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COMPARATIVE STUDY OF THE TOXICITY PROFILE IN PATIENTS RECEIVING CISPLATIN-PACLITAXEL VS CARBOPLATIN-PACLITAXEL IN OVARIAN CANCER

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ABSTRACT

Background: The standard chemotherapy for ovarian cancer includes the combination of paclitaxel and a platinum compound. Comparing cisplatin and paclitaxel, with carboplatin and paclitaxel, it has been found that substitution of the analog carboplatin for cisplatin in this combination may improve the toxicity profile. **Methodology:** 40 patients diagnosed with advanced epithelial ovarian cancer (stage III and stage IV), were recruited for the study and were divided into two groups. One group received cisplatin-paclitaxel and the other received carboplatin-paclitaxel. **Results:** Hematological toxicity namely decrease RBC, WBC, PLT, Hb and renal parameters urea creatinine, GFR decreases in cisplatin group.

KEYWORDS: Ovarian cancer, Nephrotoxicity, Hematological toxicity, Cisplatin, Carboplatin.

INTRODUCTION

Ovarian cancer represents the seventh most common women cancer in worldwide[1] and one of the leading causes of death among gynecological malignancies in India.[2] In United States, it is estimated that 22,280 women's will received a new diagnosis of ovarian cancer and about 14,240 women's died of ovarian cancer.[3] Ovarian cancer deaths in women, more

deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 75.[4] The standard chemotherapy for the treatment of ovarian cancer is platinum analogue (cisplatin, carboplatin) with combination paclitaxel.[5]

For the past decade the treatment of advanced ovarian cancer has generally comprised maximal debulking surgery followed by combination chemotherapy. Cisplatin has been the most active single agent.[6]

Cisplatin (cis-diamminedichloroplatinum CDDP) is used for the treatment of solid tumors, including ovary, head, neck, lung, and bladder. While cisplatin induces various toxicities including myelosuppression, ototoxicity and nephrotoxicity the major dose-limiting side effect.[7] Nephrotoxicity was reported in the initial clinical trials of cisplatin chemotherapy.[17] Now, it is recognized that the prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment. 4,18 Clinically, cisplatin nephrotoxicity is often seen after 10 days of cisplatin administration and is manifested as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels. 4,19,20 On the other hand, the long-term effects of cisplatin on renal function are not completely understood, but it is believed that cisplatin treatment may lead to subclinical but permanent reduction in glomerular filtration rate.[21]

There are several mechanisms for the development of nephrotoxicity due to oxidative stress, inflammation, mitochondrial dysfunction, DNA adducts and cytotoxicity to the tubular epithelial cells.[8] The evidence suggest that accumulation of cisplatin in the mitochondria of renal cells, altering mitochondrial bioenergetics, increasing the level of reactive oxygen species (ROS), decreasing mitochondria calcium absorption, and causing renal tubular cell death due to release of pro-apoptotic factors.[9]

This is comparative study of cisplatin plus paclitaxel versus paclitaxel plus carboplatin as first line chemotherapy for patients with ovarian cancer. The aim of this study was to compare the toxic effect of these two regimen on blood parameters, renal function and oxidative stress.

Very few studies have been done in Bihar comparing the response and toxicity of cisplatin-paclitaxel with carboplatin-paclitaxel. Hence this study is significant in the current setting.

MATERIAL AND METHODS

Study design

Study was conducted as a Prospective observational study in the SS hospital and research institute Kankarbagh Patna. Study period was from August 2015 to April 2016. Patients were informed about the investigative nature of this study and obtained consent and willingness to participate prior to this study.

Forty patients diagnosed with epithelial ovarian cancer (stage III and stage IV), were re-cruited for the study and were divided into two study group's i.e. Group A: 23 patients receiving cisplatin plus paclitaxel, Group B: 17 patients receiving carboplatin plus paclitaxel.

Inclusion criteria

1) Histological diagnosis of epithelial ovarian carcinoma-stage III and IV.
2) Patient with adequate renal functions and hematological values.
3) Age between 28-75 years.

Exclusion criteria

1) Patients not willing to participate in the study.
2) Patients with a history of systemic hypertension, pulmonary hypertension and DM.
3) Patient with Cases of urogenital tract cancer, Cases of systemic diseases, Cases Of renal failure,

All the two study groups were examined for their different hematological, and renal parameters and their results were collected for final analysis.

Treatment plan

Patients were randomly assigned to receive cisplatin plus paclitaxel or carboplatin plus paclitaxel. Each regimen consisted of four cycles of chemotherapy repeating at 21 days. Patients received Paclitaxel 175mg/m^2 as a continuous intravenous infusion over 3 hours. Patients in the cisplatin arm received cisplatin at a dose of 75 mg/m^2, administered as a slow continuous intravenous infusion. The dose of carboplatin (AUC-7.5) was calculated using the Calvert formula, with creatinine clearance.

Statistical Analysis

The data was analyzed using statistical Package for Social Sciences (SPSS) and parametric data were expressed as mean ± standard deviation. The comparison of the mean values within

the group was done using paired t-test and the differences were considered statistically significant if $P < 0.05$.

RESULTS

The age of patients included in the study ranged between 28 and 75 years. Of the total forty patients, contributed by 23 patients from cisplatin group and 17 from carboplatin group (Table 1).

Table 1: Patients' characteristics according to treatment group.

Characteristics	Cisplatin+Paclitaxel (n=23)	Carboplatin+Paclitaxel) (n=17)
Age-yr		
Mean±SD	45.95±10.08	49.35±14.33
Median	48	50
Range	28-62	21-75
Stage- no (%)		
III	12 (52.2)	10 (58.8)
IV	11 (47.8)	7 (41.2)

Table 2: Comparison of hematological, renal function and oxidative stress changes in Group A and Group B, before and after 4th cycle of chemotherapy.

	Group A (N = 23) (Paclitaxel + Cisplatin)			Group B (N = 17) (Paclitaxel + Carboplatin)			*p*-value Group 1 *vs.* Group 2
Characteristics	**Baseline Mean ± SD**	**After 4th cycle Mean ± SD**	***p-value***	**Baseline Mean ± SD**	**After 4th cycle Mean ± SD**	***p-value***	**Baseline**
Hematological							
RBC	4.3±0.4	3.5±0.4	0.000*	4.4±0.5	4.1±0.5	0.067	0.438
WBC	13.6±4.3	6.0±1.6	0.000*	12.6±2.2	7.0±1.5	0.000*	0.399
PLT	301.9±144.5	157.8±18.5	0.000*	294.9±153	198.7±53.6	0.003*	0.883
Hb	11.3±0.6	9.1±1.0	0.000*	11.2±0.9	10.0±0.9	0.000*	0.510
Renal function							
Urea	31.6±6.6	68.8±18.9	0.000*	28.9±4.6	49.4±5.8	0.000*	0.158
Creatinine	0.6±0.05	1.8±0.6	0.000*	0.67±0.06	1.4±0.1	0.000*	1.000
GFR	100.7±9.5	34.1±9.8	0.000*	102.0±10.3	41.3±6.3	0.000*	0.702
Oxidative stress							
MDA	22.5±4.0	45.4±8.6	0.000*	22.6±3.2	39.7±5.8	0.000*	0.940

Data are mean ± SD values. An independent-sample t test was used to examine significant changes.

*p-value of <0.05 was considered statistically significant.

RBC-Red blood cells, WBC-White blood cells, PLT-Platelets count,

Hb- Hemoglobin, GFR- Glomerular filtration rate, MDA- Malondialdehyde.

Table 3: Difference between group-A and group-B.

Parameters	Group-A	Group-B	P-value
RBC	0.74±0.51	0.30±0.62	0.018
WBC	7.61±4.31	5.53±2.09	0.074
PLT	144.13±146.29	96.23±115.49	0.271
Hb	2.28±1.07	1.16±0.88	0.001
Urea	-37.17±18.57	-20.47±7.70	0.001
Creatinine	-1.19±0.64	-0.78±0.19	0.014
GFR	66.60±13.99	60.64±11.90	0.164
MDA	-22.90±9.18	-17.12±6.20	0.030

Table 3 shows the percent difference changes between group A and group B after 4th cycle of chemotherapy.

Table 4: Comparison of toxicities between cisplatin+paclitaxel and carboplatin+paclitaxel after 4th cycle of chemotherapy in ovarian cancer patients.

	Cisplatin+paclitaxel (n=23)				Carboplatin+paclitaxel (n=17)			
	Grades				Grades			
Toxicity	1	2	3	4	1	2	3	4
Neutropenia	7(30.4)	6(26.1)	6(26.1)	4(17.4)	6(35.3)	7(41.2)	4(23.5)	-
Anemia	4(17.4)	15(65.2)	4(17.4)	-	7(41.2)	10(58.8)	-	-
Thrombocytopenia	-	18(78.3)	5(21.7)	-	3(17.6)	13(76.5)	1(5.9)	-
Creatinine	8(34.8)	13(56.5)	2(8.7)	-	11(64.7)	6(35.3)	-	-
GFR (stages)	-	-	16(69.6)	7(30.4)	-	-	17(100)	-

DISCUSSION

In our study, there were 40 females age group between 28 and 75 years (Table 1). Cisplatin + paclitaxel and carboplatin + paclitaxel are common combination of drug regime used for the treatment. In this study, plasma urea, creatinine levels and glomerular filtration rate were used to evaluate how well the kidney is working after chemotherapy was used in ovarian cancer treatment.

In our study, Age and gender distribution among all the groups was almost equal therefore we presume that the entire body organ including kidney and bone marrow would be uniformly affected.

Anemia in cancer patients is multifactorial, resulting from nutritional deficiencies, decreased production of red blood cells, increased loss /destruction of blood and may occur as a either a direct effect of the cancer or due to chemical factors produced by the cancer.[10] In our study we observed a significant fall (p =0.000) in total red blood cell count in group-A treated patients and not significant in group-B treated patients. The results of this study also observed that Hb concentration was significantly decreased only in cisplatin treated group. Similar results decreased were obtained in the study by Ranjee et al.[11] It was suggested that the anemia could be due to difference in time of maturation of the erythroid series. However, LevI A, et al.[12] hemolysis was blamed for the production of anemia. It has been proved[13] that cisplatin therapy inhibits the production of renal erythropoietin which results in a lower RBC production.

A significant fall was observed in platelet count in both groups after forth cycle of chemotherapy.

The major side effect of cisplatin is nephrotoxicity that may restrict the therapeutic use of cisplatin. Nephrotoxicity is found in 28-36% patients who received a single dose (50 mg/m2) of cisplatin (Tezcan et al., 2013).[14] Although cisplatin show dose dependent nephrotoxicity and decrease glomerular filtration rate (GFR), increased serum creatinine and urea level. In this study in cisplatin group, 56.6% (in grade-II) and (8.7% in grade-III) patients developed nephrotoxicity in the form of raised serum creatinine, while in carboplatin group 35.3% (only) patients only in grade-II. While cisplatin caused all grades of toxicity - grade 1(30%), grade 2(17.5%), grade 3 (2.5%); only grade 1 toxicity was seen in carboplatin (5%). Andreas du Bois also reports similar results in his study.[15]

CONCLUSION

The thrombocytopenia were more in the carboplatin group compared to cisplatin group. Nephrotoxicity and neurotoxicity were more in cisplatin group. Response to therapy was identical in both the treatment groups.

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REFERENCES

1. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics. CA Cancer J Clin., 2005; 55: 10-30.
2. Www. the American Cancer Society.org.in
3. http://www.cancer.org/cancer/ovariancancer/detailedguide/ovarian-cancer-key-statistics.
4. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et. al. Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. N Engl J Med., 2006; 354: 34-43.
5. Ozols RF, The case for combination chemotherapy in the treatment of advanced ovarian cancer. J. Clin. Oncol. 1985; 3: 1445.
6. Sastry J and Kellie SJ. Severe neurotoxicity, ototoxicity and nephrotoxicity following high-dose cisplatin and amifostine. Pediatric hematology and oncology. 2005; 22: 441-445.
7. Yao X, Panichpisal K, Kurtzman N and Nugent K. Cisplatin nephrotoxicity: a review. The American journal of the medical sciences, 2007; 334: 115-124.
8. Santos NA, Bezerra CS, Martins NM, Curti C, Bianchi ML, Santos AC. Hydroxyl radical scavenger ameliorates cisplatin-induced nephrotoxicity by preventing oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria. Cancer Chemotherapy Pharmacol, 2008; 61: 145-155.
9. Suzuki K, Usami T, Sudoko H, Ohtawara Y, Tajima A, Kawabe K, et al. Experimental study on carboplatin toxicity-a comparison with cisplatin. Gan to Kagaku Ryoho, 1988; 5: 2153-2158.
10. Sharma RM, Bundela MK, Choudhary U, Choudhary S, Kalwar A, Mathur KC. A comparative study: effect of platinum compounds viz cisplatin, carboplatin, oxaliplatin. Indian Journal of Clinical Anatomy and Physiology, 2015; 2: 97-104.
11. LevI A, Aroney RS, Dalley DN. Hemolytic anemia after cisplatin treatment. Br Med J., 1981; 282: 2003-04.

12. Wood PA, William Hrushesky JM. Cisplatin-associated anemia: An erythropoietin deficiency syndrome. Clin Invest, 1995; 95: 1650-1659.
13. Tezcan S, Izzettin FV, Sancar M, Yumuk PF, Turhal S. Nephrotoxicity evaluation in outpatients treated with cisplatin-based chemotherapy using a short hydration method. Pharmacol Pharmacy, 2013; 4: 296-302.
14. Bois AD, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/ paclitaxel as first-line treatment of ovarian cancer .Journal of the National Cancer Institute, 2003; 95: 1320-1329.