Bevacizumab and weekly dose-dense paclitaxel and carboplatin in recurrent epithelial ovarian carcinoma: A phase II trial

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Abstract:

Aim: The aim of this research was intended to assess the efficiency and safety of combining bevacizumab with weekly dose-dense carboplatin (C) and paclitaxel (T) in the treatment of platinum-resistant/sensitive recurrent epithelial ovarian cancer (EOC) that had been treated previously with three weekly cycles of paclitaxel/carboplatin (TC).

Methods: We included 32 patients having recurrent EOC who were previously given 3 weekly TC. The subjects administered bevacizumab 10 mg/kg per two weeks in addition to weekly paclitaxel 80 mg/m2, following that carboplatin AUC 2 on the 1st, 8th, and 15th days of a 28-day cycle for six scheduled cycles. All participants in the study received bevacizumab on a maintenance basis (15 mg/kg every three weeks). The toxicity, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) were the primary endpoints.

Results: The ORR was at 62.5%. The median PFS was 14 months, and the 2-year PFS was 34.4%. The median OS was 20 months (95% confidence interval [CI] 16.9-23.1), and the 2-year OS was 37.8%.

Adverse effects associated with treatment were tolerable, with just a single patient (3.1%) developing grade 4 neutropenia. The most often reported non-hematological side effect was grade 3 hypertension, which occurred in seven patients (21,9%).

Conclusion: Bevacizumab in combination with dose-dense weekly TC is effective and tolerated properly in patients with recurring EOC previously treated with TC administered every three weeks.

Keywords: Bevacizumab, paclitaxel, carboplatin, recurrent epithelial ovarian carcinoma

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Introduction:

The most prevalent malignant tumor in gynecology is ovarian epithelial carcinoma [1]. Ovarian cancer is one of the commonly prevalent kinds of cancer and the main trigger of death related to cancer [2]. It is the seventh most prevalent cause of gynecological mortality related to cancer globally [3,4,5].

Regrettably, the majority of epithelial ovarian cancers (EOC) appear at a late stage (75% stages III & IV). Seventy–eighty% of patients will relapse, necessitating palliative chemotherapy, as a second line, in order to preserve quality of life and delay disease development [6]. Resistance to platinum is linked to a poor outcome in recurrent EOC patients [7,8].

Additionally, conventional treatment techniques, such as chemotherapy and surgery, have produced poor results in recurrent EOC, with median progression-free survival (PFS) of 3–4 months and median overall survival (OS) of approximately 12 months reported in the majority of phase III trials [9,10].

Immunohistochemistry and targeted therapies give hope for recurrent EOC patients. Additionally, discovering biomarkers for targeting-therapies is critical for the proper diagnosis and treatment of cancer [1,11, 12].

As a result, developing innovative approaches for detecting EOC early in its course, as well as developing tailored treatment programs for recurring EOC, are critical steps toward increasing clinical effectiveness and safety [13].

The USA Food and Drug Administration (FDA) authorized bevacizumab (Avastin) for the use in conjunction with chemotherapy in treating women having platinum-resistant, recurrent ovarian cancer (ROC). Platinum progression free interval (PFI) was defined as the interval between the last platinum

chemotherapy and progressive disease (PD). Platinum-sensitivity was defined as recurrence greater than 12, while months platinum-resistant disease was defined as progression or recurrence within 6 months, while disease recurrence between 6 and 12 months was defined as intermediate platinum-sensitive disease [14].

The FDA reached its judgment as a result of the results of the phase 3 AURELIA research, which demonstrated that adding bevacizumab to chemotherapy lead to a statistically significant increase in PFS and objective response rate when compared to conventional chemotherapy only [15].

The efficiency and safety of chemotherapy combined with bevacizumab in Korean subjects having ovarian cancer in a real-world context were similar to the findings of a controlled randomized research [16].

7Subsequent phase 3 randomized studies [4,9,17] demonstrated considerably higher survival among the patients of the bevacizumab group in comparison with the chemotherapy group. Additionally, the bevacizumab groups had a much higher percentage of objective response [4,9,17].

Our study is a phase II trial conducted on female patients with recurrent EOC previously treated with three weekly cycles of paclitaxel carboplatin to assess the efficiency and tolerability of bevacizumab 10 mg/kg every two weeks combined with weekly paclitaxel 80 mg/m2, following which carboplatin AUC 2 was given on the 1st, 8th, and 15th days of a 28-day cycle. All participants in the study received bevacizumab on a maintenance basis (15 mg/kg every three weeks).

Patients and Methods:

During the period of December 2016 to January 2020, 32 female subjects having all cases of recurrent EOC including platinum sensitive, platinum resistant and intermediate platinum sensitive patients [14] were recruited in the Clinical Oncology Department at Tanta University Hospital. Patients included were between the ages of 18 and 70 years, have a ≤ 2 performance status (PS) of Eastern Cooperative Oncology Group (ECOG) , have an acceptable reserve of bone marrow (ANC count ≥ 1.5 x 109/L, WBC count ≥ 3.5 x 109/L, hemoglobin ≥ 10 g/dL and platelets ≥ 100 x 109/L), have an acceptable liver function (less than 2 transaminases) and have an acceptable kidney function (creatinine clearance measured ≥ 60 mL/min).

Modified WHO criteria was used to define progressive disease [16]. Additionally, any new pleural effusion or ascites associated with the condition was deemed progressing disease.

Patients having existing serious or secondary malignancy, uncontrolled medical diseases (e.g., uncontrolled hypertension (HTN), past history or presence of thrombosis or hemorrhages, severe peripheral neuropathy, persistent immune-compromised states, uncontrollable infection, clinically significant cardiac disease, non-healing wound, ulcer, or bone fracture) were excluded.

Study Design

This is a prospective single-arm phase II trial conducted at an institution. The procedure was approved by the Ethics Committee of Tanta University's Faculty of Medicine, and an informed consent form was completed by all patients prior to the start of any therapy.

Treatment Plan and Dose Medication

Weekly paclitaxel 80 mg/m2 was administered intravenously over a period of 60 minutes (dissolved in 500 ml 5% glucose), following that, carboplatin AUC2 (in 250 ml of 0.9% saline) was intravenously administered during a period of 30 minutes on the 1st, 8th, and 15th days of a 28-day cycle, as well as bevacizumab 10 mg/kg every two weeks for six planned cycles. Treatment was terminated if the illness progressed or if significant toxicity occurred. All patients in the study received bevacizumab at a dose of 15 mg/kg every three weeks as maintenance medication. Cycles were performed in an outpatient setting. All patients were appropriately treated with antiemetic, antacid, antihistaminic, and corticosteroid medications.

Prior to each cycle, laboratory examinations with normal range organ functions were performed. Throughout the trial, adverse events were tracked. Except for alopecia and weariness, full clearance of any toxicity was necessary. A one-week delay was permitted if any toxicities did not resolve. G-CSF was not permitted for preventive usage except in cases of grade 3&4 neutropenia, both therapeutic and prophylactic. Guidelines for dosage adjustment of chemotherapy were congruent with accepted clinical practice. No dosage decrease of bevacizumab was authorized.

Patient Assessment

Assessment of Clinical Benefit

Every three rounds, tumor response was assessed. Medical history, physical and gynecological examinations, transvaginal ultrasound (TVU), chest, abdomen, and pelvic CT scans, and CA125 measurement were performed before to and throughout therapy. Full and partial response, stable illness, and advancing disease were defined using modified WHO criteria [18], along with the overall response rate, complete and partial responses were included. While the rate of illness control includes full remission, partial remission, and stable disease. CA125 levels were not employed as the only indication of progressing illness in the absence of radiologic or clinical evidence of tumor growth.

Assessment of Toxicity

The severity of toxicity was determined using the National Cancer Institute's standard Nomenclature Guidelines for side effects (NCI-CTC, version 4.0) [19].

Primary and Secondary Endpoints

The study's primary outcomes were overall toxicity and response.

The PFS and total survival were secondary end objectives.

Statistical Analysis:

The Kaplan-Meier technique [20] with SPSS [Statistical package] (version 20) was used to determine (OS) rates from the commencement of bevacizumab with dose-dense weekly paclitaxel (T) and carboplatin (C) until the final visit of follow-up or death. The time interval from the start of bevacizumab with dose-dense weekly T and C and the first indication of disease progression or death in the absence of disease progression was defined as PFS. The Kaplan–Meier technique was used to evaluate OS and PFS [20], with the log-rank test used to determine statistical significance. The mean and standard deviation of quantitative data were estimated. The exact procedure was used to compute the 95 percent confidence intervals (95 percent CIs). For qualitative data, the Chi-square or Likelihood Ratio was utilized; for quantitative data, the ANOVA test was used. All P values were two-tailed; a significance level of 0.05 was used.

Results:

Patient characteristics:

Table 1 lists the basic demographic and medical characteristics of all participants. The mean of the age of the patients was 57.07 years (Ranging 35- 70 years). At first presentation, 78.13% of all patients had a stage III or IV pathological subtype, and 26 patients (81.25%) had a serous pathological subtype. over half of the patients suffered a grade III tumor (19 patients, 59.4%). The majority of patients had an ECOG performance level of 1. (71.9%).

Treatment Administration

A total of 174 cycles of bevacizumab in addition to weekly paclitaxel and carboplatin were given with a median of 5.4 cycles ranging from 3 to 6) per patient. All the studied patients continued maintenance therapy as bevacizumab 15 mg/kg every 3 weeks. No dosage reductions were seen, and only two individuals had dose delay of weekly paclitaxel and carboplatin for one week. Bevacizumab dose reduction was not permitted.

Patients' response to those drugs

The total response rate (20/32) was 62.5% (including full and partial responses). Overall response rates were 33.3% (39) for platinum-resistant patients, 60% (6/10) for intermediate platinum-sensitive patients, and 84.6% (11/13) for platinum-sensitive patients, respectively, with one (11.1%), two (20%), and five (38.46%) patients achieving complete response (CR, confirmed by PET- study). Stable disease (SD) was observed in two (22.22) cases that were platinum-resistant, two (20%) cases that were intermediate platinum-sensitive, and two (15.38%) cases that were platinum-sensitive, whereas progressive disease (PD) was observed in four (44.4%) platinum-resistant patients, two (20%) intermediate platinum-sensitive patients and two (15.38%) platinum-sensitive patients (Table 2). Six participants progressed according to the research protocol.

Survival

As previously stated under patients and methods, all of our patients were followed on a regular basis, and no one was lost to follow-up throughout this investigation. Mean PFS was 18.6 months (95% CI 15.1-22.0). Median PFS was 14 months (95%CI, 11.2-16.8), 2-year PFS was 34.4% (Fig.1).

During the observation period, fourteen patients died. Mean OS was 23.5 months (95%CI 20.4-26.5), and Median OS was 20 months (95%CI 16.9-23.1), 2-year OS was 37.8% (Fig.2).

Toxicity

This regimen's toxicity profile was well tolerated in our research, with just one (3.1%) and eight (25%) patients experiencing grade 4 and grade 3 neutropenia, respectively. Two patients (6.25%) had grade 3 anemia, while two patients (6.25%) developed grade 3 thrombocytopenia.

Hypertension was the most often occurring grade 3 non-hematological adverse event, occurring in seven (21.9%) of the patients in our research (Table 3). One patient (3.1%) died as a result of treatment-related complications owing to large intestine rupture.

Table 3. Hematologic and non-hematologic Grade 3&4 toxicity of the bevacizumab in addition to dose-dense weekly paclitaxel and carboplatin in the management of the 32 patients with platinum-resistant/sensitive recurrent EOC

Toxicity	Grade 3 no. (%)	Grade 4 no. (%)
Non-hematologic Toxicity		
Anorexia	3 (9.4)	0.0
Stomatitis/ pharyngitis	2 (6.3)	0.0
Nausea/vomiting	3 (9.4)	0.0
Peripheral neuropathy	4 (12.5)	0.0
Proteinuria Bleeding	1 (3.1)	0.0
Diarrhea	1 (3.1)	0.0
GI perforation	2 (6.3)	0.0
Thromboembolic event	1 (3.1)	0.0
Congestive heart failure	2 (6.3)	0.0
Leukoencephalopathy syndrome	1 (3.1)	0.0
Hypertension	6 (21.9)	0.0
Hematologic Toxicity		
Neutropenia	8 (25.0)	1 (3.1)
Anemia	2 (6.3)	0.0
Thrombocytopenia	2 (6.3)	0.0

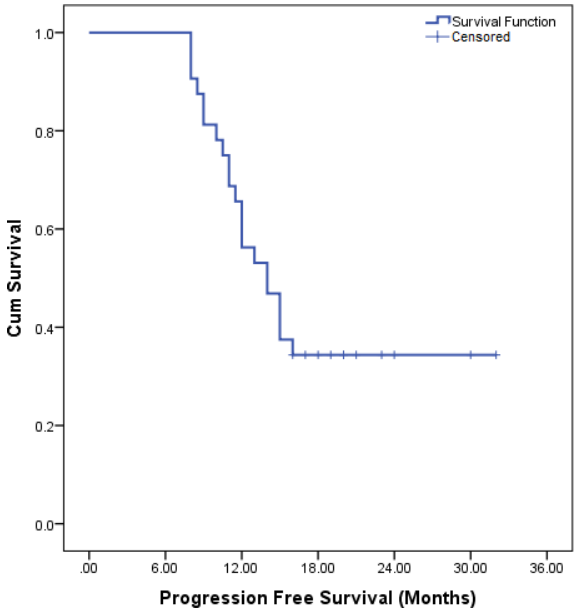

Figure 1. Kaplan–Meier curve of PFS

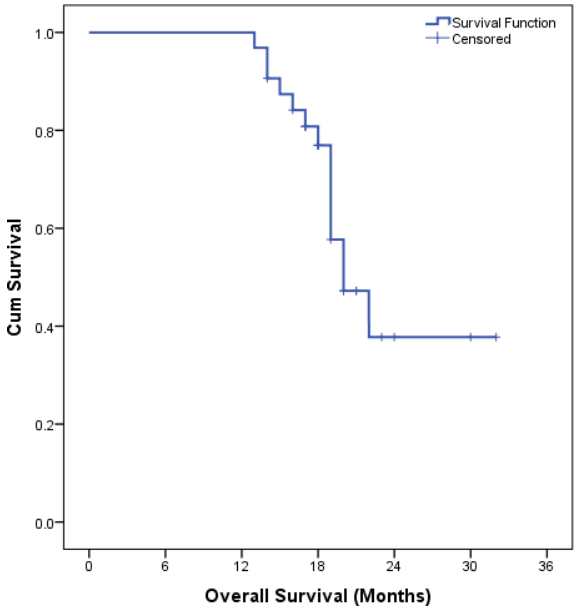

Figure 2. Kaplan–Meier curve of OS. Median OS time was 20 months

Table 1. Demographic characteristics at baseline

Characteristic	Type								P-value
	Platinum Resistant		Intermediate platinum sensitive		Platinum sensitive		Total		
	N= 9	%	N= 10	%	N= 13	%	N= 32	%	
Age (years)									
Median	60.0		64.0		59.0		60.0		
Mean	57.8		61.4		58.0		57.1		0.243
Range	40- 70		35- 70		38- 70		35-70		
FIGO stage									
Stage I	1	11.1	1	10.0	2	15.4	4	12.5	
Stage II	1	11.1	1	10.0	1	7.7	3	9.4	0.908
Stage III	3	33.3	6	60.0	7	53.8	16	50.0	
Stage IV	4	44.5	2	20.0	3	23.1	9	28.1	
Pathological type									
Serous	8	88.9	8	80.0	10	76.9	26	81.2	
Endometroid	1	11.1	0	0.0	1	7.7	2	6.3	0.627
Mucinous	0	0.0	1	10.0	1	7.7	2	6.3	
Clear cell	0	0.0	1	10.0	1	7.7	2	6.2	
ECOG performance Status									
0	2	22.2	3	30.0	4	30.8	9	28.1	
1	5	55.6	4	40.0	6	46.1	15	46.9	0.968
2	2	22.2	3	30.0	3	23.1	8	25.0	
Tumor Grade									
Grade I	1	11.1	1	10.0	2	15.4	4	12.5	
Grade II	2	22.2	2	20.0	5	38.5	9	28.1	0.800
Grade III	6	66.7	7	70.0	6	46.1	19	59.4	

Table 2. Tumor response to bevacizumab in addition to dose-dense weekly paclitaxel and carboplatin

Response	Type						Total	
	Platinum resistant		Intermediate platinum sensitive		Platinum sensitive			
	N	%	N	%	N	%	N	%
Complete response (CR)	1	11.1	2	20.0	5	38.5	8	25.0
Partial response (PR)	2	22.2	4	40.0	6	46.1	12	37.5
Stable disease (SD)	2	22.2	2	20.0	2	15.3	6	18.7
Progressive disease (PD)	4	44.4.0	2	20.0	0	0	6	18.8

Discussion:

Ovarian cancer has a poor prognosis, roughly at 12 months. Until date, the molecular pathways driving ovarian cancer carcinogenesis and prognosis have remained largely unknown [3]. The majority of participants having end stages EOC will relapse at some point (the chance of recurrence after initial treatment is between 60% and 70%) and will need palliative chemotherapy in the second line [5,21,22,23]. Second-line palliative chemotherapy has been shown to be superior to optimal supportive treatment in recurrent EOC patients, with the goal of preserving an adequate quality of life, controlling symptoms, and, if feasible, extending longevity [16, 24,25].

Due to their observed synergistic effects, combining bevacizumab with chemotherapy may provide the most benefit [26]. Chemotherapy, on the other hand, may have antiangiogenic effects [27] and stabilize the tumor vasculature, increasing sensitivity to the effects of later VEGF-blocking treatment [28].

We utilized bevacizumab 10 mg/kg every two weeks combined with weekly paclitaxel 80 mg/m2, following which carboplatin AUC 2 was given on the 1st, 8th, and 15th days of a 28-day cycle for six scheduled cycles, until severe toxicity or disease progression necessitated withdrawal. All patients in the study received bevacizumab at a dose of 15 mg/kg every three weeks as maintenance medication. Over 75% of our patients underwent six cycles, and the treatment schedule and dosages were chosen in accordance with the results of a prior AURELIA open label randomized phase III study [15]. This therapy schedule appears to be clinically effective (81.2 % disease control rate). This is in consistency with Takasaki et al., [6] earlier published findings who reported disease control rate of 88.9% for the arm of patients received bevacizumab plus chemotherapy in recurrent EOC patients (88.9%) which is statistically significantly higher in comparison with the chemotherapy alone group (41,4%). Similarly, Pujade-Lauraine et al, [15] reported that bevacizumab added to chemotherapy significantly enhanced ORR in comparison to chemotherapy only.

In this study, we observed a median PFS of 14 months in patients with recurrent EOC treated with bevacizumab and chemotherapy (95% CI, 11.2- 16.8).

In 2020 Pfisterer et al, [9] in their multi-center, randomized, open-label, phase 3 trial, held in 159 different academic centers in France, Australia, Germany, Austria, and the United Kingdom reported a median PFS of 13·3 months (95% CI 11·7–14·2) in experimental group of patients (345 patients) with recurrent EOC treated with chemotherapy plus bevacizumab.

Coleman et al, [17] recorded a median PFS of 13.8 months for the arm of patients received bevacizumab plus chemotherapy. PFS showed significantly longer median with bevacizumab added to chemotherapy (13.8 months [13.0–14.7]) compared to chemotherapy alone (10.4 months [95% CI 9.7–11.0]). Similarly, Takasaki et al,[6] in their single- institutional retrospective study at National Defense Medical College Hospital, Tokorozawa, Saitama, Japan on 47 patients demonstrated that the group of patients received chemotherapy plus bevacizumab regimens had an improved PFS over that in the group of patients received chemotherapy alone ($p < 0.01$). They concluded that chemotherapy plus bevacizumab was the better prognostic factor of PFS [hazard ratio (HR) 0.17, $p < 0.01$]. This is consistent with previous published AULERIA trial which showed that combining bevacizumab with cytotoxic agents enhanced PFS for patients with recurrent EOC [15].

In our study, the median OS of 20 months (95%CI 16.9-23.1), was better than reported in the AURELIA open label randomized phase III Trial which reported OS of 16.6 months (95% CI, 13.7 to 19.0) in chemotherapy plus bevacizumab arm [15]. This disparity may be explained by the inclusion of participants in the AURELIA research who were switched from chemotherapy only to bevacizumab at the time of advancement. This finding was attributed to one of the reasons for the lack of improvement in OS in the combination of bevacizumab and cytotoxic drugs arm in patients with recurrent EOC. However, we excluded crossover from chemotherapy to a bevacizumab-containing regimen during illness progression in our trial.

Our study's median OS of 20 months (95% CI 16.9-23.1) was lower than Takasaki et al. [6] chemotherapy plus bevacizumab arm, where the median OS was not met. The reason for this might be because Takasaki et al. [6] findings were impacted by a unique idea of

bevacizumab beyond progression. Beyond progression, bevacizumab is administered continuously in the event of recurrence following treatment with a bevacizumab-containing regimen. This technique was chosen in light of discoveries showing cancer cells enhanced metastasis in the presence of short-term anti-angiogenesis therapy [29]. However, in our study, bevacizumab was only given until progression was observed. Our median OS of 20 months (95%CI 16.9-23.1) was also lower than the median OS of Pfisterer et al, [26] chemotherapy plus bevacizumab experimental group, in which the median OS was 31.9 months (95% CI 28.5–34.8). This difference may suggest that carboplatin–pegylated liposomal doxorubicin–bevacizumab used in Pfisterer et al, [9] experimental group may be more suitable regimen than our platinum-paclitaxel and antiangiogenic treatment regimen for patients with ROC. Similarly, Coleman et al, [17] reported in their study a better median OS in the chemotherapy plus bevacizumab group of 42.2 months (95% CI 37.7–46.2) than reported in our study (20 months). Our study's findings vary from those previously stated Coleman et al, [17] multicenter, randomized, open-label, phase 3 trial in which 674 women were enrolled in this study being a prospective one arm phase II single institution study that included only 32 patients with recurrent EOC.

Toxicity is a critical factor to consider when treating individuals with recurrent illness with chemotherapy. This regimen's toxicity profile was well tolerated in our research, with just one (3.1%) and eight (25%) patients experiencing grade 4 and grade 3 neutropenia, respectively. Two patients (6.25%) had grade 3 anemia, while two patients (6.25%) developed grade 3 thrombocytopenia.

Hypertension was the most often occurring grade 3 non-hematological adverse event, occurring in seven (21.9%) participants in our research. One patient (3.1%) died as a result of treatment-related complications owing to large intestine rupture. In a phase 3 study, Pfisterer et al. [9] used bevacizumab and platinum-based combinations to treat ROC. Similarly, their results discovered that the most often reported grade 3 or 4 negative outcomes were hypertension [27%] of the experimental group versus [20%] of the standard group and neutropenia (40 [12%] vs 73 [22%], respectively). Severe complications emerged in 33 (10%) of 332 experimental participants group and 28 (9%) of 329 of the standard patients' group. One patient in the experimental group died as a result of treatment (1%; large intestinal perforation) as well as two of the patients of the standard group (1%; one of intracranial hemorrhage and one of osmotic demyelination syndrome). Coleman et al. [17] used bevacizumab and paclitaxel–carboplatin treatment in their multicenter, open-label, phase 3 study. They showed that in chemotherapy plus bevacizumab group, 317 (96%) out of 325 patients experienced at least one grade 3 or worse side effects. In the chemotherapy plus bevacizumab group, the most frequently reported adverse events were hypertension (39 [12%], fatigue in 27 [8%], and proteinuria in 27 [8%]. There were nine (1%) treatment-related deaths in the chemotherapy plus bevacizumab group (febrile neutropenia [n=1], infection [n=1], secondary malignancy [n=1] and myelodysplastic syndrome [n=1]; deaths not classified using CTCAE terms: not specified [n=1], disease progression [n=3] and sudden death [n=1]).

Additionally, the frequency of our toxicities was somewhat nearly similar to that reported by Pujade-Lauraine et al, [15] and lower than that reported by Takasaki et al study [6].

Interestingly, hypertension, the most often reported grade 3 non-hematological adverse event, did not have a significant incidence rate, being documented in just 7 (21,9%) individuals in our research. Similarly, Pujade-Lauraine et al, [15] recorded ≥grade 2 hypertension in 36 (20%) patients in the chemotherapy plus bevacizumab group.

In conclusion, bevacizumab in combination with chemotherapy enables the treatment of platinum-resistant ROC efficiently and safely with low damage in extensively pretreated EOC patients. This conclusion is significant since platinum resistance eventually becomes the primary issue for the majority of individuals with ovarian cancer. However, definitive findings concerning our regimen's advantage in treating platinum-resistant illness required the analysis of prospective randomized trials involving a greater number of patients.

The field of ROC is a popular issue, with studies emerging to uncover predictive biomarkers to identify individuals most likely to benefit and to provide each patient with individualized therapy. A prospective randomized clinical study including targeted therapies and newer types of pharmaceuticals that target all isoforms of vascular endothelial growth factor (VEGF) is required to see if it may reverse acquired clinical platinum resistance in patients. However, insufficient resources make it difficult to perform repeated EOC procedures on recurring EOC patients in our nation.

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