Research Article

A prospective study on treatment of recurrent epithelial ovarian cancer with gemcitabine and pegylated liposomal doxorubicin

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Received: December 21, 2019; **Accepted:** January 30, 2020

ABSTRACT

Background: Rechallenge of a platinum-based chemotherapy is the most common approach for a recurrent platinum-sensitive epithelial carcinoma ovary. However, this carries a substantial risk of cumulative neurotoxicity. **Objectives:** In the present study, we tried to compare the efficacy and toxicities of gemcitabine pegylated liposomal doxorubicin combination regimen to rechallenge of paclitaxel-carboplatin in this setting. **Materials and Methods:** A total of 30 patients were included in the study. The patients were randomized into two groups each containing 15 patients. The study group received injection gemcitabine at the dose of 1 g/m^2 injection intravenously on day 1 and day 8 and liposomal doxorubicin 30 mg/m^2 on day 1 in a 3 weekly cycle up to a total of six cycles in absence of disease progression or unacceptable toxicities. The control group patients were treated with injection paclitaxel at a dose of 175 mg/m^2 I/V infusion and injection carboplatin at a dose considering area under the curve 6 in a 3 weekly for six cycles. **Results:** In the study arm, out of 14 patients, 4 (28.57%) patients had complete response, 6 (42.85%) had partial response, 3 (21.42%) had stable disease, and 1 (7.14%) showed disease progression. In the control arm, 6 (40%) patients out of 15 showed complete response, and 4 (26.66%) partial response. Disease progression was noted in 1 (6.66%) patient. There was less incidence of neurotoxicity compared to the control arm. **Conclusion:** Chemotherapy with a combination of gemcitabine and pegylated liposomal doxorubicin shows equivalent efficacy in platinum-sensitive recurrent ovarian cancer when compared to rechallenge of platinum-based chemotherapy. The regimen has an acceptable toxicity profile with lesser incidence of neuropathy than rechallenge of paclitaxel-carboplatin combination.

KEY WORDS: Recurrent Ovarian Cancer; Rechallenge; Platinum Sensitive; Response; Toxicity

INTRODUCTION

Ovarian cancer is one of the common gynecological malignancies. It is the 5th common cause of malignancy-related death worldwide.[1] The primary chemotherapeutic agent for epithelial ovarian cancer is a platinum-based doublet.[2] Although this regimen provides a good response, the recurrence rate is high.[3] Patients in whom the disease recurs 12 months after completion of primary platinum-based chemotherapy are called platinum sensitive.[4] In this subset of patients, rechallenge of a platinum-based chemotherapy regimen gives a good response rate.[5] However, rechallenge of a paclitaxel-carboplatin combination always carries the risk of cumulative neuropathy.[6] Hence, there has been a continuous effort for an alternative regimen to see whether non-platinum drug-based chemotherapy is also feasible. Liposomal doxorubicin, gemcitabine, etoposide, cyclophosphamide, and vinorelbine are the drugs used in the setting of recurrent epithelial ovarian cancer in different combination regimens with response rate varying from 10% to 33%, with progression-free survival (PFS) ranging from 3 to 7 months.[7,8]

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2020.12348201930012020	

Gemcitabine (2,2-difluorodeoxycitidine) is a nucleoside analog of cytidine. It inhibits the cell cycle at the S phase.[9] Several trials have demonstrated its efficacy in epithelial ovarian cancer.[10] This drug is usually well tolerated. Bone marrow suppression is the dose-limiting toxicity of this agent.[11]

In pegylated liposomal form, the doxorubicin molecule is encapsulated in a bilayer sphere of lipids.[12] This vesicle is then covered by a coat of polyethylene glycol. Liposomal encapsulation of doxorubicin results in the alteration of pharmacokinetics. Infusion of liposomal doxorubicin results in more volume of distribution in the plasma due to less leakage through tight capillary junctions into extracapillary space.[13] Since tumors have a leaky capillary network, there is a selective distribution of the drug to tumor. The liposomal covering further prevents drug uptake by the spleen and reticuloendothelial system. This results in a prolonged plasma level of drug equivalent to a continuous infusion of doxorubicin.[14]

Aims and Objectives

The objective of this study was to compare rechallenge of paclitaxel and carboplatin with a combination of gemcitabine and pegylated liposomal doxorubicin in the treatment of recurrent platinum-sensitive epithelial carcinoma of the ovary.

MATERIALS AND METHODS

Patients were eligible for this study if they had histologically or cytologically confirmed epithelial ovarian cancer progressed after 1 year of first-line chemotherapy with injectable paclitaxel and carboplatin. The inclusion criteria include (1) age 18–60 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status ≤2, (3) previously not treated with either gemcitabine or liposomal doxorubicin, (4) radiological evidence of measurable lesions, and (5) no other comorbidities.

A total of 30 patients were included in the study at NRS Medical College. The patients were randomized into two groups each containing 15 patients. One patient in the study arm defaulted during the chemotherapy cycle and hence was excluded from the study. The study group received on day 1 injection gemcitabine at the dose of 1 g/m^2 dilution in 500 ml normal saline given as an intravenous infusion over 60-min. Injection liposomal doxorubicin 30 mg/m^2 diluted in 500 ml 5% dextrose solution was infused in the second bottle over 45 min. On day 8, only injection gemcitabine was infused at the dose of 1 g/m^2 after dilution in 500 ml normal saline over 60-min. In each day, chemotherapy was preceded by standard pre-medication with injection dexamethasone, ranitidine, and ondansetron. The cycle was repeated every 3 weeks up to a total of six cycles in the absence of disease progression or unacceptable toxicities.

The control group patients were treated with injection paclitaxel at a dose of 175 mg/m^2 I/V infusion over 3 h after dilution in 500 ml normal saline. Injection carboplatin was given in the second bottle at a dose considering area under the curve six with dilution in 500 ml 5% dextrose solution.

Pre-medication in the form of oral dexamethasone 8 mg, ranitidine 150 mg, and pheniramine 25 mg started from night before chemotherapy. Injection dexamethasone, ranitidine, and ondansetron are given 30 min before chemotherapy. The cycle was repeated every 3 weeks up to a total of six cycles in the absence of disease progression or unacceptable toxicities.

The patients were evaluated at baseline and before each cycle by clinical examination, complete blood count, kidney function test, and liver function test. Serum cancer antigen 125 (CA 125) was assayed at baseline and every two cycles thereafter. Electrocardiogram and echocardiography were performed at baseline. Contrast-enhanced computed tomography scan of whole abdomen was performed at baseline and after 3rd cycle and 6th cycle. The CA-125 response was evaluated according to the method of Rustin.[15]

Response assessment was done by RECIST criteria Version 1.1.[16] A complete response was defined as complete disappearance of all measurable disease, without the appearance of any new lesion, and normalization of CA-125 level. A partial response was defined as a 30% or greater decrease from baseline in the sum of products of perpendicular diameters of all measurable lesions and without the appearance of new lesions. Stable disease was defined as a tumor that did not qualify for a complete response, a partial response, or progressive disease. Progressive disease was defined as a 20% or greater increase in the size of at least one measurable lesion, or the reappearance of any new injury, or a two-fold rise of CA 125 level in comparison to baseline. Toxicities were graded as per CTCAE version 4.0 for assessment.[17]

RESULTS

Most of the patients in both groups of this study show serous histology. Mucinous and endometrioid histology are less. Most of the patients in both groups belong to performance status (ECOG) 0 and 1 [Table 1].

In the study arm, out of 14 patients, 4 (28.57%) patients showed complete response, 6 (42.85%) partial response, 3 (21.42%) stable disease, and 1 (7.14%) had disease progression. In the control arm, 6 (40%) patients out of 15 showed complete response, and 4 (26.66%) partial response. Disease progression was noted in 1 (6.66%) patient [Table 2].

Table 1: Characteristics of carcinoma

Characteristics	Study group *n*=14	Control group *n*=15
Performance status		
0	6	7
1	6	5
2	2	3
Histology		
Serous	11	10
Mucinous	2	4
Endometrioid	1	1
Clear cell carcinoma	0	0
Grade		
1	4	3
2	3	7
3	3	4
4	4	1

Table 2: Response to treatment

Response	Study arm (%)	Control arm (%)
Complete response	4 (28.57)	6 (40)
Partial response	6 (42.85)	4 (26.66)
Stable disease	3 (21.42)	4 (26.66)
Progressive disease	1 (7.14)	1 (6.66)

Considering hematological toxicities, the severe grade of anemia was noted in 21.42% of patients in the study population in comparison to 13.33% in the control group. Grade 3–4 neutropenia was encountered in 42.84% and 39.99% patients in the study group and control group, respectively. Severe grade of thrombocytopenia was seen in 7.06% and 6.66% subjects in the study and control arm, respectively. On considering peripheral neuropathy significantly higher occurrence of all grades of neurotoxicities occurred in the study population. About 53.33% of patients in the control group suffered Grade 1–2 neuropathy and 33.33% of patients had severe degrees of neuropathy as compared to 7.14% occurrence of Grade 1–2 in the study group. There was no incidence of severe grades of neuropathy in the study group. Grade 1–2 renal dysfunction was seen in 35.71% and 53.33% patients in the study and control group, respectively. Severe grades of renal dysfunction were seen in 6.66% cases in the control arm but none of the cases in the study arm [Table 3].

Table 3: Toxicities

Toxicities	Grade 1–2 (%)		Grade 3–4 (%)	
	Study arm	Control arm	Study arm	Control arm
Anemia	9 (64.28)	8 (53.33)	3 (21.42)	2 (13.33)
Neutropenia	8 (57.14)	9 (60)	6 (42.84)	6 (39.99)
Thrombocytopenia	3 (21.42)	5 (33.33)	1 (7.06)	1 (6.66)
Emesis	9 (64.28)	5 (33.33)	3 (21.42)	1 (6.66)
Neuropathy	1 (7.14)	8 (53.33)	0 (0)	5 (33.33)
Asthenia	10 (71.42)	8 (53.33)	1 (7.06)	1 (6.66)
Renal dysfunction	5 (35.71)	8 (53.33)	1 (7.06)	1 (6.66)

DISCUSSION

Gemcitabine, as a single agent or combined with other chemotherapy, is used in the setting of recurrent, platinum-resistant disease with the varying response.[18] Gemcitabine, combined with paclitaxel, had shown response rate in up to 40% of paclitaxel-naïve patients in the second line.[19] The study by Joly *et al.* showed a response rate of 14% with a combination of gemcitabine and topotecan in platinum-resistant disease.[20] Gemcitabine/docetaxel combination showed a response rate of 25% in platinum-resistant cases.[21]

The combination of gemcitabine with liposomal doxorubicin regimen used mostly in platinum-resistant ovarian cancer patients shows response rates from 22% to 42.8%, and a median PFS and overall survival from 2.7 to 7.7, and 8.4 to 17 months, respectively.[22]

Although in recurrent platinum-sensitive epithelial ovarian cancer, the most widely embraced approach is rechallenge of platinum-based regimen. There has been researching whether nonplatins can also be used in this setting. Because the use of non-platin drugs in the setting of recurrence might increase the platinum-free interval which potentially increases the chance of response to platinum rechallenge in the future.[23] Cantù *et al*. conducted a study where cyclophosphamide, doxorubicin, and cisplatin (CAP) combination was compared against single-agent paclitaxel.[23] The PFS was significantly higher in the CAP or but in the expense of a higher incidence of hematological toxicity.

Poveda *et al*. showed a combination of trabectedin with pegylated liposomal doxorubicin that is a feasible option in partially platinum-sensitive epithelial ovarian cancer.[24] In calypso trial pegylated liposomal doxorubicin was combined with carboplatin in platinum-sensitive recurrent ovarian cancer.[25] It shows significantly improved PFS over paclitaxel-carboplatin combination (11.3 vs. 9.4 months). The study by Agostino *et al*. used gemcitabine-pegylated liposomal doxorubicin combination in relapsed epithelial ovarian cancer. In platinum-sensitive patients, an overall response rate of 45.2% (95% confidence interval [CI]: 27.7–62.7) was observed at 28 weeks of median duration.[26] Stable disease was 13 out of 31 patients (41.9%, 95% CI: 24.5–59.3) with a median duration of 35 weeks. In our study, complete response and partial response were observed in 28.57% and 42.85% of cases, respectively. These percentages are higher than the before-mentioned study. This difference may be attributed to small sample size. Disease stabilization was achieved in 21.42% cases. However, the difference in rates of response patterns is not significant compared to control arm.

On considering toxicities incidence of hematological toxicities, namely, anemia, neutropenia, and thrombocytopenia was acceptable in the study arm. The incidence of emesis was higher in the gemcitabine-PLD arm. On the other hand, the incidence of all grades of peripheral neuropathy was high in the paclitaxel-carboplatin rechallenge group. Renal dysfunction was encountered in a lower percentage of cases in the study arm. Therefore, it appears that combination chemotherapy with gemcitabine and PLD may be a reasonable option in platinum-sensitive recurrent ovarian cancer.

CONCLUSION

Chemotherapy with a combination of gemcitabine and pegylated liposomal doxorubicin shows equivalent efficacy in platinum-sensitive recurrent ovarian cancer when compared to rechallenge of platinum-based chemotherapy. The regimen has an acceptable toxicity profile with a lesser incidence of neuropathy than rechallenge of paclitaxel-carboplatin combination. However, this study incorporated a small patient population. Future research with a large number of patients is required to achieve a conclusion regarding response and toxicities and overall survival.

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How to cite this article: Das TK, Chatterjee K. A prospective study on treatment of recurrent epithelial ovarian cancer with gemcitabine and pegylated liposomal doxorubicin. Int J Med Sci Public Health 2020;9(3):224-228.

Source of Support: Nil, **Conflicts of Interest:** None declared.