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

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ABSTRACT

The standard chemotherapy for ovarian cancer includes the combination of paclitaxel and a platinum compound. Comparing carboplatin /paclitaxel with cisplatin/paclitaxel, it has been found that substitution of the analog carboplatin for cisplatin in this combination may improve the toxicity profile.

Objectives:

1) To grade toxicity (according to WHO toxicity scale) and to compare the toxicity profile of cisplatin/paclitaxel versus carboplatin/paclitaxel in advanced epithelial ovarian carcinoma.

2) To compare the performance status of patients receiving these regimens.

3) To assess the clinical response rate based on CA 125 criteria.

Methodology: 80 patients diagnosed with advanced epithelial ovarian cancer (stage III and stage IV), were recruited for the study and were divided into two groups of 40 each. One group received cisplatin-paclitaxel and the other received carboplatin-paclitaxel. All toxicities were graded according to WHO toxicity grading criteria. Response was assessed by CA 125 criteria, and patients categorized as responders or non responders based on whether raised serum CA 125 (pretreatment) values decreased by 50% during therapy.

Results: Hematological toxicity namely anemia, leucopenia and thrombocytopenia were significantly more in patients treated with carboplatin. Nephrotoxicity, ototoxicity, neurotoxicity, nausea, vomiting and diarrhea were significantly more with cisplatin(p value <0.01). Response rate was similar in both treatment arms-Cisplatin(57.5%) and Carboplatin(62.5%)(p value 0.648).

Key Words: Ovarian cancer, Hematological toxicity, Leucopenia, Thrombocytopenia

INTRODUCTION

The burden of cancer is increasing worldwide despite advances in diagnosis and treatment. The estimated count of new cancer cases in India in 2001 of 0.80 million is expected to increase to 1.22 million by 2016 as a result of change in size and composition of population. The estimated numbers were greater for females (0.406 millions, 2001) than males (0.392 millions, 2001).[1]

Ovarian cancer is an important cause of morbidity and mortality, especially in aged women. It is the deadliest of all gynecologic cancers.[2] It has been referred to as *the silent killer.* [3]

Primary surgical cytoreduction followed by chemotherapy is usually the preferred management of advanced (stage III or IV) ovarian cancer. Neo adjuvant chemotherapy has been proposed as an alternative approach to conventional surgery as initial management of bulky ovarian cancer, with the goal of improving surgical quality.[4]

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The standard chemotherapy for ovarian cancer includes the combination of paclitaxel and a platinum compound.[5] Studies comparing carboplatin /paclitaxel with cisplatin/paclitaxel have found that substitution of the analog carboplatin for cisplatin in this combination may improve the toxicity profile. Carboplatin is less nephrotoxic, ototoxic and neurotoxic than the parent compound cisplatin.[6]

Despite increasing survival rates, advanced ovarian cancer is rarely cured and more than 50% percent patients die within five years of their initial diagnosis.[7] Therefore, tolerability of treatment and maintenance of quality of life are the factors to be kept in mind during treatment. Many parameters can be used to assess the response of ovarian tumor to chemotherapy. Complete clinical remission is defined as no objective evidence of disease i.e., negative physical examination, negative CA-125 levels, and negative CT with lymph nodes < 1 cm.[8,9] In oncology, performance status quantifies terminally-ill patient's general well-being and daily activities.

Very few studies have been conducted in Kerala comparing the response and tolerability of cisplatin/paclitaxel with carboplatin/paclitaxel. Hence this study is significant in the current setting.

METHODOLOGY

Study was conducted as a Prospective observational study in the Radiotherapy department of Government Medical College, Thiruvananthapuram. Study period was from January 2012 to Dec 2012. Eighty patients diagnosed with advanced epithelial ovarian cancer (stage III and stage IV), were recruited for the study and were divided into two groups of forty each.

Inclusion criteria

1) Histological diagnosis of epithelial ovarian carcinoma-stage III and IV, surgically staged and optimally debulked
2) Patients with raised pretreatment CA 125 levels, as the response assessment were based on reduction in CA 125 levels.
3) Adequate bone marrow, renal and hepatic function
4) Age between 20-80 years.
5) WHO performance status of 0 or 1

Exclusion criteria

1) Patients not willing to participate in the study
2) Recurrent carcinoma ovary patients
3) Patients with normal CA 125 values at the beginning of chemotherapy.
4) Pregnancy
5) WHO performance status of ≥2
6) Death before completion of therapy

STUDY PROCEDURE

Patients who fulfilled the inclusion criteria were included in the study. From each patient, a written informed consent was obtained. A detailed elucidation of history and clinical examination was performed and laboratory investigations were done prior to initiation of treatment.

Treatment Plan

The treating physician allocated the patients to receive either cisplatin/paclitaxel or carboplatin/paclitaxel. Each regimen consisted of six 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. Carboplatin dose was calculated based on Calvert et al formula[10], where carboplatin dose in mg=AUC (GFR+25). Area under the plasma concentration time curve of five was the mean dose administered in the patients.

Toxicity assessment

The patients were educated about the probable side effects and personally interviewed and examined to detect the development of any such toxicity symptoms during the course of chemotherapy and review visits. Toxicities were graded according to WHO toxicity criteria.

Performance assessment

Performance statuses of the patients were estimated using the WHO performance scoring scale. Score was fixed by interviewing regarding their ability to do daily activities and self care. The change in performance status was considered as a measure to assess response and as a measure of quality of life in the current study. This scoring was performed before each chemotherapeutic cycle during all the visits. The performance score recorded after the last chemotherapy cycle was taken for analysis.

Response assessment: Measure of serum CA 125 was evaluated to assess response applying the Gynecologic Cancer Intergroup (GCIG) definition of CA 125 response to therapy of ovarian cancer. For this four samples of CA 125 were required[11]. This included two pre treatment samples, followed by a third sample obtained between the chemotherapy cycles (that showed ≥50% reduction in serum CA 125 values from pre treatment values, in case of positive response) and a confirmatory fourth sample collected after 21 days of third sample. If the serum CA 125 levels did not reduce by 50% or more, towards the completion of six cycles of chemotherapy, it was considered as 'no response'.

Statistical analysis was done and results were analysed.

RESULTS

The age of patients included in the study ranged between 43 and 77 years. The mean age was 58 years (Table 1)

Of the total eighty patients, who had tumor of epithelial origin, 80% belonged to serous adenocarcinoma type, contributed by 35 patients from cisplatin group and 33 from carboplatin group. Remaining 15% was contributed by endometrioid, clear cell and mucinous types.

Patients with stage III and IV epithelial ovarian cancer were only included in the study.75% from cisplatin arm and 70% from carboplatin arm belonged to stage III. 25% from cisplatin arm and 30% patients from carboplatin arm were at stage IV.

The major toxicities observed are listed in table 2. Hematological side effects were significantly more in carboplatin arm. All grades of anemia were observed in carboplatin arm, while no events of higher grade anemia were noted in cisplatin arm. Difference was statistically significant with p value 0.017 (table 3). All grades of leukopenia were produced by carboplatin. The incidence and severity was less in cisplatin arm (p value =0.013). While 60% patients on carboplatin developed thrombocytopenia, only 20% were affected in cisplatin arm (p value 0.007)(table 4).

Other toxicities were found to occur more frequently with cisplatin. Peripheral sensory loss was an evident neurotoxicity, which occurred in 75% patients on cisplatin arm, and only in 30% on carboplatin (p value <0.001).In cisplatin group,20% had grade 2 and 17.5% had grade 3 neuropathy. (table 5). Fifty percent patients administered cisplatin developed nephrotoxicity in the form of raised serum creatinine values. In carboplatin arm, only 5% patients developed nephrotoxicity (p value < 0.001). Ototoxicity was reported only from cisplatin arm.22.5% had grade 1 hearing loss and 5% reported grade 2 ototoxicity. Not a single case of hearing loss or tinnitus was reported from carboplatin arm. (p value <0.001)

Gastrointestinal toxicities nausea, vomiting and diarrhea were significantly more in cisplatin group. Nausea was observed with both the regimens, but with greater intensity in cisplatin group. 75% patients in cisplatin arm experienced prolonged nausea, compared to only 47.5% in carboplatin arm. The difference was statistically significant. (p value =0.046) Despite potential antiemetic regimens, vomiting was inevitable in majority of patients. 95% patients on cisplatin and 52.5% patients on carboplatin suffered vomiting. The severity of vomiting was significantly more in cisplatin arm (p value < 0.001). Loose stools were more severe in cisplatin arm, with 60% grade 1, 10% grade 2 and 2.5% grade 3 cases. In carboplatin group only grade 1 diarrhea (27.5%) was observed. Diarrhea was significantly more in cisplatin arm (p value <0.001). Alopecia occurred in all the patients receiving the chemotherapy irrespective of the arm.

Treatment efficacy was assessed using GCIG tumor response criteria[11] (based on CA 125 values) and WHO performance status. 57.5% patients in cisplatin arm and 62.5% in carboplatin arm responded to chemotherapy(p value =0.648).

P value of 0.877 indicated that the performance status on completing six cycles of chemotherapy was not significantly different between the two arms.

DISCUSSION

In this study, majority of the patients had serous type tumor (85%). In cisplatin arm, 87.5% patients and in carboplatin arm, 82.5% patients had serous adenocarcinoma of ovary. Similarly, in the study conducted by Ozols et al, 70% patients in cisplatin arm and 74% on carboplatin had ovarian cancer of serous histology.[12]

Of the eighty patients studied, 72.5% were in stage III and 27.5% in stage IV. In the study by Mc Gurie et al[7], sixty six percent had presented at stage III and thirty four percent in stage IV.

The grade of tumor denotes the degree of differentiation and plays role in predicting the response to treatment and prognosis. In the current study, both the groups were comparable with regard to distribution of grades. Of the eighty patients studied, 45% had grade III tumor. Similar results were obtained in the study by Markman et al. [13]

In cisplatin arm, 75% developed prolonged nausea compared to 47.5% in carboplatin arm. This is concurrent with the study findings of Andreas du bois et al.[14]

Despite antiemetic prophylaxis, 95% patients in cisplatin arm experienced chemotherapy induced vomiting compared to 52.5% with carboplatin. This goes in hand with the observation by Nejit et al.[15] Carboplatin does not require as vigorous hydration / anti-emetic regimens as for cisplatin. In cisplatin group, 72.5% developed diarrhea, while only 27.5% in carboplatin group had diarrhea. In the study by Andre du bois et al, it was found to occur with almost equal frequencies in both the groups. 33% patients in cisplatin arm and 24% in carboplatin arm were affected.[14]

In the current study, ototoxicity was noted only with cisplatin. But in the study by Andre du bois et al, ototoxicity occurred with both the treatment regimens. Higher proportion of patients (17 %) in cisplatin group suffered from hearing loss compared to carboplatin group (less than 9%).[14] Better methods used to detect hearing loss and the use of higher doses of carboplatin might have contributed to the higher incidence of hearing loss in their study.

In cisplatin group, 75% experienced neurotoxicity of some grade compared to 30% in carboplatin group. No severe grades of toxicity were recorded in either arm. Study by Andreas du bois et al also revealed similar results.[14]

In cisplatin arm, 50% patients developed nephrotoxicity in the form of raised serum creatinine, while it was documented in only 5% patients in carboplatin arm. While cisplatin caused all grades of toxicity - grade 1(30%), grade 2(17.5%) and grade 3 (2.5%); only grade 1 toxicity was seen with carboplatin (5%). Andreas du Bois also reports similar results in his study[14]. In the study by M Adams et al only a single patient on carboplatin developed nephrotoxicity, while in cisplatin arm,70% had high creatinine values[16].

Majority of patients in cisplatin arm developed grade 1 anemia only, and no severe grades were seen. But in carboplatin arm,10% patients developed grade 3 or grade 4 anemia(p value of 0.01).Similar results were obtained in the study by Andre du Bois et al.[14]

Leucopenia was more prevalent in carboplatin arm (85%) compared to cisplatin arm (67.5%). More severe grades were also found with carboplatin (30%) compared to cisplatin (12.5%). Similar results were observed in the study by Nejit et al.[15]

Thrombocytopenia, the characteristic side effect of carboplatin, developed in 58% patients on carboplatin, compared to 20% on cisplatin. No severe haemorrhages were documented. In the study by Andreas du Bois et al, similar results were obtained .[14]

The tumor response based on GCIG criteria was found to be almost equal in both the treatment arms. In cisplatin arm 57.5% and in carboplatin arm, 62.5% patients showed response to chemotherapy. Comparable response rates of 52% in the cisplatin arm and 61% in carboplatin arm were noted in a study by Alberts D.S et al.[17] In contrast, in the study by Mangioni et al, response rate was found to be more for cisplatin (71.6%) compared to carboplatin (51.3%).[18] Pharmacogenetic variations could have contributed to such a result.

In the current study, 60% in cisplatin arm and sixty five in carboplatin had a score zero that indicates a fully active patient capable of carrying out all predisease activities without restriction.

CONCLUSION

Anemia, leucopenia and thrombocytopenia were more in the carboplatin group compared to cisplatin arm. Nephrotoxicity, neurotoxicity and ototoxicity were more in cisplatin arm. Response to therapy was identical in both the treatment arms.

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Table 1: Mean Age in years

Age	Cisplatin	Carbopatin
Mean	58.27	57.85
SD	8.5	7.79

Table 2: Overall comparison of toxicities

Toxicity	Cisplatin		Carboplatin		p value
Anemia	26	(65 %)	32	(80 %)	0.010
Leukopenia	27	(67.5 %)	34	(85 %)	0.013
Thrombocytopenia	8	(20 %)	23	(57.5 %)	0.007
Neurotoxicity	30	(75 %)	12	(30 %)	<0.001
Nephrotoxicity	20	(50%)	2	(5 %)	<0.001
Ototoxicity	11	(27.5 %)	0	(0 %)	<0.001
Nausea	30	(75 %)	19	(47.5 %)	0.046
Vomiting	38	(95 %)	21	(52.5 %)	<0.001
Diarrhea	29	(72.5 %)	11	(27.5 %)	<0.001
Alopecia	40	(100 %)	40	(100 %)	0.634

Table 3: Anemia: Comparison between cisplatin and carboplatin regimens.

Anemia	Cisplatin		Carboplatin		Total	
	N	%	N	%	N	%
Grade0	14	35%	8	20%	22	27.5%
Grade1	24	60%	17	42.5%	41	51.25%
Grade2	2	5%	11	27.5%	13	16.25%
Grade3	0	0%	3	7.5%	3	3.75%
Grade4	0	0%	1	2.5%	1	1.25%

Table 4:Thrombocytopenia: Comparison between cisplatin and carboplatin

Thrombocytopenia	Cisplatin		Carboplatin		Total	
	N	%	N	%	N	%
Grade0	32	80%	17	42.5%	49	61.25%
Grade1	6	15%	10	25%	16	20%
Grade2	2	5%	9	22.5%	11	13.75%
Grade3	0	0%	3	7.5%	3	3.75%
Grade4	0	0%	1	2.5%	1	1.25%

Table 5: Neurotoxicity Comparison between cisplatin and carboplatin

Neurotoxicity	Cisplatin		Carboplatin		Total	
	N	%	N	%	N	%
Grade0	10	25%	28	70%	38	47.5%
Grade1	15	37.5%	8	20%	23	28.75%
Grade2	8	20%	2	5%	10	12.5%
Grade3	7	17.5%	2	5%	9	11.25%