Subash Vijayakumar. *et al.* / *International Journal of Pharmacy & Therapeutics*, 2(1), 2011, 43-47.

ISSN 0976-0342
2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

A PROSPECTIVE BASED STUDY ON CISPLATIN CHEMOTHERAPY IN A TERITARY CARE HOSPITAL

Subash vijayakumar[1*], M. Leena[1], A.Y. Rao[2]

[1]Department of Pharmacy Practice, MGM Hospital, Vaagdevi College of Pharmacy, Warangal, A.P, India.
[2]Department of Oncology, MGM Hosptial, Warangal, A.P, India.

ABSTRACT

Cisplatin remains a major antineoplastic drug for the treatment of solid tumors. It has been long-lasting and potentially debilitating toxicity which was manifested by reduced renal function. The objective of our study was to assess the renal functions in cancer patients.who is on cisplatin chemotherapy which was carried out in MGM hospital at Warangal over a period of 6 months from May 2010 to October 2010.The study consists of 28 Oral Cancer outpatients receiving cisplatin chemotherapy for a period of 6 months. Whereas, 24 (85.71%) patients were males and 4 (14.28%) patients were females. The most predominate age group was found to be 61-70yrs 41.7% and BMI shows that 46.3% of patients were weighing normally. Cancer of Palate (35.71%) was more common. Serum creatinine, BUN levels were found to be 94.25±42.95 in 1st month and 122.6±57.44 in 6th month and 32.89±11.3 in 1st month and 48.4± 15.21 in 6th month. Creatinine clearances were found to be 60.96± 16.93 at the start and 67.8± 19.3 at the end of therapy. In addition to that GFR were found to be 80.43±2.919 in the 1st month and 5.61± 2.666 in the 6th month. A positive correlation exists between rise in serum creatinine and reduced GFR which is statistically significant. Our study concludes that, there was a slight change in the renal functions with increase in serum creatinine, BUN levels, and imbalanced serum electrolytes. Proper hydration and co administration of electrolytes as a supportive care during therapy will reduce renal toxicity of cisplatin therapy.

Key words: Cisplatin, Renal toxicity, Oral cancer patients.

INTRODUCTION

The kidney normally performs a variety of functions essential for the regulation of a constant extracellular environment and maintenance of metabolic homeostasis. In order to sustain glomerular filtration and renal metabolism, the renal vascular bed receives a disproportionately large blood flow, averaging 20-25% of resting cardiac output. As a result, cells of the renal vasculature, glomerulus tubules, and interstitium are exposed to high volume of blood borne toxicants. The tubular epithelium is especially susceptible to injury, a result (Alchi B *et al*., 2005) solute and water reabsorption along the nephron, producing greater concentration of filtered toxicants in the tubular fluid than that seen in the general circulation (Ascione R *et al*., 1999) transport process resulting in high intercellular concentrations of toxicants and their metabolites, and (Baily V *et al*., 2002) high energy requirements necessary to support epithelial cell metabolism and solute transport.

Cisplatin is one of the effective chemotherapeutic agents for the treatment of human malignancies (Lippman AJ *et al*., 1973; Rossof AH *et al*., 1972; Highly DJ *et al*., 1973; Bitran JD *et al*., 1982). Although highly active, cisplatin has a number of toxicities most notably emesis, ototoxicity, nephrotoxicity, and neurotoxicity (Von Hoff DD *et al*., 1979). Cisplatin may cause acute renal dysfunction with electrolyte disturbances (Lother PJ *et al*., 1984; Blachley JD *et al*., 1981). Assessment of renal function is essential when planning treatment with some chemotherapeutic agents like cisplatin (Dubovsky EV *et al*., 1982; Rehling M *et al*., 1984). Hence we are investigating renal function in cancer patients, receiving cisplatin therapy at Oncology department of MGM hospital, Warangal by estimating Serum Creatinine Blood Urea Nitrogen [BUN], Serum electrolytes [Sodium,

Corresponding Author

Subash vijayakumar
Email ID: vijayvijay66@yahoo.co.in

Potassium, Calcium], and Glomerular filtration rate [GFR].

METHODS

The present study was conducted from May 2010 to October 2010 in the department of Oncology of Mahatma Gandhi Memorial Hospital, which is a 1000 bedded hospital situated at Warangal, A.P. The inclusion criteria for the study includes, patients receiving cisplatin therapy [6 months] of both male and female, above 18-75 years of age. Patients with newly diagnosed histologically or cytologically confirmed cancer, receiving cisplatin chemotherapy. The study was conducted after obtained informed consent from patients. Sample / Data collection was performed according to hospital regulations after approval by the Hospital administration / Ethical committee clearance. Demographic data of all patients were collected which includes name, age, gender, height, weight, disease status, concomitant diseases, and concomitant medications taken along with cisplatin chemotherapy. From each patient 5ml blood was collected in a sterile container without adding any additives. The samples were immediately centrifuged at 3000 rpm for 30 minutes and serum was separated in a labelled eppendroff's tubes and kept at 4^0C till biochemical analysis.

TREATMENT

The study populations were treated with cisplatin in 6 cycles, each of 21 days duration, 40mg/m^2 cisplatin was injected intravenously on the 1st day of the treatment, and 30mg/m^2 was given intravenously on the 3rd day and 5th day respectively in 3% saline over 3hours. All of the study populations have undergone 45 days of radiotherapy before the cisplatin treatment. A uniform hydration procedure was followed during the chemotherapy. An intravenous infusion of 3 litre isotonic saline was setup on the day of cisplatin medication. Mannitol 20% was given intravenously immediately after the completion of the cisplatin infusion. Diuresis was given by infusion with the help of 20mg furosemide. Etoposide 1gm and 5 flurouracil 750 mg were also infused along with cisplatin therapy depending on the disease type. Supportive care such as Magnesium sulphate [$Mgso_4$], Potassium chloride [KCl] and Ondostreone were also included during the course of therapy. None of the patients received other drugs known to be nephrotoxic during therapy.

INVESTIGATIONS

GFR and serum creatinine level were determined at the time of diagnosis. The serum creatinine balance was followed during treatment, before each new code and at regular interval completed chemotherapy. The following parameters were determined at the latest follow up: serum electrolyte levels. The serum was collected on the day of investigation and the above mentioned parameters were determined. The GFR was calculated by Modification of Diet in Renal Disease [MDRD Equation] GFR = 186 × Serum Creatinine [mg per dL] $^{-1.154}$ × age [years] $^{-0.203}$ × [0.742 if patient is female] × [1.210 if patient is black].

Statistical Analysis

Wilcoxon's sign rank test was used for paired samples. The 95% confidence limits were calculated non-parametrically. Spearman's rank correlation was used for correlation analysis. Values are given as median, range and P<0.5 is considered as significant.

RESULTS

Patient characteristics are shown in Table. I were 24 males and 4 females ranged in age from 31-80 years [median = 63years] and received a total of 6 cycles of the predominate age group has found to be 61-70 years. Cisplatin [100mg/cycle] chemotherapy 10 patients had cancer of palate, 8 patients had cancer of tonsil, 6 patients had cancer of larynx and 4 patients had cancer of bronchus. None of the patients received any prior cisplatin chemotherapy. Mild renal dysfunction [GFR =20-50ml/mt] occurred in 3 [10.7%] patients in spite of standard hydration protocol prior to the chemotherapy. This was noted after 1st month in one patient and after 2nd and 5th months in other 2 patients respectively. Table II Shows the mean±SD of serum creatinine at the time of diagnosis [pre-chemotherapy] was 84.86±7.989 and 11.07±376 at the end of the therapy [6th cycle]. This shows the mean increase in serum creatinine was 25.84µmol/L [P=0.04]. The mean ± SD of BUN at the time of diagnosis was 31.04±7.624 and 44.07±11.03 at the end of the therapy the mean increase in BUN was 13.03mg/dl observed.

Table I. Characteristics of 28 patients who received the Cisplatin Therapy

Patients Characteristics	No. of Patients (N=28)
Gender	
Male	24
Female	4
Age (Years)	
18-30	0
31-40	2
41-50	6
51-60	4
61-70	**11**
71-80	5
Types of Cancer	
Larynx	6
Tonsil	8
Palate	10
Bronchus	4
Prior cisplatin therapy	0
No prior cisplatin therapy	0

Table II. Representing the statistical data of study parameters

Study Parameters	Cisplatin Therapy	Mean	Median	SD	SED	r^2	P Value
Serum Creatinine (µmol/l)	Start of Treatment	84.86	85.31	7.989	1.510	0.3766	0.0482*
	End of Treatment	110.7	108.8	37.65	7.114		
Blood Urea Nitrogen (mg/dl)	Start of Treatment	31.04	30.0	7.624	1.441	0.5050	0.0061**
	End of Treatment	44.07	41.5	11.03	2.084		
Serum Sodium (mmol/l)	Start of Treatment	142.1	140	5.416	1.023	0.7764	P<0.0001**
	End of Treatment	130.9	129.5	11.03	2.085		
Serum Potassium (mmol/l)	Start of Treatment	4.257	4.20	0.4533	0.08567	0.7329	P<0.0001***
	End of Treatment	3.561	3.50	0.7295	0.1379		
Serum Calcium (mmol/l)	Start of Treatment	9.443	9.45	0.5527	0.1045	0.5630	0.0018**
	End of Treatment	8.793	8.85	1.019	0.1926		
GFR (ml/min)	Start of Treatment	82.63	84.50	9.542	1.803	0.3945	0.0377*
	End of Treatment	63.36	62.50	14.93	2.821		

SD- Standard deviation, SED- Standard deviation error, Spearman's rank correlation= r2 , *-significant, **-very significant, ***- highly significant

Fig I. Representing individual values of GFR before and after cisplatin therapy

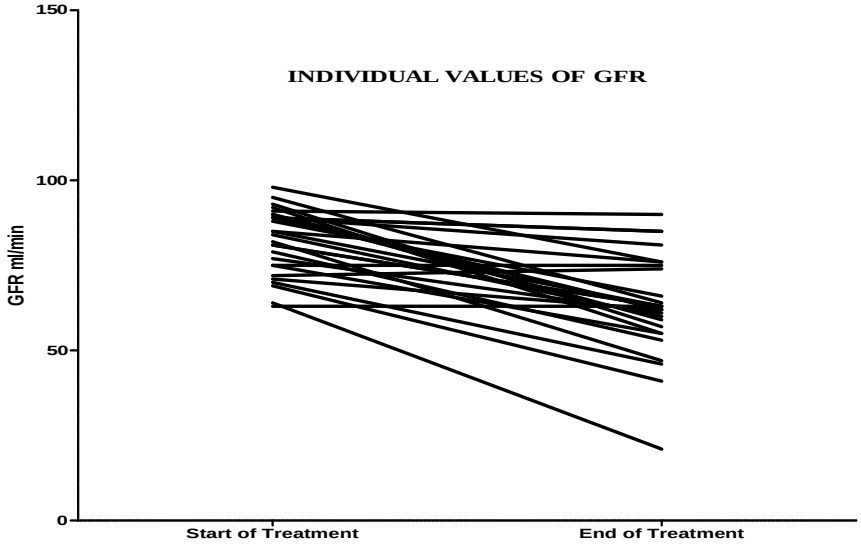

Table II shows the mean ±SD of the serum electrolytes at the time of diagnosis and the end of the therapy. The mean ± SD of serum sodium, potassium. and calcium were found to be 142.1±5.415,4.25±0.4533,9.443±0.5527 at the time of diagnosis [pre-chemo] and 130.9±11.03, 3,561±0.7295, 8.793±1.019 at the end of the therapy [6th cycle] respectively. A correlation exist between start and end of the therapy with r^2=0.7764 [P<0.0001], 0.7329 [P<0.0001] and 0.5630 [P=0.0018] which statistically significant for serum electrolytes. More than >50% of the study population shows decline of serum potassium and sodium levels, and 32.14% of the patients have shown

decline in serum calcium levels than the normal range. Mild renal dysfunction was developed [GFR 20-50ml/min] in 3 patients [10.7%] in spite of standard hydration protocol prior to the chemotherapy. This was noted after 1st month in one patient and 2nd month in another 2 patients.

The mean values of GFR 82.63±9.542 from the time of diagnosis until the latest investigation are shown in the Table II. The decline of GFR at the completion of 6 cycles of chemotherapy was 63.36±14.93 [P<0.0377]. A significant co-relation was found between the change in GFR and the concomitant change in serum creatinine values.

DISCUSSION

Cisplatin [cis-diaminedichloroplatinum II, CP] is a major antineoplastic drug for the treatment of various forms of cancer (Nakashima T *et al*., 1990; Taguchi T *et al*., 2005). However, cisplatin and its analogs accumulate in the kidney causing nephrotoxicity, thus limiting its long-term clinical use (Aranyl I *et al*., 2003). Several strategies and agents were utilized to protect cisplatin treatment but were not found suitable for clinical practice (Ali BH *et al*., 2006).

Cisplatin is a acute nephrotoxic changes are seen in the proximal and distal tubule and in the collecting duct, where as the glomeruli seems to be sparse (Dentino M *et al*., 1978; Gonzalez-Vitae JC *et al*., 1997). Biochemically azotemia also founded (Loehrer PJ *et al*., 1984; Blachley JD *et al*., 1981) as well as sign of tubular damage, [example urinary wasting of magnesium (Blachley JD *et al*., 1981; Schilsky RL *et al*., 1979) and tubular proteinuria (Cohen AI *et al*., 1981; Jones BR *et al*., 1980)

If a high urinary output is secured during treatment, nephrotoxicity is found to be at least partly preventable, the long-term effect on renal function has not, however been greatly investigated dentino *et al*., 1978 found a reduction in 24hrs creatinine clearance during cisplatin treatment. Reduction remain stable for 24 hrs Meijer *et al*., 1983 found that a reduction in GFR [iothalmate clearance] in 8 patients during cisplatin treatment remain un alter during 6 month of maintenance therapy and during a 12 month follow up period.

Our results are in accordance with Modified Diet in Renal Disease [MDRD] equation because it is well with GFR measured by iothalamate clearance (Levy AS *et al*., 2003; Manjunath G *et al*., 2001). We found that 22ml/min [P<0.001] median decline in GFR after completion of cisplatin therapy. The changes in serum creatinine level suggest that the reduction in GFR must have taken place during treatment to remain stable afterwards. The estimation of CrCl or GFR using mathematical formulae is quick, easy, and cheap. However, the estimations must be accurate to be useful. They rely on physical and serum parameters that influence and act as surrogates for renal function. These parameters can be variable and the most variable of these parameters is serum creatinine. Creatinine production is influenced by age, gender, muscle mass and nutritional status. The latter two variables are difficult to measure directly. Diurnal variations of up to 30% in serum creatinine have been observed and are thought to reflect dietary intake (Gabriel R *et al*., 1986) similar findings were observed in the study. In the present study more than 50% of the population shows decline of serum potassium and sodium levels and more than 30% of them shows decline of serum calcium levels than the normal ranges. Tamim *et al.*, 2010 stated that cisplatin damages the proximal tubules, a major site of sodium and calcium reabsorption, and this leads to urinary electrolytes wasting. So the decline of serum electrolytes observed during the study confirms the urinary electrolyte wasting. Though, there was a fall of calcium levels observed during the cisplatin therapy except few patients age> 60years others did not experience any convulsions, dehydration, parathesia and carpopedal spasm, which are the common side effecting hypocalcemia.

CONCLUSION

Our study concludes that change in renal functions with increase in serum creatinine, BUN levels, and imbalanced serum electrolytes during cisplatin therapy. In future, supplementation of antioxidants during therapy may reduce renal injury, hence large number of clinical studies needed to confirmed prevention of nephrotoxicity in cancer patients.

REFERENCES

Alchi B, Nishi, S, kondo D, kaneko Y, et al. Osteopontin expression in acute renal allograft rejection *kidney Int*. 67, 2005, 886-96.

Ali BH, Moundhri SM. Agents ameliorating or augmenting the nephrotoxicity of cisplatin and other platinum compounds: a review of some recent research. *Food Chem Toxico*, 44, 2006, 1173-83.

Aranyl I, Safirstein RL. Cisplatin nephrotoxicity. *Semin nephrol*, 23, 2003, 460-64.

Ascione R, Lioyd CT, underwood, MJ, Gomes, WJ, et al. On pump versus off-pump coronary revascularization: evaluation of renal function. Ann. *Thorac. Surg*, 68, 1999, 493-98.

Baily V, Zhang Z, Meier W, Cate R, et al. Shedding of kidney injury molecules-I, a putative adhesion protein involved in renal regeneration. *J. Biol Chem*, 277, 2002, 39739-48.

Bitran JD, Desser RK, Bilings AA, Kozloff MF, et al. Acute nephrotoxicity following cis dichlorodiammine-platinum. *Cancer*, 49, 1982, 1784-788.

Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. *Ann Intern Med*, 95, 1981, 628-32.

Cohen AI, Harberg J, Citrin DL. Measurement of urinary β2-microglobulin in the detection of cisplatin nephrotoxicity. *Cancer Treat Rep*, 65, 1981, 1083-85.

Dentino M, Luft FC, Yum MN, Williams SD, et al. Long term effect of cis-diaminedichloride platinum [CDDP] on renal function and structure in man. *Cancer*, 41, 1978, 1274-84.

Dubovsky EV, Russel CD. Quantification of renal function with glomerular and tubular agents. *Semin Nucli Med*, 12, 1982, 308-29.

Gabriel R. Time to scrap the creatinine clearance. *Br Med J*, 293, 1986, 1119-120.

Gonzalez-Vitae JC, Hayes DM, Cvitkovic E, Sternberg SS. The renal pathology in clinical trials of cis-platinum [II] diamminedichloride. *Cancer*, 1997, 1362-71.

Highly DJ. Wallace HJ Jr, Holland JF. Cis-diammine dichloroplatinum [NSC-119875]: a phase 1study. *Cancer chemother Rep*, 57, 1973, 459-63.

Jones BR, Bhalla RB, Mladek J et al. Comparison of methods of evaluating nephrotoxicity of cis-platinum. *Clin pharmacol Ther*, 27, 1980, 557-562.

Levy AS, Coresh J, Balk E, Kausz AT, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification [PMID: 12859163]. *Ann intern Med*, 139, 2003, 137-47.

Lippman AJ, Helson C, Helson L, Krakoff IH. Clinical trials of cis-diammine dichloroplatinum. *Cancer chemother Rep*, 57, 1973, 191-00.

Lother PJ, Einhorn LH. Cisplatin. *Ann Intern Med*, 100, 1984, 704-13.

Manjunath G, Sarnak MJ, Levey AS. Prediction equation to estimate glomerular filtration rate: an update. *Curr Opin nephrol Hypertens*, 10, 2001, 785-92.

Meijer S. Mulder NH, Sleifer DT et al. Influence of combination chemotherapy with cis-diammine-dichloro-platinum on renal function: Long-term effects. *Oncology*, 40, 1983, 170-73.

Nakashima T, Maehara Y, Kohnoe S, Hayashi I, et al. Histologic differentiation and chemosensitivity of Human Head and Neck squamouse cell carcinomas. *Head Neck*, 12, 1990, 406-10.

Rossof AH, Slayton RE, Perlia CP. Premilinarly clinical experience with cis-diammine dichloroplatinum. *Cancer*, 30, 1972, 1451-56.

Schilsky RL, Anderson T. Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. *Ann Intern Med*, 90, 1979, 929-31.

Rehling M, Moller ML, Thambdrup B, et al. Simultaneous measurement of renal clearance and plasma clearance of 99m Tc labeled DTAB, 51 Cr labeled EDTA and inulin in man. *Clinic Sci*, 66, 1984, 613-19.

Taguchi T, Nazneen A, Abid MR, Razzaque MS. Cisplatin-associated nephrotoxicity and pathological events. *Contrib nephrol*, 148, 2005, 107-21.

Von Hoff DD, Schilsky R, Reichert CM, et al. Toxic side effects of cis-dichlorodiammineplatinum [II] in man. *Cancer Treat rep*, 63, 1979, 1527-1531.