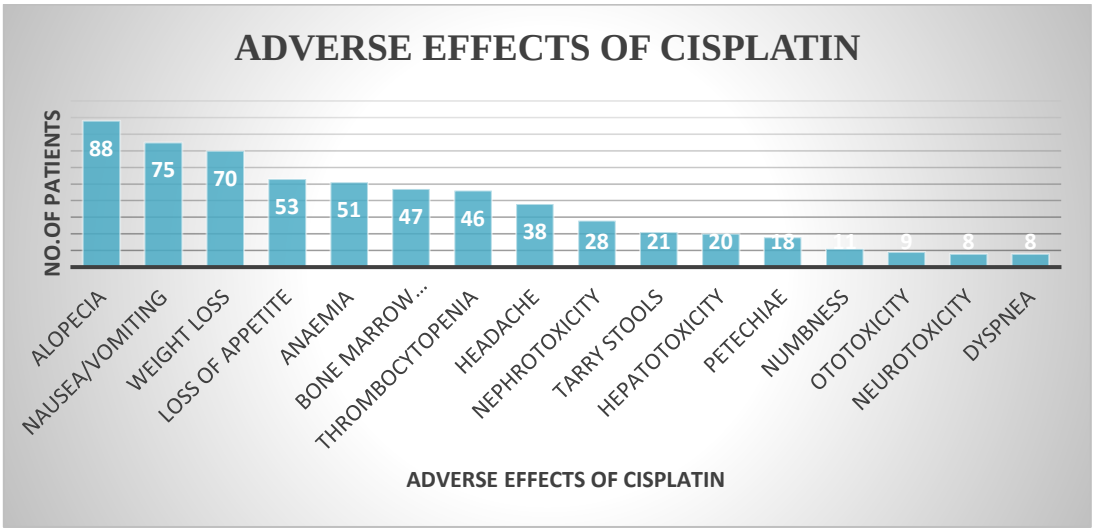


TABLE 4 : Distribution of adverse effects of Cisplatin

ADVERSE EFFECT OF CISPLATIN	FREQUENCY(n=100)	PERCENTAGE
ALOPECIA	88	88%
NAUSEA/VOMITING	75	75%
WEIGHT LOSS	70	70%
LOSS OF APPETITE	53	53%
ANAEMIA	51	51%
BONE MARROW DEPRESSION	47	47%
THROMBOCYTOPENIA	46	46%
HEADACHE	38	38%
NEPHROTOXICITY	28	28%

TARRY STOOLS	**21**	**21%**
HEPATOTOXICITY	**20**	**20%**
PETECHIAE	**18**	**18%**
NUMBNESS	**11**	**11%**
OTOTOXICITY	**9**	**9%**
NEUROTOXICITY	**8**	**8%**
DYSPNEA	**8**	**8%**

FIGURE 3. Distribution of renal function tests

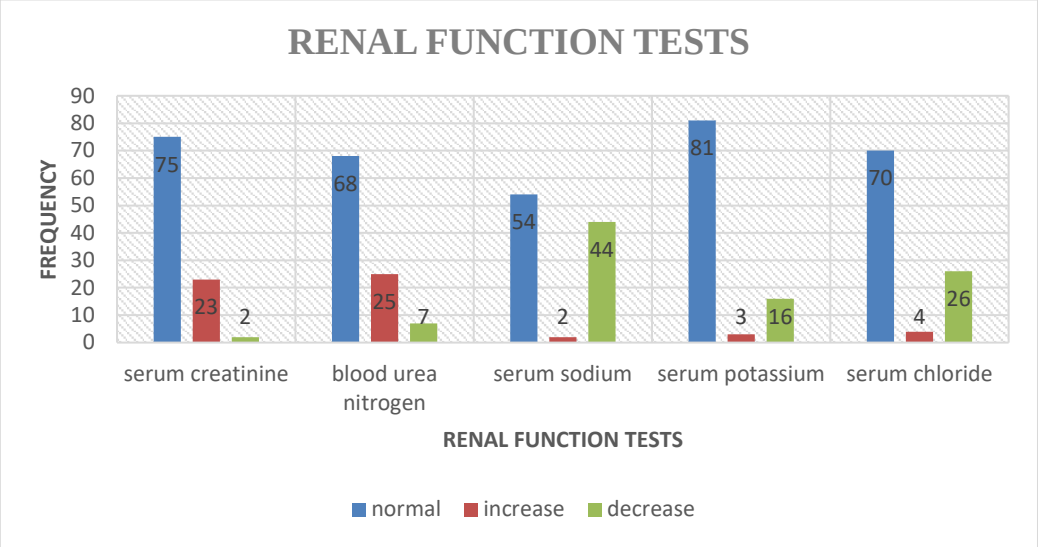


TABLE 5. Chi-Square test

	Age		
	Pearson Correlation ®	**P Value**	**N**
Age	**1**		**100**
Sr. Cr (0.5-1mg/dl)	**.455****	**.000**	**100**
BUN(7-18mg/dl)	**.380****	**.000**	**100**
Sr. Na (136-144 mg/dl)	**-.276****	**.005**	**100**
Sr. K (3.6-5.1 mg/dl)	**-.203***	**.043**	**100**
Sr. Cl (98-107 mg/dl)	**-.245***	**.014**	**100**

IV. DISCUSSION & CONCLUSION

- Cisplatin, an anti-cancer drug, has shown effective results in treating various types of cancers, but it also comes with some unintended consequences.
- Nephrotoxicity: Cisplatin can cause damage to the kidneys, leading to reduced kidney function or even acute kidney injury (AKI). This occurs because cisplatin accumulates in the kidneys, causing oxidative stress and inflammation. Correlation between age group and renal function tests showed that there is a significant association between them.
- Ototoxicity: One of the most significant side effects of cisplatin is its potential to cause hearing loss and damage to the inner ear. This is due to the drug's impact on the sensory hair cells and nerves responsible for hearing and balance.
- Neurotoxicity: Cisplatin can cause nerve damage, leading to symptoms such as numbness, tingling, or weakness in the extremities. This is thought to result from damage to peripheral nerves.
- Nausea and Vomiting: Cisplatin treatment often triggers severe nausea and vomiting. This side effect can impact a patient's quality of life and even lead to dehydration and nutritional deficiencies.
- Bone Marrow Suppression: The drug can suppress bone marrow activity, leading to a decrease in the production of red blood cells, white blood cells, and platelets. This can result in anemia, increased susceptibility to infections, and bleeding issues.
- Allergic Reactions: Some individuals may experience allergic reactions to cisplatin, which could include symptoms like red spots on skin, itching, and difficulty breathing.

- Gastrointestinal Effects: Cisplatin treatment may lead to gastrointestinal issues such as diarrhea, constipation, and appetite loss.
- The study examined a sample population of 100 subjects and presented various findings through pie charts and graphs. In terms of age distribution, the majority of subjects were in the 41-60 age group (55%), while the 61-80 age group had the fewest subjects (19%). Gender-wise, females comprised the majority (63%) of developing cancer. In terms of social history, 28% of subjects had a history of tobacco chewing, 31% used alcohol, and 41% were smokers,15% had a history of surgery,16% had a family history of cancer. In terms of cancer stages, 61% of subjects were diagnosed at Stage-III, followed by 26% at Stage-IV, and 13% at Stage-II. No subjects were diagnosed at Stage-I.
- In terms of treatment, 67% underwent radiation therapy with cisplatin, while 23% had only chemotherapy. Most subjects (41%) received chemotherapy during the 4th cycle, with none in the 1st cycle. The distribution of cisplatin usage showed that 93% received cisplatin, 4% received a Cisplatin-Gemcitabine combination, 2% received Cisplatin-Capecitabine, and 1% received Cisplatin-Paclitaxel combinations.
- In terms of cancer types, 52% were diagnosed with cervical cancer, 24% with carcinoma of the mouth, and smaller percentages with various other types.
- The adverse effects of cisplatin were observed, with alopecia being the most common (88 individuals). Other effects included nausea and vomiting (75 subjects), weight loss (70 individuals), loss of appetite (53 cases), anemia (51 instances), and various others. Lastly, renal function tests were examined, with different subjects showing variations in serum creatinine, blood urea nitrogen, serum sodium, serum potassium, and serum chloride levels.
- The chi-square test results reveal a significant relationship between age groups and the levels of BUN (7-18mg/dl). The Pearson Chi-Square, Likelihood Ratio, Fisher's Exact Test, and Linear-by-Linear Association tests all indicate a p-value of less than 0.001, indicating strong statistical significance. This suggests that there is an association between age groups and BUN levels within the specified range.
- The study was carried out in 100 subjects who were diagnosed with cancer and using Cisplatin drug regimen.
- The study included the use of Cisplatin in different types of cancer and the unintended consequences of the therapy.
- The results shown that administering Cisplatin to elderly individuals is resulting in AKI (Nephrotoxicity).
- The drug Cisplatin is predominantly employed in the treatment of cervical and oral cancers.
- Individuals who consume cigarettes, alcohol, and tobacco are particularly susceptible to cancers.
- Majority of the subjects were diagnosed at Stage-III
- Most effective choice of therapy found to be Chemotherapy and Combinational Therapy. Cervical cancer patients often receive a combination of Chemotherapy and Radiotherapy for optimal effectiveness.
- Carboplatin is replaced with Cisplatin for patients at risk of AKI. It is an alternative option.
- Long term use of cisplatin can lead to Nephrotoxicity, Ototoxicity, Hepatotoxicity.
- Rare adverse reactions like Petechiae, dyspnea is observed in the subjects
- Other unintended effects like Alopecia, nausea/vomiting, weight loss, loss of appetite, bone marrow depression, headache, tarry stools, numbness, thrombocytopenia have been observed in the subjects.

CORRELATION ANALYSIS:

- The chi-square test results between age group and renal function tests suggesting a strong statistical significance. Sr.Cr and BUN are positively correlated (P value<0.005) and ,Sr .N, Sr .K , Sr .Cl are negatively correlated (P>0.005)
- These findings provide a comprehensive overview of the study population's demographics, cancer types, treatment modalities, and associated medical parameters.

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