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Addition of epirubicin to conventional chemotherapy in patients with advanced ovarian cancer: sequential therapy - a retrospective evaluation

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Aim: To evaluate the effectiveness of the addition of epirubicin to conventional chemotherapy as a first-line therapy for stage III–IV epithelial ovarian cancer.

Materials and methods: A total of 132 patients who had undergone primary cytoreductive surgery between January 1998 and March 2003 were enrolled in the study. Twenty-four cases were excluded. Out of the remaining 108 subjects, 35 received epirubicin/paclitaxel/carboplatin (Group EPC) and 73 were treated with paclitaxel/platinum (cisplatin or carboplatin) (Group PC).

Results: The median follow-up period was 66.5 months. The clinical complete response was 94% in the EPC group and 97% in the PC group. The recurrence rate in the first 6 months after treatment was significantly higher in the PC than the EPC group (47% vs. 23%, P = 0.018). Triplet chemotherapy was not found to improve 2- and 5-year disease-free survival (DFS) statistically. No significant difference in overall survival was observed between the 2 groups (80% vs. 83% at 2 years and 56% vs. 57% at 5 years for the PC and the EPC group, respectively). The main toxicity in both groups was hematological, and it was particularly severe in the EPC group.

Conclusion: The addition of epirubicin to the standard treatment protocol yielded an improvement in the DFS rate that was not statistically significant and caused a tolerable increase in toxicity.

Key words: Epithelial ovarian cancer, gynecological oncology, chemotherapy

1. Introduction

Improved chemotherapeutic protocols have increased the 5-year survival rate for ovarian cancer, which rose from 37% in the mid-1970s to 53% in the late 1990s (1). While the chemotherapy protocols in the 1970s were composed of chemotherapeutics basically containing alkylating agents, particularly cyclophosphamide, by the 1980s platinum-based chemotherapy became more common. In a study of the Gynecologic Oncology Group, the cyclophosphamide and cisplatin combination was compared with paclitaxel (taxane derivative) and cisplatin, and it was reported that paclitaxel improved survival in the patients with incompletely resected advanced-stage epithelial ovarian cancer (2). After the 1990s, combined paclitaxel and platinum-based (carboplatin or cisplatin) chemotherapy has been generally accepted as the preferred chemotherapy regimen for ovarian carcinoma.

The standard treatment procedure in epithelial ovarian cancer consists of optimal or suboptimal cytoreductive surgery followed by 6 cycles of taxane and platinum combination chemotherapy. The total response rate obtained with this treatment is 70%–80% (2,3). However, patients who respond to this initial treatment suffer a recurrence rate of 50%–75% within 18 to 28 months (4). The response rate of second-line chemotherapy for recurrent cases is very low, with reported rates ranging between 10% and 25% (5,6).

These treatment failures in ovarian cancer have inspired research into new treatment options, including the addition of a third drug to the chemotherapy regimen. The third agent can be applied as consecutive chemotherapy (7), consolidation chemotherapy (8), or combination chemotherapy. Combination chemotherapy has been most thoroughly studied. Drugs that have been studied as a third agent include etoposide (9), topotecan

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(10), irinotecan (11), gemcitabine (12), and anthracyclines such as doxorubicin (13).

In the Ovarian Cancer Meta-Analysis Project, 4 studies comparing the cyclophosphamide and cisplatin combination with combined cyclophosphamide, doxorubicin, and cisplatin were reviewed, and the addition of doxorubicin to the treatment protocol was reported to reduce the mortality rate by 16% in the 10-year follow-up period (14).

Subsequent studies showed that epirubicin, an anthracycline derivative of doxorubicin, had anticancer effects that were equivalent to those of doxorubicin with less cardiac and other toxicities (15). It is critical to ensure that any drug considered as a third agent is demonstrated to show no cross-reactivity with the other 2 drugs, taxane and platinum-based drugs, in the protocol, and that the third agent acts via a different mechanism. In theory, epirubicin fulfills both of these criteria, since paclitaxel acts by stabilizing microtubule formation to prevent their depolarization and carboplatin binds to DNA to inhibit its synthesis, while epirubicin prevents DNA from forming a double helix by binding to nucleic acids and inhibiting the topoisomerase I and II enzymes.

In this study, the standard chemotherapy combination of paclitaxel and platinum (carboplatin or cisplatin) was compared with a triple chemotherapy combination consisting of epirubicin, paclitaxel, and carboplatin, with the specific objective of evaluating the effect of epirubicin on survival and toxicity in patients with epithelial ovarian cancer.

2. Materials and methods

One hundred and thirty-two subjects who all underwent cytoreductive surgery followed by chemotherapy between the years 1998 and 2003 for advanced ovarian cancer were enrolled in this study.

2.1. Patients' eligibility

Patients were considered for enrollment if they had histologically proven stage III or IV epithelial ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging system following optimal or suboptimal surgery (16).

2.2. Chemotherapy schedule

One group received paclitaxel with cisplatin (Group PC-cis; n = 34), the second group received paclitaxel with carboplatin (Group PC-cb; n = 39), and the third group (Group EPC; n = 35) was given epirubicin, paclitaxel, and carboplatin.

In Group PC, treatment started with paclitaxel (175 mg/m^2 in 500 mL of 0.09% NaCl solution infused over 3 h), followed either by carboplatin (calculated according to AUC = 6, infused in 1000 mL of 5% dextrose solution over 1 h) or cisplatin (75 mg/m^2 infused in 1000 mL of normal saline solution over 2 h with 500 mL of 20% mannitol). Patients in Group EPC were given epirubicin (60 mg/m^2 in 250 mL of 5% dextrose infused over 2 h), followed by paclitaxel (175 mg/m^2) and then carboplatin (AUC = 6).

Before chemotherapy was given, the following criteria were met: 1) adequate bone marrow function [white blood cell (WBC) count ≥3000/mL, neutrophils ≥1500/mL, platelets ≥100,000/mL, hemoglobin ≥10 mg/dL]; 2) adequate hepatic function [total bilirubin, aspartate transferase (AST), and alanine transaminase (ALT) of less than twice normal levels]; and 3) sufficient renal function (glomerular filtration rate ≥60 mL/min).

Treatment was administered every 21 days. Patients received chemotherapy premedication, with an oral dose of 20 mg of dexamethasone and an H_2 receptor antagonist, both 14 h and 7 h prior to chemotherapy, as well as an intravenous administration of both an H_1 receptor antagonist and a 5-HT_3 receptor antagonist 1 h before chemotherapy. Patients did not receive granulocyte colony-stimulating factor or erythropoietin prophylaxis. Hematology and biochemistry tests (WBC, hemoglobin, platelets, urea, creatinine, AST, ALT, and total bilirubin) were done every 10th day after each cycle to assess each patient's ability to tolerate the chemotherapy regimen and to detect potential toxicity, which was assessed according to the World Health Organization criteria and was evaluated per patient and per cycle (17). An electrocardiogram was taken before the first cycle of chemotherapy.

2.3. Second-look laparotomy

Before 2003, a second-look laparotomy (SLL) procedure was offered and performed for the patients with epithelial ovarian cancer in our clinic.

After 6 courses of chemotherapy, patients who were in complete clinical remission according to the imaging methods and who had a CA-125 value of not greater than 35 IU/mL were offered SLL to evaluate the effectiveness of chemotherapy. If the patient accepted, SLL was performed within 6 weeks of the end of chemotherapy and consisted of exploration of the abdomen via a midline incision allowing access to the upper abdomen. Cytology samples were collected from ascites or peritoneal washing fluid. Any adhesions were separated with sharp and blunt dissection to enlarge the observation field, and were themselves biopsied. All peritoneal surfaces were carefully checked and then biopsied, as were the serosal surfaces of the bowel. Any suspicious region was resected. Biopsy samples were taken from any areas of the retroperitoneum that appeared suspicious; otherwise, random biopsies were taken. All samples were examined intraoperatively by frozen section. The mean number of samples taken during the surgical procedure was 30. Secondary cytoreduction was performed for the patients who were found to have a gross tumor at SLL. Salvage chemotherapy was applied in cases with a proven disease after SLL.

The effectiveness of each chemotherapy regimen was evaluated based on both SLL results and survival. Both 2-year and 5-year disease-free survival (DFS) and overall survival (OS) results were analyzed. At first, the 3 groups were compared with each other. After that, data of the PC-cis and PC-cb groups were combined into one group, named Group PC. Group PC and Group EPC were compared to each other for survival rates.

Since carboplatin and cisplatin are known to have different toxicity profiles, the cisplatin arm (PC-cis subgroup) of Group PC was excluded from toxicity assessment, leaving a total of 74 patients to be evaluated. One researcher carried out all toxicity assessments. The toxicity rates were compared between the 2 groups (Group PC vs. Group EPC). Kaplan–Meier survival analysis, an analysis of variance table test, and a chi-square test were used for statistical analysis. The cut-off for statistical significance was set at $P < 0.05$.

3. Results

Twenty-four of the 132 patients who met the inclusion criteria and who were enrolled in the study were later excluded from the study. Among these, 15 patients failed to present for follow-up after chemotherapy or SLL, 3 patients had a second malignancy, 3 patients gave up chemotherapy (after the 1st, 2nd, and 5th cycle, respectively), 1 patient died because of reasons unrelated to the disease, 1 patient had a primary malignancy that could not be defined with certainty, and in 1 case the interval between consecutive cycles of chemotherapy exceeded 6 weeks.

The median age of the remaining 108 patients was 51.6 years (range: 20–71). Details of the diagnosis and treatment for the patients in each study group are shown in Table 1. There was no statistically significant difference among the groups except for mean age, which was lower in the EPC group (Table 1).

Table 1. The characteristics of the patients according to chemotherapy regimens.

Characteristics		Group EPC, mean (median; range) (n = 35)	Group PC, mean (median; range) (n = 73)	P
Age (years)		47.6 (48; 20–68)	53.6 (54; 23–71)	0.005*
CA 125 (U/mL)		1244 (416; 8–2500)	658 (432; 7–5950)	0.310
Stage	III	35	69	0.158
	IV	-	4	
Cell type	Serous	29	60	0.575
	Endometrioid	4	5	
	Mucinous	1	1	
	Mix	-	4	
	Unclassified	1	3	
Grade	1	7	5	0.125
	2	16	38	
	3	12	30	
Peritoneal cytology	Negative	10	16	0.466
	Positive	25	57	
Cytoreductive surgery	Optimal	35	66	0.058
	Suboptimal	-	7	
Second look laparotomy	Not performed	8	19	0.310
	Performed	27	54	
Follow-up (months)		61.3 (62; 3–130)	66.9 (74; 5–113)	0.467
Time to recurrence (months)		21.5 (12; 1–95)	9.7 (3;1–95)	0.012*
Time to death (months)		42.4 (38; 5–108)	37.5 (31; 3–87)	0.441

*: Statistically significant.

Group EPC included 35 subjects and Group PC contained 73 subjects (39 in the PC-cb subgroup and 34 in the PC-cis subgroup). The optimal cytoreductive surgery rate and mean follow-up period were similar in these groups (Table 1). A total of 654 chemotherapy cycles were assessed.

3.1. Survival analysis

Among the 108 patients included in the study, 5 were lost to follow-up at 18, 20, 22, 48, and 60 months of the treatment, respectively. All these patients were in the PC group: 3 in PC-cb and 2 in PC-cis. Among these 5 patients, 4 patients underwent SLL. In the 3rd and 4th patients there were findings of disease. The remaining 3 patients in this group suffered from recurrence (at 5, 9, and 14 months after the last cycle of treatment). Since each of the 5 patients were included in the DFS analysis, the 4th was also included in the 2-year OS and the 5th was also included in the 5-year OS analysis.

The clinical complete response rates were similar between the 2 groups (94% in Group EPC and 97% in Group PC, P = 0.443). SLL was offered to 103 patients who achieved clinical complete response and it was performed for 81 patients (15 patients refused, and SLL could not be performed for 7 patients because of medical problems). In 43% of patients in the PC group and 22% of patients in the EPC group, SLL revealed residual disease (P = 0.051). Thereby, the histopathological response rate was 78% and 57% for triplet chemotherapy and the standard treatment modality, respectively. This difference reached only borderline statistical significance.

Seventy-eight patients (72.2%) had recurrence at a mean interval of 13.5 months. Recurrence within the first 6 months after chemotherapy was significantly more common in the PC group than the EPC group (47% vs. 23%, respectively; P = 0.018). The time elapsed between therapy and recurrence was significantly longer in Group EPC than in Group PC (P = 0.012). Sixty patients died (55.6%), with a mean of 39.2 months between the end of treatment and death. Within the EPC group, the mean time between treatment and death was 42.4 months (median: 38; range: 5–108), compared to 37.5 months in Group PC (median: 31; range: 3–87; P = 0.441) (Table 1).

Two- and 5-year survival were compared both among the subgroups (PC-cb vs. PC-cis, PC-cb vs. EPC, and PC-cis vs. EPC) and between the 2 main groups (PC vs. EPC). Although DFS rates at 2 and 5 years were lower and the OS rates were higher when the PC-cis subgroup was compared with the PC-cb subgroup, these differences were not statistically significant (Table 2).

There was no statistically significant difference in survival rates between Group EPC and either of the 2 subgroups.

When the 2 main groups were compared, triplet chemotherapy did not provide statistically significant improvement in 2- and 5-year survival rates. However, the triplet chemotherapy group had an approximately 15% greater 2-year DFS (P = 0.118; Table 2). At the end of 5 years, this improvement fell to 8% (P = 0.380). The improved DFS rates obtained with triplet chemotherapy were not observed in OS (P = 0.725 and 0.952 for 2- and 5-year OS, respectively).

Tablo 2. Two- and 5-year survival rates according to chemotherapy regimens.

Chemotherapy	2-year survival		5-year survival	
	DFS† (%)	OS‡ (%)	DFS† (%)	OS‡ (%)
Group PC-cb	41	78	32	52
Group PC-cis	31	82	26	60
p	0.354	0.719	0.527	0.516
Group PC-cb	41	78	32	52
Group EPC	51	83	37	57
p	0.393	0.625	0.676	0.652
Group PC-cis	31	82	26	60
Group EPC	51	83	37	57
p	0.071	0.887	0.286	0.842
Group PC	36	80	29	56
Group EPC	51	83	37	57
p	0.118	0.725	0.380	0.952

†DFS; Disease-free survival, ‡OS; Overall survival

3.2. Toxicity

The most common toxicity in both groups (Groups PC and EPC) was hematologic. Grade 3–4 neutropenia and anemia were more common in Group EPC in terms of both the number of patients and the number of cycles (Table 3). No difference in thrombocytopenia was seen between the EPC and PC-cb subgroups. Grade 3–4 neutropenia was seen in 36% of the cycles in Group EPC and in only 12% of the cycles in Group PC-cb. Febrile neutropenia was observed only in Group EPC. Febrile neutropenia was observed in 3 patients (8.6%) in a total of 5 cycles (2.4%). It occurred in the 2nd cycle in 2 patients and in the 5th cycle in the remaining patient. In 2 patients, the second episode of febrile neutropenia was observed in the consecutive cycle.

No grade 4 toxicity was observed aside from hematologic toxicity. However, grade 3 hepatic, renal, and gastrointestinal system toxicity were seen (Table 3). Nausea, vomiting, and diarrhea were more common in Group EPC. All patients suffered from at least grade 2 alopecia. Grade 3 alopecia was particularly marked in Group EPC (Table 3). Neuropathy, pain, and constipation rates were similar between the 2 groups. The neuropathy was not of sufficient severity to affect the patients' daily lives.

No patient died, no patient discontinued chemotherapy, and no patient required dose reduction due to toxicity. However, delays between cycles of chemotherapy did occur. The delay rate per patient and per cycle was higher in Group EPC, although it was not statistically significant. While the chemotherapy cycles per person were delayed in 34% of patients in Group EPC, this rate was 37% in Group PC (20% in PC-cb, 17% in PC-cis; P = 0.219). The delay rates per cycle were 7% in Group EPC and 8% in Group PC (5% in PC-cb, 3% in PC-cis; P = 0.309). Hematologic toxicity was the most common cause for delay of chemotherapy cycles. Thirteen of the 14 cycle delays that occurred in Group EPC were caused by hematological toxicity and the remaining 1 delay was because of hepatic toxicity. In Group PC-cb, 10 delays were for hematological reasons and 1 delay was due to hepatic toxicity. In Group PC-cis, 4 delays were because of hematological reasons and 3 delays were due to hepatic and renal toxicity.

4. Discussion

In this study, we found that although adding epirubicin to standard treatment as a third agent yielded an approximately 15% improvement in 2-year DFS and an 8% improvement in 5-year DFS, it had no significant effect on survival. This triple chemotherapy protocol also delayed the occurrence of recurrence. Addition of epirubicin to the standard treatment protocol significantly reduced the rate of platinum resistance from 47% to 23%. The interval between treatment and recurrence markedly increased from an average of 9.7 months to 21.5 months. Moreover, the pathological complete response rate increased from 57% to 78% with addition of epirubicin. Nevertheless, this effect reached only borderline statistical significance (P = 0.051). Although there was an 8% improvement in 2-year OS, there was no apparent effect in 5-year OS. The time interval between treatment and death was the same in the groups treated with and without epirubicin and OS was similar between the subgroups. As a result, long-term follow-up revealed no advantage of epirubicin on survival. The relative youth of patients in the EPC group might explain the observed improvement in DFS.

DFS rates ranging between 16.4 and 19.5 months have been reported for ovarian cancer treated with epirubicin, paclitaxel, and either cisplatin or carboplatin (18–20). In this study, there was an average of 21.5 months between the end of treatment and the time of recurrence for patients in Group EPC.

For triplet chemotherapy in which epirubicin is added to first-line chemotherapy, clinical response rates of over 80% have been reported, with complete response rates between 33% and 64% (19,20). Romanini et al. reported a pathological response rate of 27.3% when the chemotherapy was given every 28 days (19). In the current study, the clinical complete response rate with triplet chemotherapy was 94% and the pathological complete response rate was 78%, compared to 97% and 57% in Group PC, respectively.

Kristensen et al. reported that the addition of epirubicin to the standard treatment protocol for ovarian cancer improved the complete response rate by 10% (21). However, further analysis of those data revealed that epirubicin had no effect on DFS time (22). Similarly, Pujade-Lauraine et al. demonstrated that the addition of epirubicin improved neither DFS nor OS rates (18).

Although side effects of the treatment were most prominent in Group EPC, they were tolerated by the patients and they were manageable for the physicians. The most severe toxicity was hematologic, which was responsible for 13 of the 14 delays in sequential chemotherapy cycles. Aside from hematological toxicity, no other grade 4 toxicity was encountered.

Epirubicin is commonly used at doses of 50, 60, or 75 mg/m^2. Vermorken et al. used high-dose (150 mg/m^2) epirubicin as second-line chemotherapy in ovarian cancer. Bone marrow depression, mucositis, nausea, and vomiting were the main reported toxicities in that study, and one patient died from toxic side effects (23).

The addition of epirubicin as a third agent to the standard therapy is associated with neutropenia and febrile neutropenia. Du Bois et al. reported that grade 3–4 neutropenia occurred in 52% of the cycles in which epirubicin was administered at a dose of 60 mg/m^2 and in

Table 3. Toxicity rates in patients and cycles according to chemotherapy regimens.

Toxicity			Grade	Group EPC (%)	Group PC-cb (%)	P
Hematologic toxicity	Neutropenia	Per person	0	-	13	<0.001*
			1–2	26	54	
			3–4	74	33	
		Per cycle	0	22	44	<0.001*
			1–2	42	44	
			3–4	36	12	
	Anemia	Per person	0	-	31	0.001*
			1–2	77	69	
			3–4	23	-	
		Per cycle	0	31	65	<0.001*
			1–2	64	35	
			3–4	5	-	
	Thrombocytopenia	Per person	0	63	79	0.185
			1–2	26	18	
			3–4	11	3	
		Per cycle	0	85	95	0.001*
			1–2	12	4	
			3–4	3	1	
Mucositis		Per cycle	0	67	61	0.394
			1–2	29	35	
			3	4	4	
Hepatic toxicity		Per cycle	0	95	89	0.068
			1	4	9	
			2–3	1	2	
Nausea and vomiting		Per cycle	0	43	71	0.001*
			1	40	22	
			2–3	17	7	
Diarrhea		Per cycle	0	85	89	0.008*
			1	8	2	
			2–3	7	9	
Proteinuria		Per cycle	0	90	92	0.267
			1	9	5	
			2–3	1	4	
Hematuria		Per cycle	0	94	93	0.148
			1–2	6	7	
Alopecia		Per person	2	3	18	0.037*
			3	97	82	
Neuropathy		Per person	0	17	3	0.340
			1–2	83	97	
Pain		Per person	0	-	5	0.704
			1–2	100	95	
Constipation		Per person	0	34	44	0.413
			1–2	66	56	

*: Statistically significant.

60% of the cycles in which the dose was 75 mg/m^2 (24). In the current study, grade 3–4 neutropenia was significantly more common in Group EPC, occurring in 36% of cycles. The rate of febrile neutropenia has been reported between 5.5% and 17% (18,21,25). We observed febrile neutropenia only in Group EPC, where it occurred in 8.6% of cycles. Anemia was also markedly elevated in Group EPC, with grade 3–4 anemia occurring in 5.2% of cycles, a rate similar to that reported by du Bois et al. (3% and 4% for doses of 60 mg/m^2 and 75 mg/m^2, respectively) (24). However, the rates of grade 3–4 thrombocytopenia reported by du Bois et al. (13% and 23% for doses of 60 mg/m^2 and 75 mg/m^2, respectively) were quite different from the rates observed in the current study. Although, as in this study, du Bois et al. encountered no grade 4 toxicity other than hematological toxicity, other studies have reported grade 4 neuropathy and vomiting (18,21).

One limitation of this study was the small number of patients. Therefore, use of epirubicin in triplet chemotherapy in ovarian cancer should be explored in further, multicenter studies.

In conclusion, the addition of epirubicin to the standard treatment protocol yielded an improvement in the DFS rate that was not statistically significant and caused a tolerable increase in toxicity. Nevertheless, it did not provide a clear benefit in survival.

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