Original Article

An Observational Study on Tolerability and Safety of Cisplatin Chemotherapy in Various Cancer

Nikhilesh Andhi*, Aluru Sravya, Sate Praneetha, Sri Romoju Govinda Raghavi, Kancharla Kusuma

Department of Clinical Pharmacy Practice, Samskruti College of Pharmacy JNTU, Hyderabad, Telangana, INDIA.

ABSTRACT

Aim: To find out the safety and tolerability of cisplatin either given as individual therapy or in combination with other anticancer drugs or with radiotherapy. **Materials and Methods:** A prospective observational study was conducted in the oncology department (inpatient) of tertiary care hospital. The data was collected from the in-patient department after considering inclusion and exclusion criteria for a period of 6 months. Safety was analyzed using EORTC scales and Tolerability was assessed by collecting the laboratory data every week of the therapy. Statistical tools like Chi-square test were applied to the data by using SPSS software. **Results:** A total of 107 cancer patients, female patients predominated over males. Most common age group were under of 51-60 years. All the patients in our study were treated with cisplatin in combination with radiotherapy than monotherapy or in combination with other anticancer drugs. Higher incidence of tongue cancer cases were reported followed by less number of anal cancer cases. The quality of life and the functioning ability of cancer patients are calculated via EORTC scale. The QOL is highest in esophageal cancer patients and the lowest in cervical cancer patients. The social functioning of the subjects is very good in every cancer whereas the physical functioning is decreased in anal and buccal cancer patients. The cisplatin is given in the combination with radiotherapy for a total of 6 weeks. Every week after the therapy, the blood samples were collected and the toxicities are checked. Nausea and vomiting, fatigue, loss of appetite, insomnia are the side effects seen during the therapy. Few cases of Hematological toxicities like reduction in Hb count, PCV, lymphocyte count and increase in Neutrophil count were seen. By this, we can say that cisplatin is well tolerated and is safe in the chemotherapy with minimal side effects. **Conclusion:** Cisplatin is well tolerated in adults who are diagnosed with various cancers with minimal side effects which were controlled with supportive therapy. Whereas no serious ADRs reported in the study and no recurrence of the disease was observed. Thus, cisplatin is beneficial in the treatment of various cancers as it is safe and well tolerated.

Keywords: Cisplatin, ADR, Re-occurrence, Hb, PCV, Safety and tolerability, Various cancers, EORTC scale.

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Address for correspondence:
Dr. Nikhilesh Andhi,
Assistant Professor, Department of Clinical Pharmacy Practice, Samskruti College of Pharmacy, Kondapur, Ghatkesar Medchal-501301, Telangana, INDIA.
Email id: 2016marsn@gmail.com

INTRODUCTION

Cisplatin, cisplatinum, cis-diammonium dichloroplatinum. It is a metallic coordination compound with a geometry of a square planar. Color: white/deep yellow to yellow-orange crystalline powder at room temperature, Solubility: It is slightly soluble in water. Soluble in mimethylprimanide and N, N dimethylformamide.[1] Initially it was discovered by Rosenberg through serendipitous observation that neutral platinum complexes inhibited division and filamentous growth of Escherichia coli.[2-5] FDA approved cisplatin is used in treatment of Ovarian cancer,[6-7] testicular cancer, bladder cancer. Off label use is when benefits are more than risk.[8]

Cisplatin use in Various Cancers with Doses Adult

Metastatic Testicular Tumour: 20mg/m^2/day IV for 5days repeated every 3 weeks.

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Advanced Bladder Cancer: 50-70mg/m^2 IV cycle q 3-4 weeks.

Metastatic Ovarian Carcinoma: 75-100mg/m^2 IV per cycle q 4 weeks with cyclophosphamide.[9]

Other off-label indications include: Metastatic, advanced and refractory cancers like Hodgkin lymphoma, Non-hodgkin lymphoma, Penile cancer, H&N, Thymoma, Osteosarcoma, Multiple Myeloma, Mesothelioma.[10-12]

Pediatric Indication: Cisplatin doesn't have many indications for children. When used, it's for historically aggressive cancers. Sometimes useful in treating Germ cell cancers, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma but universal dosing guidelines are not available.[13-17]

Pre-treatment Hydrations: 1-2 L fluid infused for 8-12 hr before dose.

Cis configuration of cisplatin is essential for the anti-neoplastic activity of the drug.[18] Cisplatin undergoes hydrolysis in water and chloride concentration is essential in determining the hydrolysis or aquation (aquation is a process of substitution reaction in which the ligand is substituted by water molecules.) of cisplatin but high concentrations of chlorine in blood plasma prevents hydrolysis. Cisplatin upon entering into the cell the chloride concentration goes down which promotes aquation. In the cytoplasm of the cell the chloride atoms of the cisplatin get replaced by water molecules and thus a hydrolyzed or an aquated product is formed. This aquated product is a strong electrophile which can react with any nucleophile like sulfhydryl group of protein and nitrogen donor atoms in nucleic acids. DNA is the primary target of cisplatin.[12,19-21] Cisplatin covalently binds to the N7 position of the purine base by cross linking between nitrogenous bases and forms an adduct. This cross-linkage between the residues is highly responsible for cytotoxicity. Cytotoxicity causes cell damage by blocking the transcription cell division leading to apoptotic cell death. Adduct formation can be 1-2 intrastrand d(GpG), 1-2 intrastrand d(ApG) representing 90% and 10% respectively.[22-23]

Absorption, Fate, and Excretion: After intravenous administration, cisplatin has an initial plasma elimination t1/2 of 25-50 min; concentrations of total (bound and unbound) drug fall thereafter, with a t1/2 of ≥24 hr. More than 90% of the platinum in the blood is covalently bound to plasma proteins. The unbound fraction, composed predominantly of parent drug, diminishes within minutes.

High concentrations of cisplatin are found in the tissues of the kidney, liver, intestine, and testes but poorly penetrate into the CNS. Only a small portion of the drug is excreted by the kidney during the first 6 hr; by 24 hr, up to 25% is excreted, and by 5 days, up to 43% of the administered dose is recovered in the urine, mostly covalently bound to protein and peptides. Biliary or intestinal excretion is minimal.

Half-life elimination(terminal): 24hr to 47days

Protein bound: >90%

Excretion: Urine(90%); feces(10%)

Clearance: 15L/hr/m^2

Vd: 11L/m^2 [24]

In cisplatin-chemotherapy, some well-known ADR's identified include-Nausea(76-100%), Vomiting (76-100%),[25] Nephrotoxicity(28-36%), Ototoxicity,[26-27] especially in children(31%), Myelosupression(25-30%),[28] Anaphylaxis(1-20%), Alopecia.[29-30]

The contraindications include -Hypersensitivity to cisplatin, other platinum compounds, Severe myelosuppression, renal impairment, hearing impairment, Pregnancy, lactation.[31]

The main objectives of the study is Safety of cisplatin in chemotherapy of various cancers either given alone or in combination with other drugs, Safety of cisplatin along with radiation therapy, Tolerability of cisplatin.

MATERIALS AND METHODS

Study area

The study was conducted in Oncology department in Tertiary care hospital. The data collection format was verified and authenticated by the hospital preceptors for the study.

Study Duration and population: The study included 107 patients from in-patient department who are diagnosed from cancer and were on the cisplatin chemotherapy. Data was collected by interviewing the patient and care-providers for duration of 6 months.

Study design

Study is a prospective observational study. The data form included Socio-demographic information included age, sex, height, weight, BSA. Laboratory data included

Serum creatinine, creatinine clearance, Haemoglobin, RBC, WBC, Differential WBC count, Platelets. Various side effects associated with chemotherapy were evaluating using EORTC scale (European Organisation for Research and Treatment of Cancer).

The patients who have creatinine clearance <20/ml, HIV, HbsAg +ve subjects, Lactating women, Pregnant women, Poor general condition. Poor co- morbidities., Patients who are unwilling to participate were excluded from the study.

Descriptive statistics was done by using SPSS software to determine mean and standard deviation of collected data. The statistical tool Chi square test was performed to determine *p*-Value between the different collected data (like BMI vs dose, BSA vs dose, types of cancer vs drug side effects, dose vs symptoms, dose vs platelets, dose vs hemoglobin, dose vs PCV, dose vs neutrophils, dose vs lymphocytes, dose vs monocytes). The *p*-value is used to determine the statistical significance with in statistical hypothesis significance for safety and tolerability of cisplatin. The *p*-value was set at < 0.05 and confidence interval was 95%.

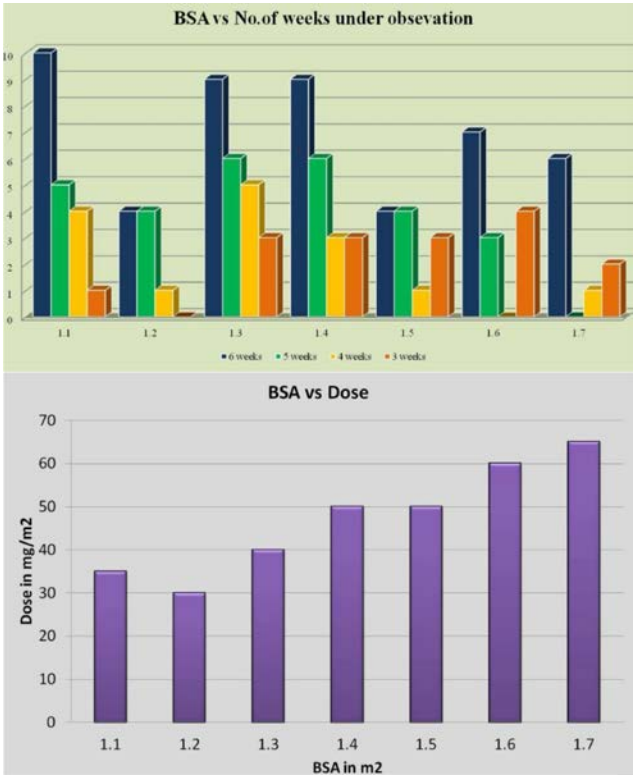
RESULTS

In our study, 107 patients were included as per our criteria. Table 1 indicates the socio-demographic details of the patients who have undergone Cisplatin chemotherapy. Female patients (54%) seems to be predominant than male patients (46%). The most common age group who were diagnosed with cancer were between 51 to 60 years. Among 107 subjects, there were more no. of individuals having a healthy weight and least no. of obese patients. Figure 1 shows the BSA of patients per every week. This graph explains how BSA varied according to weeks and shows the dose of cisplatin according to the BSA. For 1.1m^2 of BSA 35mg dose of cisplatin was given, 1.2m^2- 30mg, 1.3m^2 – 40mg; 1.4m^2 – 50mg; 1.5m^2 – 50mg; 1.6m^2 – 60mg; 1.7m^2 – 65mg

Table 1: Socio Demographics.

Category	Sub-category	No. of Patients
Age	30-40 years	19
	41-50 years	25
	51-60 years	42
	>60yrs	21
Gender	Males	49
	Females	58
BMI	Under weight	30
	Normal or healthy weight	47
	Over weight	18
	Obese	12
Types of Cancer	Oesophagus cancer	10
	Anal cancer	5
	Post cricoids cancer	20
	Buccal cancer	7
	Tongue cancer	35
	Cervical	30

Above table represents the category, sub-category, no. of patients included in our study.

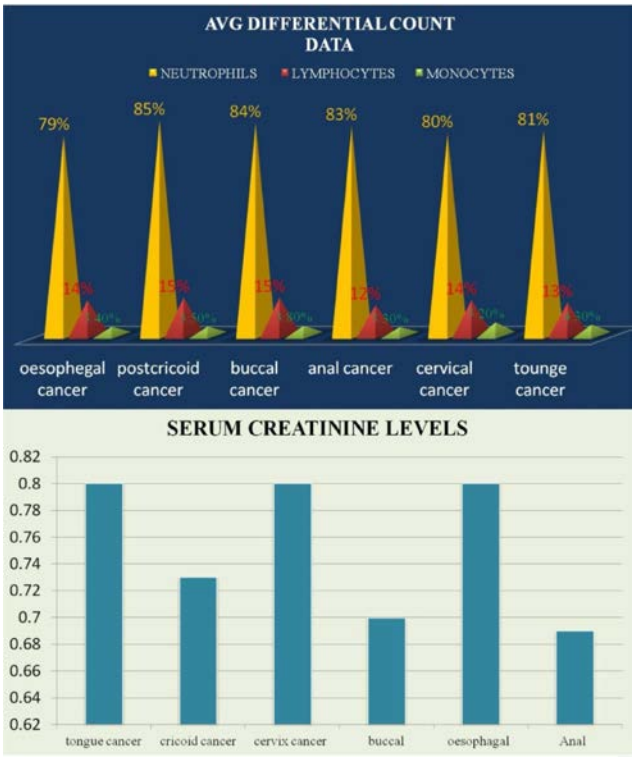


Above, in the first image, X axis has BSA in m^2 and Y axis has no. of weeks. In the second image, X axis has BSA in m^2 and Y axis has Dose in mg/m^2.

Figure 1: BSA vs number of weeks under observation and BSA vs Dose.

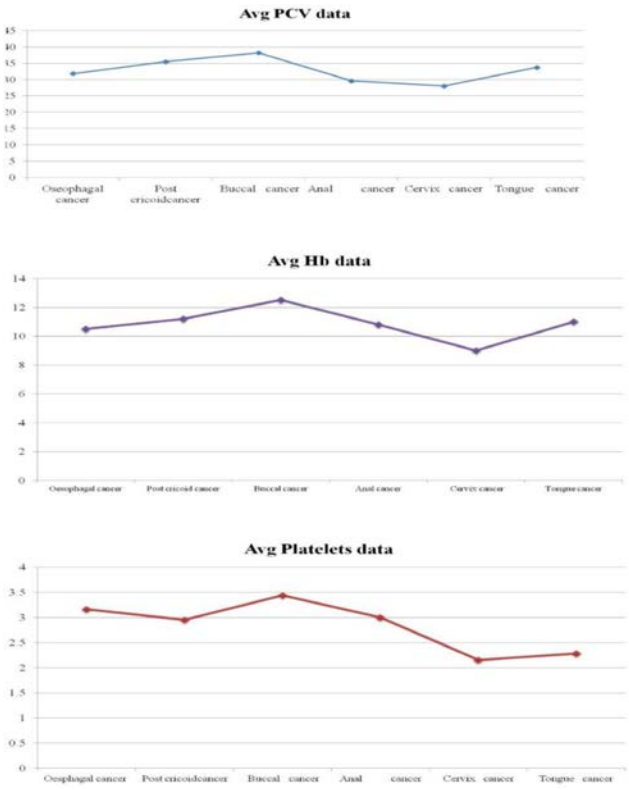
Figure 2 explains about the differential WBC count data and Serum creatinine level in different types of cancers. The differential WBC count graph shows an increase in the Neutrophil count in esophageal cancer 79%, cervix cancer 80%, Post cricoid cancer 85%, Buccal cancer 84%, Anal cancer 83%, Tongue cancer 81%. There is a decrease in the Lymphocyte count in all the cancers Esophageal cancer 14%, Post cricoid cancer 15%, Buccal cancer 15%, Anal cancer 12%, Cervical cancer 14%, Tongue cancer 13%. Whereas, monocyte count remains in the normal range. The average serum creatinine level of pt's who have undergone chemotherapy remained normal.

Figure 3 explains the average PCV, Hb, Platelet count in patients of different cancers who have undergone



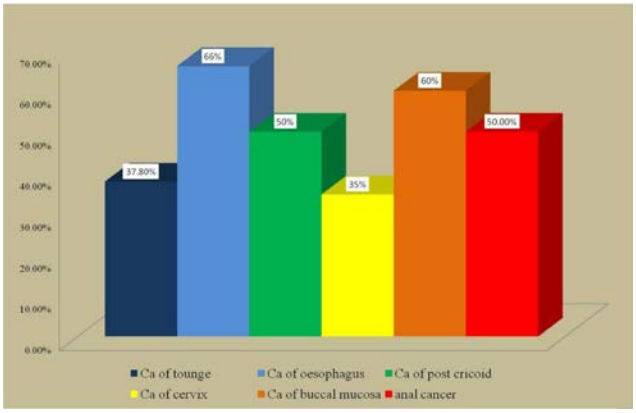
Above graph represents the variations in serum creatinine and differential WBC count with respective cancers.

Figure 2: Average Differential WBC count and Average serum creatinine in different cancers.



In above graphs X axis constitutes types of cancers and y axis represents the range of the lab values.

Figure 3: Average PCV, Hb, Platelet data in different cancers.



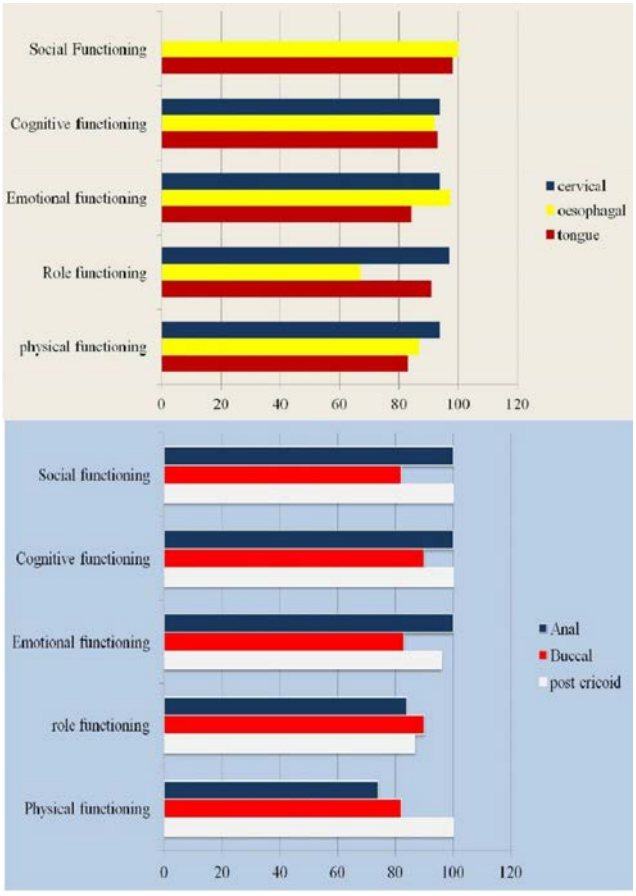
In the above graph X axis represents different types of cancers and Y axis represents the percentage with respective cancers.

Figure 4: Global Score in all types of cancer patients.

cisplatin therapy. They show that the PCV score was below the normal range in all cancers i.e., Esophagus cancer 31.8%, Post cricoid 35.5%, Anal cancer 29.6%, Cervix cancer 28%, Tongue cancer 33.7% except for Buccal cancer whose score was closer to the normal range 38.2. Hb plot explains about the average Hb data of the patients. It shows that the level of hemoglobin decreased in all the patients of different cancers who have undergone chemo but very few fell under anemic category. The values are: Esophagus cancer 10.5 mg/dl, Post cricoids cancer 11.2 mg/dl, Buccal cancer 12.5 mg/dl, Anal cancer 10.8 mg/dl, Cervix cancer 9 mg/dl, Tongue cancer 11 mg/dl. Average platelet graph explains that the average platelet count remained in normal range.

Figure 4 explains about the Global score in all the patients. Global score was calculated with the use of EORTC scale (European organization for Research and Treatment of Cancer). The graph portrays the Quality of life of patients who have undergone cisplatin therapy. The highest score is of Esophageal cancer 66% followed by buccal cancer 60%, post cricoid 50%, anal cancer 50%, tongue cancer 37% and the lowest is for cervix cancer 35%.

Figure 5, Table 2 shows the functioning score of all cancers. The data explains that Physical functioning is highest in Post cricoid 100% and lowest in Anal cancer 74%. Role functioning is highest in cervical cancer 97% and lowest in Esophageal cancer 67%. The highest emotional functioning is seen in Anal cancer 100% and lowest in Buccal cancer 83%. Cognitive functioning is highest in Buccal 100% and post cricoid cancer 100% and seen less esophageal cancer 92%. The highest social functioning is seen in Esophageal 100%, Cervical 100%, Anal 100%, Post cricoid 100% cancers and less in Buccal cancer 95%.



In the above graph X axis represents scoring and Y axis represents the different types of functioning.

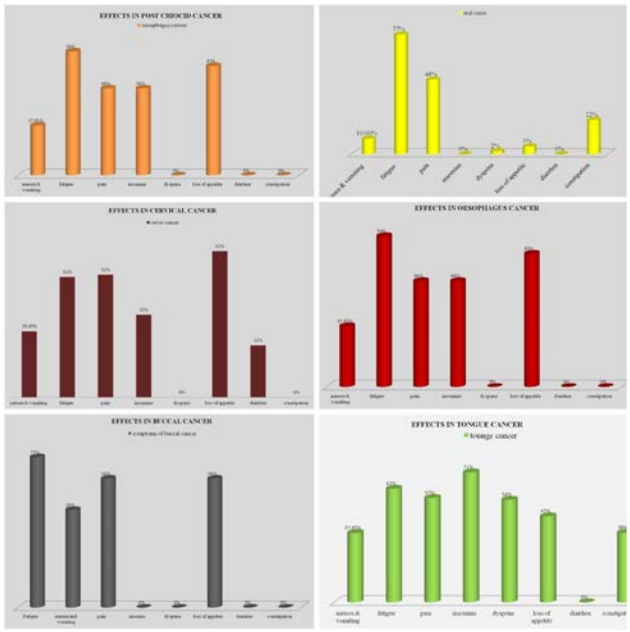
Figure 5: Functional scores of Different types of cancers.

In the above, the Table represents the percentages of Functional score in different types of cancer

Figure 6 shows the effects of cisplatin in Esophagus cancer, Anal cancer, Cervical cancer, Post cricoids cancer, Buccal cancer, Tongue cancer. This was calculated by using EORTC scale. In Tongue cancer among the observed effects, insomnia 71% seems to be most, Nausea and vomiting 37.8% was seen less. Diarrhea was not seen in any individual. In cervical cancer, Loss of appetite 62% seems to be the most, diarrhea 22% was seen less. Dyspnea and Constipation were not seen in any individual. In post cricoid cancer, fatigue 94% was seen the most, nausea and vomiting 37.85% was seen less. Diarrhea, Constipation, Dyspnea was not seen in any individual. In buccal cancer among the observed effects, fatigue 77% was seen the most, nausea and vomiting 50% was seen in a smaller number of patients. Insomnia, Dyspnea, Diarrhea, Constipation is not seen. In anal cancer among the observed effects, fatigue 77% was seen most and less no of patients showed dyspnea 2%. Diarrhea, Insomnia was not seen in any individual. In esophagus cancer, fatigue 94% was seen in more no

Table 2: Functional scores of different types of cancer.

	Tongue cancer	Esophageal cancer	Cervical cancer	Post cricoids cancer	Buccal cancer	Anal cancer
Physical functioning	83%	87%	94%	100%	82%	74%
Role functioning	91%	67%	97%	86.75%	90%	84%
Emotional functioning	84%	97.3%	94%	96%	83%	100%
Cognitive functioning	93%	92%	94%	100%	90%	100%
Social functioning	98%	100%	100%	100%	82%	100%



In the above graph X axis represents different types of effects and Y axis represents the percentage of the effects.

Figure 6: Effects score in different types of cancer.

of patients. Nausea and vomiting 37.85% was seen in less number. Diarrhea, Constipation, Dyspnea is not seen in any individual.

DISCUSSION

A prospective observational study, "On Safety and Tolerability of Cisplatin in the Chemotherapy of Various Cancers" was conducted in secondary care hospital in inpatient department. Using the data collection forms, a total of 107 patient's data was collected.

As per our study among 107 patients, 54% of cases were females and 46% of cases were males. The data

regarding the QOL, should that the findings resembled to research reported by Ji-younhan.[32] In our study the QOL of esophageal cancer patients is high (i.e., 66%) and the least QOL (i.e., 35%) was seen in patients with cervical cancer, were as the buccal cancer has 60% of QOL and the carcinoma of post-cricoid and anal has 50% of QOL, 37.8% of QOL was seen in the tongue cancer patients.

Among 107 patients Tongue cancer incidence was more followed by cervix cancer and the least was Anal cancer this finding were similar to research report by Swati Sharma, L Satyanarayana.[33]

In the present study, 11% patients were obese which is similar to Kathleen Y. Wilson, Kenneth carson and Graham A. Colditz.[34] Patients with normal or healthy weight were more 44%. 28% of patients were underweight and overweight was found to have in 17% of patients.

Mary C White, ScD, Dawn M Holman,[35] conducted a study in which most of the patients diagnosed with all new cancers are of older adults. In our study, 39% of patients of age 50-60 years and 20% of patients of age >60years are diagnosed to have different types of cancers, which suggests that risk of cancer is higher in the people aged above 50 years.

Functioning score: Social functioning, cognitive functioning, emotional functioning, role functioning, physical functioning. The highest social functioning is seen in Esophageal 100%, Cervical 100%, Anal100%, Post cricoid 100% cancers, followed by tongue cancer 98% and buccal cancer 95%. Cognitive functioning is highest in Buccal 100% and post cricoid cancer 100% followed by Cervical 94% and buccal 94 % cancers, tongue cancer 93% esophageal cancer 92%. The highest emotional functioning is seen in Anal cancer 100% followed by, esophagus cancer 97.34%, post cricoid cancer 96%, cervical cancer 94.34%, tongue cancer 84%, buccal cancer 83%. Role functioning is highest in cervical cancer 97% followed by tongue cancer 91%, Buccal cancer 90%, Post cricoid cancer 86.75%, Anal cancer 84%, Esophageal cancer 67%. Physical functioning is highest in Post cricoid 100% followed, by cervical 94%, esophageal 87%, buccal 83%, tongue 82%, Anal cancer 74%.

The symptom of nausea and vomiting is high in esophagus and buccal cancers with a percentage of 50%. A high range of Fatigue symptom is in the patients of esophagus with 94% and in patients with tongue cancer with 62%. The pain score is high in buccal, post cricoid and esophageal patients with a range of 66%. Insomnia and dyspnea are seen in 71% and 56% of tongue cancer patients with the highest range respectively. 83% of post cricoid cancer patients and 62% of cervical cancer patients found to have loss of appetite. Constipation is seen in tongue and anal cancer patients with a range of 38% and anal 22% respectively. By, this study we can say that cisplatin is a choice of drug which can treat a variety of cancers without any effects in the adults. During the course of our study no patient is found to have any of ADRs of cisplatin. The nephrotoxicity of cisplatin is well tolerated by the pretreatment hydrations. Therefore, safety of cisplatin is high which will benefit in the treatment of variety of cancers especially tongue, anal, buccal, esophageal, cervical and post cricoid.

A total of 6 cycles of cisplatin therapy was completed in 49 patients and 5 cycles completed in 28 patients. 15 and 15 patients were observed for 4weeks and 3 weeks of cisplatin therapy. Cheng Lee Chaw, Lesley Tylor, Paddy Niblock.[36] conducted a study which is similar to our study. We found that there is a steep decrease in hemoglobin concentration in blood is seen and the other hematological toxicities seen are decrease in PCV, lymphocytes. The nephrotoxicity is well controlled by the pretreatment hydrations of patients before 24 to 72 hr of cisplatin therapy and also by the post treatment hydrations for 24 to 48 hr after the treatment. Hence the cisplatin is well tolerated in adult patients who are diagnosed with various cancers.

It was observed from our study that, cisplatin produces some of the side effects like fatigue, nausea and vomiting, insomnia, loss of appetite, constipation, dyspnea, insomnia. It is well tolerated with minimal hematological toxicities. No severe ADRs were reported in the study due to cisplatin therapy. The therapy with cisplatin shows less toxic, tolerable and feasible so, the treatment with cisplatin benefits the patients with variety of cancers due to its safety and tolerability profiles. In our study there were no patients with cisplatin resistance and cancer reoccurrence.

CONCLUSION

The incidence of cancer is more in females than in males and this incidence is seen in age group of 51 to 60 years. Most of the subjects came under healthy category when BMI was measured.

EORTC global health score showed that patients who suffered from esophageal cancer showed good quality of life and cervix cancer patients showed poor quality of life. In functional status, cervical cancer and post-cricoid cancer subjects showed better social functioning and other cancer subjects showed good social functioning.

Cognitive score was seen well in cricoid cancer and anal cancer and other cancers showed good results in cognitive function.

The patients who have undergone cisplatin therapy had common side effects like loss of appetite, fatigue, pain, insomnia, nausea and vomiting and the effects which are least seen are diarrhea, constipation, dyspnea. Supportive therapy like multivitamin drugs, Anti-emetics, anti-spasmodic, stimulant laxatives, anti-histamines, H1 receptor antagonists, mouth washes were given to improve patient's condition.

Laboratory evaluation proved that both hemoglobin and PCV were decreased in patients who have undergone the therapy, Neutrophil count increased, Lymphocyte count decreased, Monocytes, platelet remained normal. To bring these parameters back to normal a healthy diet with rich of nutrients is recommended. It is also suggested to take rest as much as possible. Emotional support is very much necessary to every patient who is going through the therapy.

No patient had their therapy started if the serum creatinine levels exceeded 1.2. Pre hydration was done is each and every patient who has undergone the therapy and weekly serum creatinine reports showed normal levels. Resistance was not observed in any patient.

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It is a moment of gratification and pride to look back with a sense of contentment at the long-travelled path, to be able to recapture some of the fine moments, to be able to thank infinite number of people, some who were with me from the beginning some who joined us at some stage during the journey, whose kindness, love and blessing has brought this day. We wish to thank each one of them from the core of my heart.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reactions; **BMI:** Body Mass Index; **BSA:** Body surface area; **CNS:** Central Nervous System; **DNA:** Deoxyribo Nucleic Acid; **EORTC:** European Organization for Research and Treatment of Cancer; **FDA:** Food and Drug Administration; **Hb:** Hemoglobin; **HIV:** Human Immunodeficiency Virus; **PCV:** Packed Cell Volume; **QOL:** Quality of Life; **RBC:** Red Blood Corpuscles; **SPSS:** Statistical Package for the Social Sciences.

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