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CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY IN CANCER PATIENTS RECEIVING MICROTUBULE AGENTS & PLATINUM COMPOUNDS

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common dose-limiting toxicities associated with anticancer therapy, particularly in patients receiving microtubule-targeting agents (paclitaxel, docetaxel, vincristine, and vinblastine) and platinum compounds (cisplatin, carboplatin, and oxaliplatin). CIPN adversely affects sensory, motor, and autonomic nerve function, leading to symptoms such as numbness, tingling, burning pain, impaired proprioception, muscle weakness, and reduced quality of life. These complications frequently necessitate dose reduction, treatment delays, or discontinuation of chemotherapy, potentially compromising therapeutic outcomes. **Objective:** To review the incidence, risk factors, pathophysiological mechanisms, clinical manifestations, assessment methods, prevention strategies, and management of chemotherapy-induced peripheral neuropathy in cancer patients receiving microtubule agents and platinum-based chemotherapy. **Methods:** A comprehensive review of published literature was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Peer-reviewed articles, clinical practice guidelines, systematic reviews, meta-analyses, and randomized controlled trials published in English were evaluated. Studies focusing on the epidemiology, mechanisms, diagnosis, prevention, and treatment of CIPN associated with microtubule agents and platinum compounds were

included. **Results:** The incidence of CIPN varies according to the chemotherapeutic agent, cumulative dose, treatment duration, and patient-related factors such as age, diabetes mellitus, nutritional deficiencies, and pre-existing neuropathy. Platinum compounds primarily induce neuronal damage through DNA adduct formation, oxidative stress, mitochondrial dysfunction, and dorsal root ganglion injury, whereas microtubule agents disrupt axonal transport by destabilizing or excessively stabilizing microtubules, resulting in distal axonal degeneration. Current evidence supports duloxetine as the pharmacological agent with the strongest evidence for the treatment of painful CIPN, while preventive strategies remain limited. Emerging interventions, including neuroprotective agents, exercise-based rehabilitation, cryotherapy, compression therapy, and neuromodulation techniques, have demonstrated variable efficacy and require further investigation. **Conclusion:** Chemotherapy-induced peripheral neuropathy remains a significant clinical challenge in oncology, particularly among patients receiving microtubule-targeting agents and platinum compounds. Early identification of high-risk patients, routine neurological assessment, patient education, individualized chemotherapy planning, and multidisciplinary supportive care are essential to minimize the burden of CIPN. Continued research into predictive biomarkers, neuroprotective therapies, and evidence-based management strategies is needed to improve patient outcomes, preserve quality of life, and optimize cancer treatment.

KEYWORDS: Chemotherapy-induced peripheral neuropathy, CIPN, Microtubule agents, Taxanes, Vinca alkaloids, Platinum compounds, Cisplatin, Oxaliplatin, Paclitaxel, Neurotoxicity, Cancer, Quality of life.

INTRODUCTION

Despite much advances in the field of medicine and technology, cancer is still a scary word and almost everyone knows that they get very sick or die from cancer. Cancer is a very fatal disease with high incidence that threatens health and family in society. Cancer is defined as a disease in which a group of abnormal cells grow uncontrollably by ignoring the normal rules of cell division.

Normal cells subjected to signals that dictate whether the cells should divide, differentiate in to another cell or die. These cells develop a degree of autonomy from these signals results in uncontrolled proliferation. If this proliferation continues and spread, it can be fatal. Almost all cancer related deaths are due to tumor spreading which is known as metastasis. Cancer as a disease involves changes in cell genome that produce proteins that disrupt the cellular

balance between cell division and quiescence, resulting in continuous cell division that form cancers.

TYPES OF CANCER

The term cancer comprises more than 100 diseases affecting nearly every part of the body. A tumor can be either benign(often it is harmless, neither invading nor spreading to other body sites) or malignant(results in metastasis).Pathologically, cancers are classified into three categories which are mentioned below:

Carcinoma: It is the most common type of cancer that starts in the cells that make up the skin and tissue lining organs such as liver and kidneys. It occurs many parts of the body and some common types of carcinoma includes: squamous cell carcinoma, renal cell carcinoma, ductal carcinoma in situ, invasive ductal carcinoma.

Sarcoma: It is a rare kind of cancer which is different from much more form of carcinomas, because they occur in a different kind of tissues like connective tissues and these type of tumors are most common in bones, muscles, tendons, cartilage, nerves, fat and blood vessels of arms and legs.

Lymphoma and Leukemia: Lymphoma is a cancer that occurs in the cells of the immune system. various types of lymphomas are T-cell lymphoma, B-cell lymphoma, hodgkin lymphoma, non-hodgkin lymphoma and lymphoproliferative lymphomas. Leukemia is a blood cancer caused by increased number of immature or abnormal leukocytes. The major types of leukemia are acute lymphocytic leukemia(ALL), acute myelogenous leukemia(AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia(CML).

CARCINOGENESIS: ETIOLOGY AND PATHOGENESIS OF CANCER

Carcinogenesis or oncogenesis or tumorigenesis means mechanism of induction of tumours. Agents which can induce tumours are called carcinogens. Initiation and progression of cancer depends on external factors (tobacco, chemicals, radiation and infectious organisms) as well as internal factors(mutations that occur from metabolism and inheritance, hormones, immune conditions).

Pathogenesis of cancer can be viewed as multi step process

Involving four main steps as follows:

1) Mutation and tumour initiation

Genetic alteration leads to mutation in a single cell that results in tumour cell formation by abnormal proliferation.

2) Cell proliferation and tumour progression

As the tumour progression continues, additional mutations occurs within the tumour cells. These additional mutations become dominant within tumour cell and shows rapid growth and division.

3) Clonal selection and malignancy

Tumour cell proliferation leads to new clone of tumour cells with rapid growth and certain properties like invasion, survival and metastasis. This process is known as clonal selection. If these clonal selection continues throughout tumour development, the tumour grows rapidly and malignancy will be increased.

4) Metastasis

Metastasis is a process in which tumour cells migrate and spread the cancer to different sites from where they originated. The stages of metastasis are: local invasion, intravasation, transport, extravasation, formation of micrometastasis, colonisation.

CANCER TREATMENT

Early advances ensures that the cancer can be controlled. some of the treatments as mentioned below may control cancers.

Radiation, Surgery, Chemotherapy, Hormone therapy, Stem cell transplant
Target therapy.

CHEMOTHERAPY OF CANCER

The National Cancer Institute defines chemotherapy as drugs that treat cancer cells. Chemotherapy kills cancer cells by damaging DNA, interrupts with DNA synthesis or inhibiting cell division. Unlike radiation and surgery, which targets specific areas, chemo can work throughout the body. Most chemotherapy agents target rapidly proliferating cells, like those of skin, hair, intestine and bone marrow ,that's why side effects like alopecia, loss of appetite, nausea, vomiting and bone marrow depression occurs frequently while taking

chemotherapy. Chemotherapy can be given by various routes such as intra-arterial, intraperitoneal, intrathecal, intravenous, topical and oral route.

CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

CIPN is a common progressive adverse effect of many chemotherapy agents After chemotherapy, approximately 70% of cancer patients have painful neuropathy at 6 months improving to around 35% at 1 year. Even though different chemotherapies have variable characteristics, but symptoms tend to be predominantly sensory. Sensory toxicity is the predominant feature consists of positive and negative symptoms. Positive symptoms are paresthesia, dysaesthesia, cold and mechanical hypersensitivity. Negative symptoms include numbness, loss of vibration sense, proprioception and deep tendon reflexes.

Chemotherapy induced peripheral neuropathy is caused by many of the most commonly used chemotherapy agents including taxanes (paclitaxel, docetaxel), platinum compounds (oxaliplatin, cisplatin), vinca alkaloids (vincristine) and protease inhibitors (bortezomib), immunomodulatory agents(thalidomide).

The mechanism by which neurotoxic chemotherapeutic agents can damage the nervous system structures and cause CIPN involves microtubule disruption, oxidative stress, mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage, immunological processes and neuroinflammation.

DIAGNOSIS

ASSESSMENT OF CIPN

The Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy and other oncology settings. The National Cancer Institute issued the Common Terminology Criteria for Adverse Events (CTCAE). These measures rely upon patient self-reporting which consists of five graded scores which are the weighted sums of the questions in their section. Each grade varies with both motor and sensory symptoms.

The higher the grade the greater disability i.e., a grade of grade 4 will be the maximum disability and a grade of 1 is equivalent to asymptomatic level. Five grades includes physical functioning, Activities of daily living The Instrumental ADL refer to preparing meals,

shopping for groceries or clothes, using the telephone, managing money. Self-care ADL refers to bathing, dressing/undressing, feeding self, using the toilet, taking medications, and not bedridden and role limitations due to effects of chemotherapy, and general health perceptions.

Type of Neuropathy	Grade - 1	Grade -2	Grade - 3	Grade - 4	Grade - 5
Sensory	Presence of deep Tendon reflexes or paresthesia loss	Moderate symptoms Limiting instrumental ADL	Severe symptoms limit in self-care ADL	Life threatening indication of urgent intervention	Death
Motor	Asymptomatic clinical/ diagnostic observation only.	Moderate symptoms Limiting instrumental ADL	Severe symptoms limit in self-care ADL	Life threatening indication of urgent intervention	Death

METHODOLOGY

Study site: Both In patient ward & Out patient Department of Oncology, Tertiary care Hospital, Kakinada.

Study Duration: Six months

Sample size: 150 cases

Study Design: Prospective observational study

Inclusion Criteria

- Patients with oncologic disease under potential neurotoxic chemotherapy
- Patients of both Genders
- Patients with all type of cancers
- Patients of both diabetic and non diabetic were included

Exclusion criteria

- Patients with multiple comorbidities.
- Patients who are not under potential neurotoxic chemotherapy
- Patients with traumatic injuries.
- Patients with metabolic problems

RESULTS

GENDER ANALYSIS: A total study population of 150 patients has been assessed for the study. Among these population majority were of females constituting of 86% (n=129) and males of 14% (n=21).

TABLE 1.

GENDER DISTRIBUTION		
Gender	**Frequency**	**Percent**
Male	**21**	**14**
Female	**129**	**86**
Total	**150**	**100**

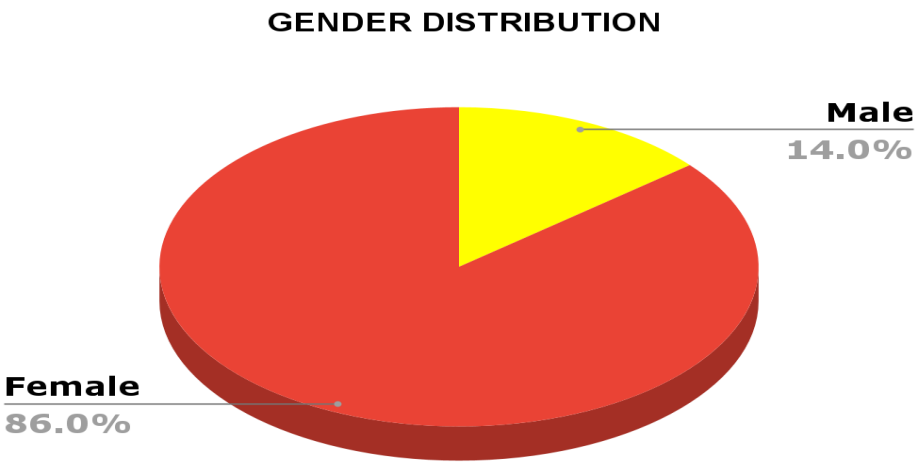


Fig. No. 1: Gender Distribution In Study Population.

AGE DISTRIBUTION: According to the study in the study population the highest population were between ages of 41-50 years constituting of 35.3%(n=53) and lowest age group of 71-80 years, constituting of 2% (n=3) and another respective age groups were mentioned below (table 2).

TABLE 2.

AGE DISTRIBUTION IN STUDY POPULATION		
Age	**Frequency**	**Percentage**
Below 30 years	6	4.0
31-40 years	12	8.0
41-50 years	53	35.3
51-60 years	49	32.7
61-70 years	27	18.0
71-80 years	3	2.0
Total	150	100.0

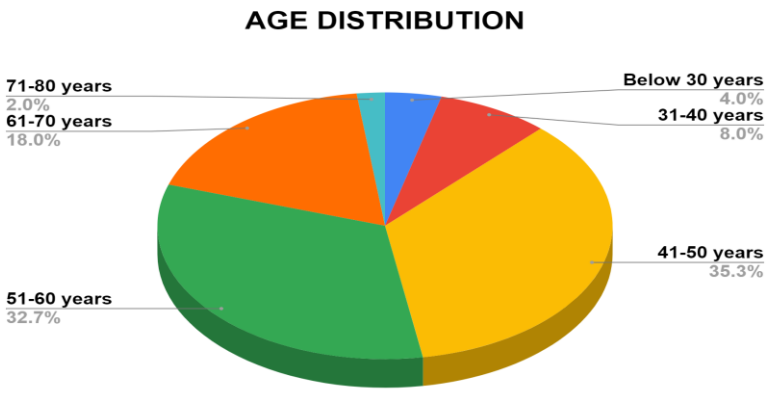


Fig. No. 2: Age Distribution In Study Population.

AGE GENDER DISTRIBUTION: According to the study the mean value of age gender distribution of the patients included in the study i.e upto 30 was of 3 (n=6), 31-40 was of 6 (n=12), 41-50 were of 26.5 (n=53), 51-60 were of 24.5 (n=49), 61-70 were of 13.5 (n=27), 71-80 were of 1.5 (n=3).

TABLE 3.

AGE GENDER DISTRIBUTION					
AGE	**MALE**	**FEMALE**	**MEAN**	**SD**	**P VALUE**
UPTO 30	2	4	3	1	0.016936
31-40	1	11	6	5	
41-50	6	47	26.5	20.5	
51-60	6	43	24.5	18.5	
61-70	1	26	13.5	12.5	
71-80	0	3	1.5	1.5	
Total	16	134	75	59	

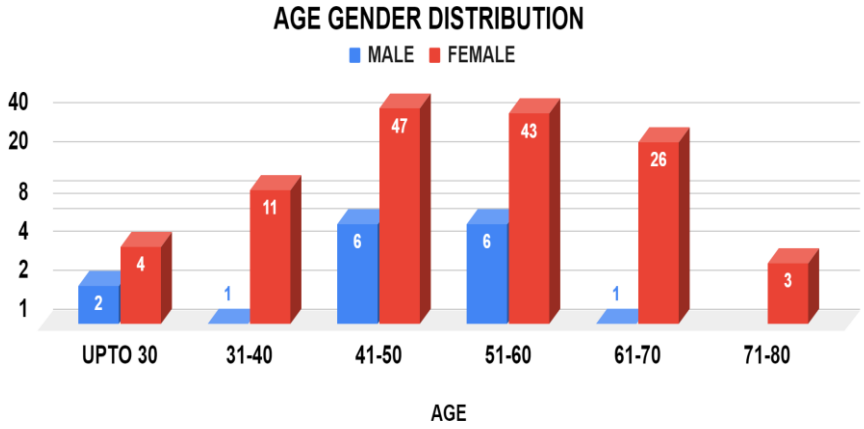
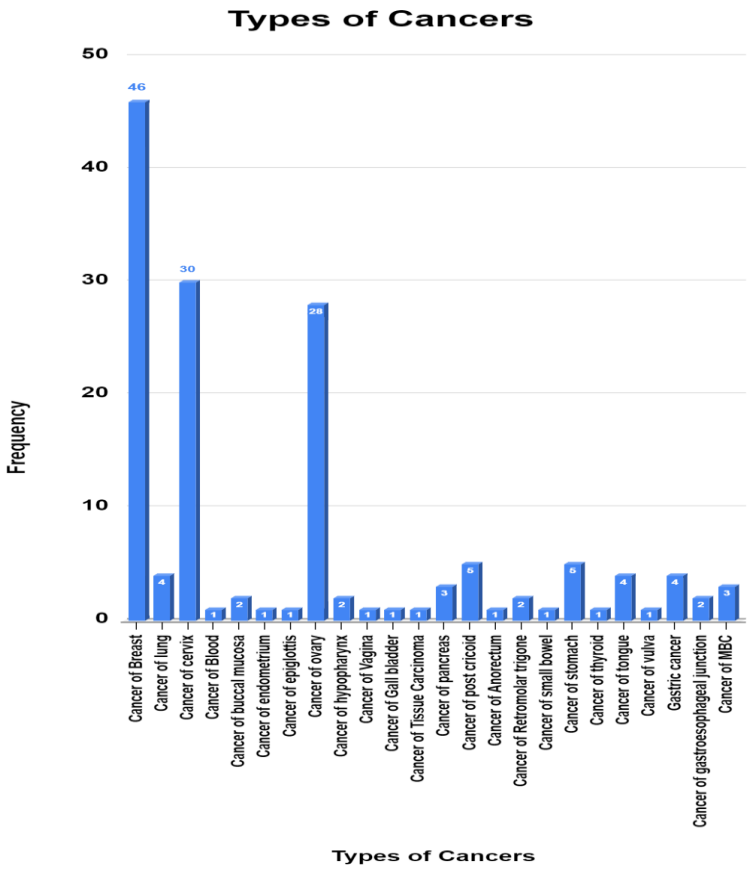


Fig. No. 3: Age Gender Distribution Among Study Population.

DISEASE DISTRIBUTION: According to the study there were various kinds of cancers involved in the study population as the greater extent were of the breast cancer patients constituting of 30.7%(n=46) and other types of cancers were mentioned below.

TABLE 4.



GRADE ANALYSIS: According to the study in the study population there was an grading of 5 grades. Grade 1 constituting of 52.7%(n=79) & Grade 2 constituting of 14.0% (n= 21) whereas Grade 3 constituting of very less percentage of 2.7%(n=4), 30.7%(n=46) of study population exhibit no grading.

TABLE 5.

ANALYSIS OF GRADES		
Grades	**Frequency**	**Percentage (%)**
Grade 1	79	52.7
Grade 2	21	14.0
Grade 3	4	2.7
None	46	30.7
Total	150	100.0

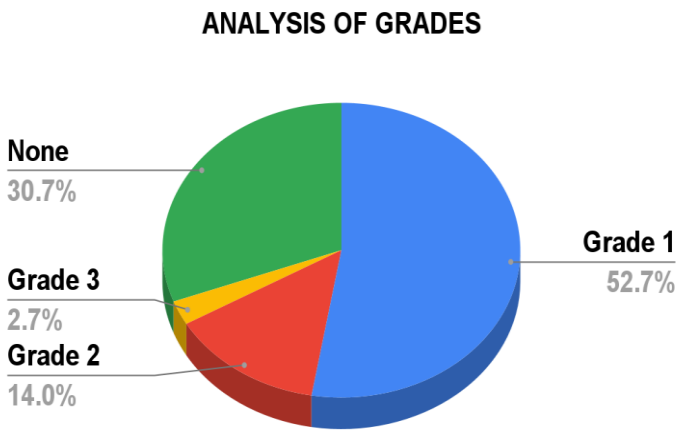


Fig. No. 5: Analysis Of Grades Of Cipn In Study Population.

GRADING OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY(CIPN) WITH DRUGS: According to the study the incidence of CIPN with drugs in grading was mentioned below.

TABLE 6.

ANALYSIS OF CIPN OF DRUGS			
Drugs	**Grade – 1**	**Grade - 2**	**Grade -3**
Paclitaxel	18	11	0
Cisplatin	25	1	1
Docetaxel	8	0	0
Oxaliplatin	6	3	0
Vincristine	1	0	0
Carboplatin	2	1	1
Docetaxel + Carboplatin	2	1	0
Paclitaxel + Carboplatin	15	7	2
Total	77	24	4

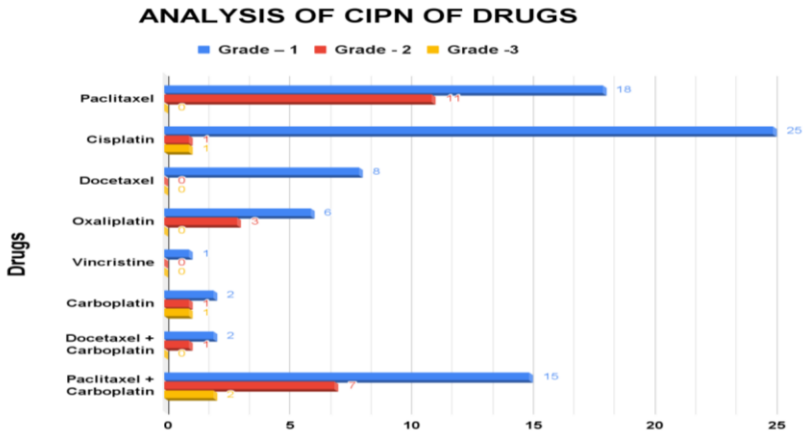


Fig No. 6: Analysis Of Cipn Of Drugs In Study Population.

AGE WISE GRADING DISTRIBUTION: According to the study the mean value of of the patients included in the study i.e upto 30 was of 0.00 (n=5), 31-40 was of 0.00(n=11), 41-50 were of 01.00(n=29), 51-60 were of 2.00 (n=39), 61-70 were of 0.00 (n=19), 71-80 were of 0.00 (n=2).

TABLE 7.

AGE WISE GENDER DISTRIBUTION									
S.NO	**AGE**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**	**GRADE 5**	**MEAN**	**SD**	**P VALUE**
1	UPTO 30	4	1	0	0	0	0	1.5	0.36629
2	31-40	8	3	0	0	0	0	3.1	
3	41-50	27	1	1	0	0	1	10.6	
4	51-60	27	10	2	0	0	2	10.3	
5	61-70	12	7	0	0	0	0	4.9	
6	71-80	2	0	0	0	0	0	0.8	

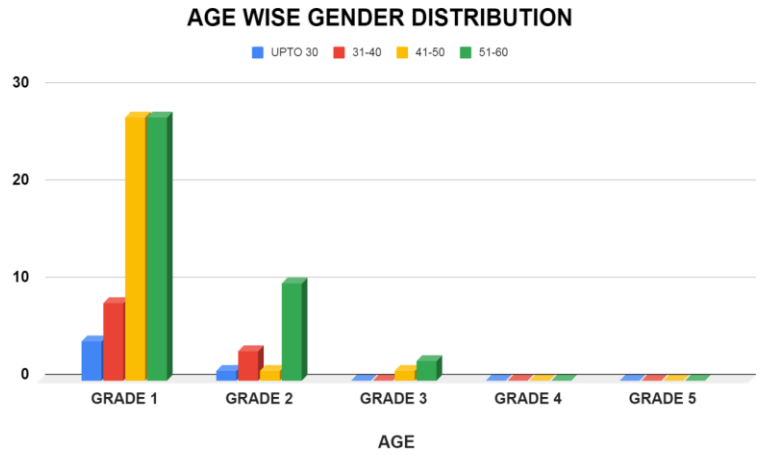


Fig. No. 7: Age Wise Gender Distribution Among Study Population.

GENDER WISE DRUGS DISTRIBUTION: According to the study the mean value of gender wise drug distribution of the patients included in the study i.e males of 2.50(n=20) females of 11.50 (n=129).

TABLE 8.

GENDER WISE DRUG DISTRIBUTION												
S. NO	**GENDER**	**Paclitaxel**	**Cisplatin**	**Docetaxel**	**Oxaliplatin**	**Carboplatin**	**Paclitaxel + Carboplatin**	**Docetaxel + Carboplatin**	**Vincristine**	**Mean**	**SD**	**P VALUE**
1	**MALE**	**3**	**5**	**2**	**7**	**0**	**3**	**0**	**0**	**2.5**	**2.40**	**0.4673**
2	**FEMALE**	**38**	**37**	**16**	**3**	**7**	**25**	**2**	**1**	**11.5**	**14.48**	

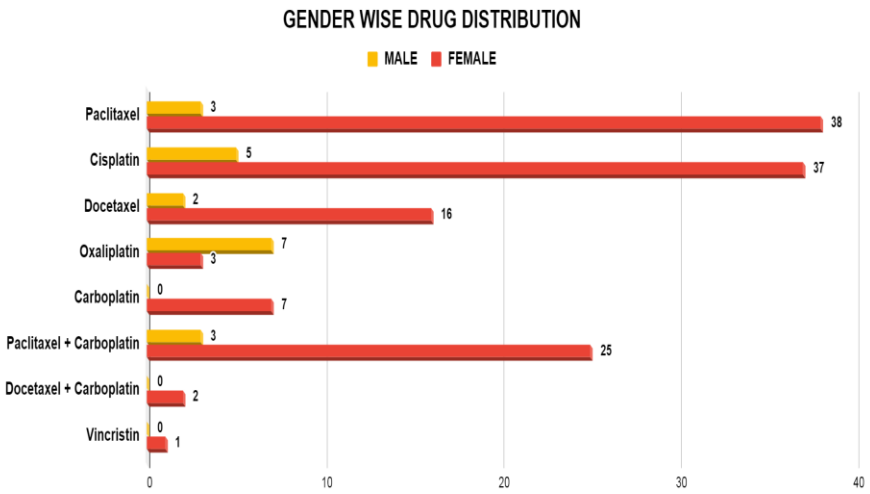


Fig. No. 8: Gender Wise Drug Distribution Among Study Population Incidence Of Chemotherapy Induced Peripheral Neuropathy (Cipn) Of Drugs In Total Study Population.

According to the study the incidence of CIPN for the drugs among the study population was been analysed. The highest incidence is for Cisplatin constituting of 28%(n=42) and lowest incidence for Vincristine 1% (n=1) and the other drugs causing CIPN in the study population was mentioned below.

TABLE 9.

INCIDENCE OF CIPN OF DRUGS		
DRUGS	**FREQUENCY**	**PERCENTAGE**
Paclitaxel	41	27%
Cisplatin	42	28%
Docetaxel	18	12%
Oxaliplatin	11	7%
Paclitaxel + Carboplatin	28	19%
Carboplatin	7	5%
Docetaxel + Carboplatin	2	1%
Vincristine	1	1%

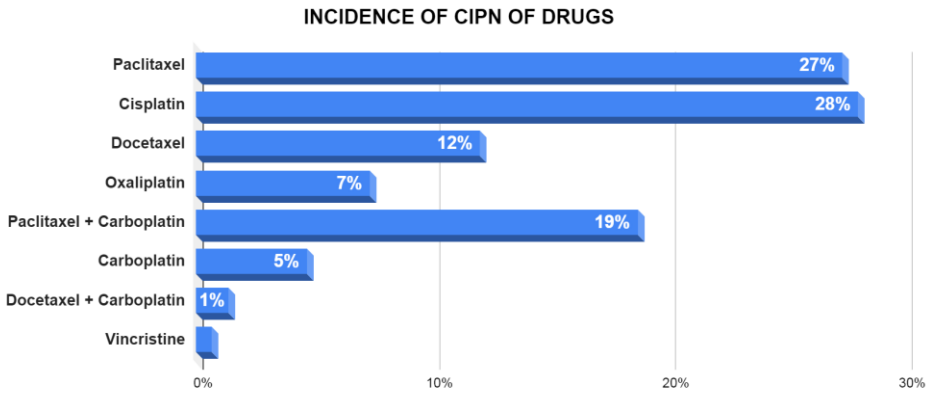


Fig. No. 9: Incidence Of Cipn Of Drugs In Study Population.

DISTRIBUTION OF COMORBIDITIES(Diabetes): According to the study the comorbidities of female was of 84.21%(n=16) and males of 15.79%(n=3)

TABLE 10.

DISTRIBUTION OF COMORBIDITIES (Diabetes)		
COMORBIDITIES (Diabetes)	**Frequency**	**Percentage**
Male	3	15.79
Female	16	84.21
Total	19	100.00

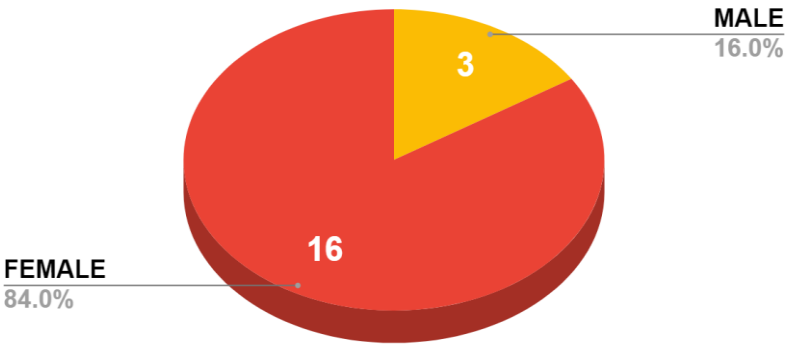


Fig No. 10: Distribution of Comorbidities (Diabetes) In Study Population.

DISTRIBUTION OF COMORBIDITIES (Hypertension): According to the study the comorbidities of female was of 80% (n=16) and males of 20% (n=4)

TABLE 11.

DISTRIBUTION OF COMORBIDITIES (Hypertension)		
COMORBIDITIES (Hypertension)	**Frequency**	**Percentage**
Male	4	20.00

Female	16	80.00
Total	20	100.00

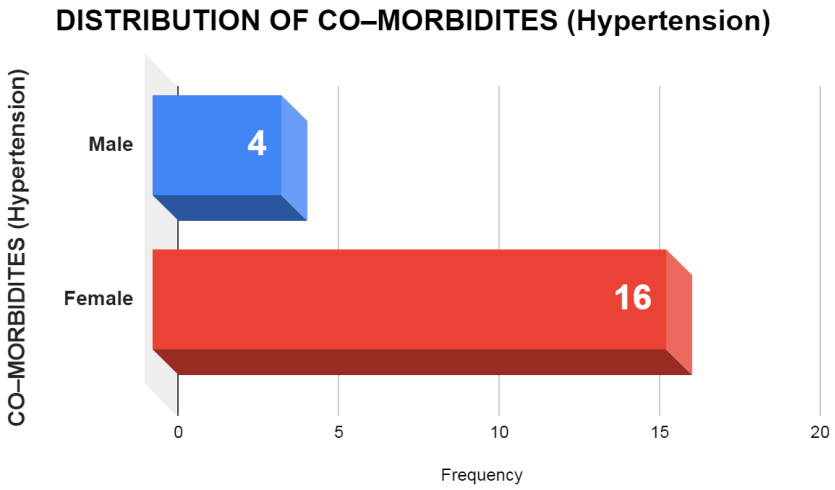


Fig. No. 11: Distribution of Comorbidities (Hypertension) In Study Population.

DISTRIBUTION OF COMORBIDITIES (Thyroid): According to the study the comorbidities of female was of 100%(n=6) and males of 0.00%(n=0).

TABLE : 12

DISTRIBUTION OF COMORBIDITIES (Thyroid)		
COMORBIDITES (Thyroid)	**Frequency**	**Percentage**
Male	0	0.00
Female	6	100.00
Total	6	100.00

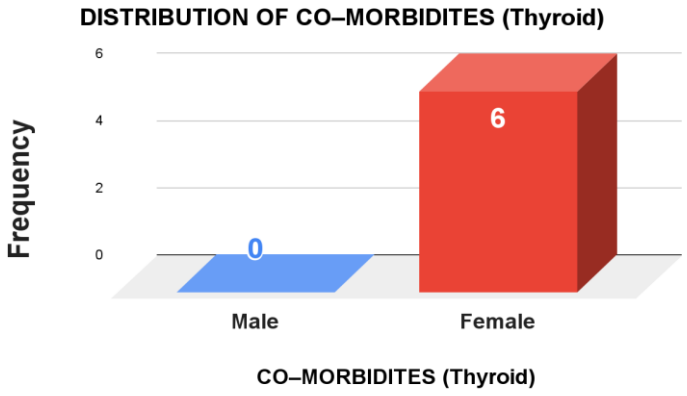


Fig. No. 12: Distribution of Comorbidities (Thyroid) In Study Population.

CLASS WISE DRUG DISTRIBUTION: According to the study the CLASS WISE DRUG DISTRIBUTION of Microtubules was of 51.19%(n=86) and Platinum compounds of 48.81% (n=82).

TABLE 13.

CLASS WISE DRUG DISTRIBUTION (Microtubules Vs Platinum compounds)		
CLASS	**Frequency**	**Percentage**
Microtubules	86	51.19
Platinum compounds	82	48.81

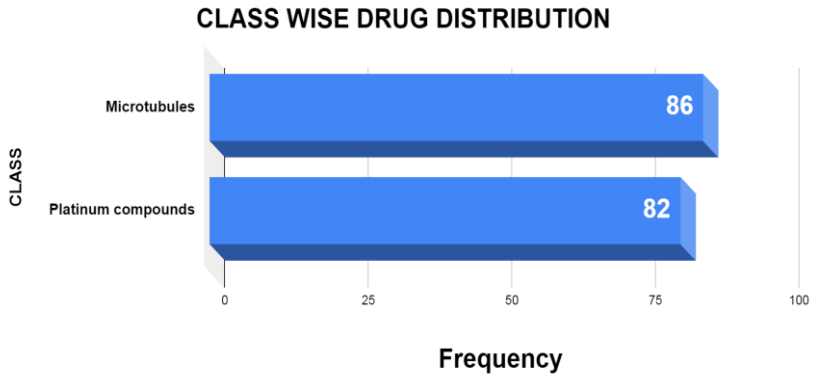


Fig. No. 13: Class Wise Drug Distribution In Study Population.

DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Microtubules): According to the study the DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Microtubules) of TAXELS was of 85 and VINCA ALKALOIDS of 01.

TABLE 14.

DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Microtubules)		
TAXELS (85)	PACLITAXEL	64
	DOCETAXEL	21
VINCA ALKALOIDS (01)	VINCRISTINE	1
	VINBLASTINE	0

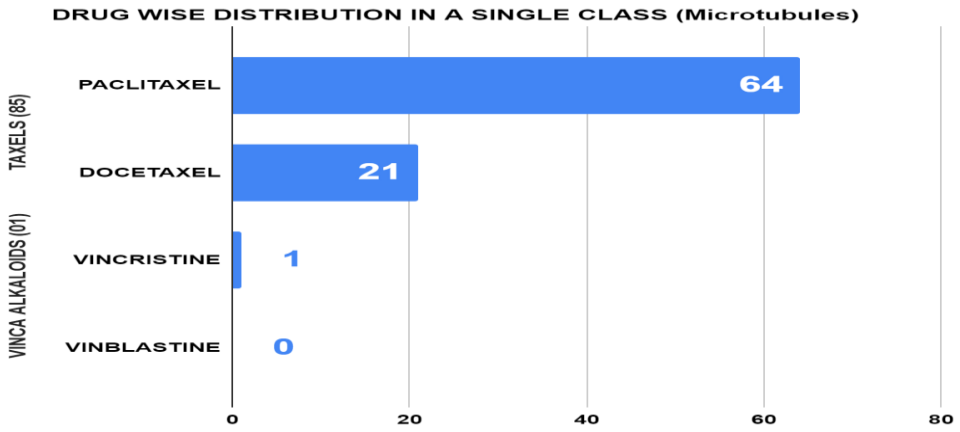


Fig. No. 14: Drug Wise Distribution In A Single Class In Study Population.

DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Platinum Compounds)

According to the study the DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Platinum Compounds) of CISPLATIN was of 40, CARBOPLATIN of 33 and CARBOPLATIN of 09.

TABLE 15.

DRUG WISE DISTRIBUTION IN A SINGLE CLASS (Platinum Compounds)	
CISPLATIN	40
CARBOPLATIN	33
OXALIPLATIN	9

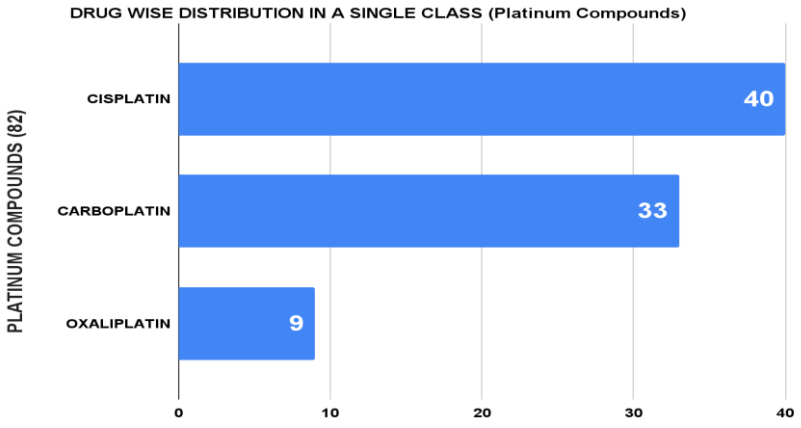


Fig. No. 15: Drug Wise Distribution In A Single Class In Study Population.

CUMULATIVE DOSE OF DRUGS: According to the study the median cumulative doses of drugs paclitaxel having dose of (960 mg/m2), Oxaliplatin(500 mg/m2), Docetaxel(550 mg/m2), Cisplatin(200 mg/m2), Vincristine (60 mg/m2), Carboplatin(1050 mg/m2).

TABLE 16.

CUMULATIVE DOSE OF DRUGS	
DRUG	**MEDIAN CUMULATIVE DOSE**
Paclitaxel mg/m2	960
Oxaliplatin mg/m2	500
Docetaxel mg/m2	550
Cisplatin mg/m2	200
Vincristine mg/m2	60
Carboplatin mg/m2	1050

CONCLUSION

Based on the Results and Discussion, We are concluding that chemotherapy induced peripheral neuropathy affects more than half of the patients receiving neurotoxic chemotherapy, with a significant negative impact on the patients who are using Microtubule agents and platinum compounds due to the persistence of symptoms for long periods, So, the symptoms are very difficult to estimate. It is essential to grade the severity and long- term effects of CIPN correctly. The purpose of this study is to find out the incidence in patients using Microtubule agents and platinum compounds.

The major findings in our study includes

In our study population females are more compared to males out of 150 sample sizes.

In our study, the incidence of CIPN was 70%. In our study population most of the patients presented with 52.66% (n=79) grade I CIPN, 14%(n=21) grade II, and 2.6% (n=1) developed grade III CIPN.

No comorbidity was statistically significantly associated with a higher risk of CIPN in our study. The highest incidence of CIPN was associated with paclitaxel 27.6%(n=29), and with cisplatin 25.7%(n=27), followed by oxaliplatin 8.57%(n=9), and with docetaxel 7.6% (n=8) with Vincristine 0.95% (n=1), Carboplatin 3.8%(n=3.8).

We also observed that for paclitaxel a median cumulative dose of 1050 mg/m2 was associated with a higher incidence of CIPN. Carboplatin is less neurotoxic compared with cisplatin or oxaliplatin, 0.60% of patients receiving carboplatin may develop neuropathy. No

clinical significant difference was found in our study regarding the patients receiving single agent regimen or combination of chemotherapeutic drugs, regarding the severity of CIPN.

This study also sought to explore how comorbidities effects the quality of life. Duration of untreated illness had no impact on worsening of quality of life, because once the treatment begins, the disease condition gets better.

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