

Addition of bevacizumab to adjuvant chemotherapy paclitaxel and carboplatin for cancer ovary. is there a difference?

Abstract

Purpose: Angiogenesis plays a role in the biology of ovarian cancer. Bevacizumab is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF). The aim of this study was to assess the effect of addition of bevacizumab to the standard therapy in women with ovarian cancer as regard survival and toxicity. **Methods:** Thirty women with ovarian cancer were enrolled in this prospective study. Half of the patients were randomly assigned to standard chemotherapy (carboplatin and paclitaxel) given every 3 weeks for 6 cycles (chemotherapy group; CT) and the other half received the same regimen plus bevacizumab, given concurrently every 3 weeks for 6 cycles (bevacizumab-chemotherapy group; BEV-CT). Outcome measures included progression free survival (PFS), overall survival (OS) and toxicities after follow up at least 2 years.

Results: 86.7% of CT group patients had serous histologic type, while 93.4% in BEV-CT group. Eastern Cooperative Oncology Group (ECOG) performance status scale was 0 & 1 in all CT group patients, but 93.4% for BEV-CT group. PFS at 24 months was 18.2 months in CT group comparing with 21.8 months in BEV-CT group ($P = 0.043$). The median OS was 22.8 months in CT group comparing with 24 months in BEV-CT group, with no significant difference ($P = 0.143$). Bevacizumab was associated with more toxic effects. Hypertension of grade ≥ 2 was 26.7% versus 6.6% in CT group. Proteinuria and gastrointestinal (GI) perforation grade ≥ 2 were more in BEV-CT group. While vomiting, diarrhea and abdominal pain were more in the CT group.

Conclusion: Bevacizumab was found to improve PFS in patients with ovarian cancer. However, there is no significant difference as regard OS with tolerated toxicities. Further researches are needed to identify predictive and prognostic markers of response to bevacizumab in order to help patient selection and treatment benefit.

Keywords: Ovarian cancer, Bevacizumab, Survival, Toxicity

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Yasser M Saleh,^{1,3} Waleed Hammam^{2,3}

¹Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt

²Lecturer of Clinical Oncology, oncology department, Kaser El Eini, Cairo University, Egypt

³Consultants Clinical Oncology, Saudi-German Hospital Group, KSA

Correspondence: Yasser M Saleh, Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt, Tel +201067849030, Email dr_yassarms@yahoo.com

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Introduction

Ovarian cancer is considered the 4th most common cause of cancer-related deaths in women, with an about 200.000 new cases and 125.000 deaths occurring yearly all over the world. Symptoms diagnosing the disease are non-specific, including abdominal discomfort or fullness, dyspepsia and bloating, which may be similar to other conditions thus resulting in a delay in diagnosis.¹ About 90% of all ovarian cancers are epithelial ovarian cancer (EOC) and arising from the ovarian surface epithelium or mullerian derivatives.² EOC is highly curable when it is confined to the ovaries, with expected 5-year survival up to 90%. However, it is rarely diagnosed at an early stage because the disease causes few specific symptoms when it is localized to the ovary. More than 70% with EOC present with advanced stage III or IV, which is associated with high morbidity and mortality.³ Current management of advanced disease includes surgical tumor debulking, followed by adjuvant platinum-and taxane-based chemotherapy.⁴ An approach to improve the outcome of treatment in EOC has focused on modifying the dose, schedule and route of administration of chemotherapy. The use of intra-peritoneal chemotherapy has been reported to improve outcomes although, an increase in the toxicity.⁵ Recently, the administration of intravenous (IV) paclitaxel on a weekly schedule improves PFS and OS.⁶ Another recently approach

is the administration of chemotherapy in the neoadjuvant setting, before surgical resection in contrast to conventional postoperative chemotherapy. Although it is associated with optimal cytoreduction and lower postoperative adverse events, it did not improve OS.⁷ Therefore, the combination of carboplatin and paclitaxel remains the standard chemotherapy regimen in advanced ovarian cancer, however, OS for patients with advanced disease is poor and the 5-year survival is only 27%.⁸ Also, the majority of women with advanced stages recur within 5 years with emerging a drug resistance.³ Angiogenesis was found contributing to solid-tumor growth and metastasis.⁹ EOC cell lines were found frequently expressing the VEGF.¹⁰ In literatures, high serum VEGF levels correlated with a higher risk of death or recurrence in ovarian cancer.¹¹ Also, it has been implicated in the peritoneal dissemination and development of malignant ascites¹² which is inversely linked with survival.^{13,14}

One of the promising approaches in the treatment of EOC is the inhibition of such angiogenesis, which is thought to enhance the effects of chemotherapy by normalization of primitive tumor vasculature, increasing tumor oxygenation and enhancing delivery of cytotoxic drugs.¹⁵ Phase- II trials of bevacizumab in ovarian cancer patients had revealed tumor responses and prolonged disease-free progression in those patients.¹⁶⁻¹⁸ This prospective study was planned to assess

adding of bevacizumab to the adjuvant standard drugs (paclitaxel and carboplatin) as a first-line treatment of EOC as regard OS, PFS and toxicities.

Methods

Patients

This prospective study was done in the period between January-2011 and December- 2015 in Saudi-German Hoapitals group at KSA. This study enrolled 30 female patients with ovarian cancer that confirmed histologically to be [FIGO] stage II - III EOC. Inclusion criteria were; age > 18 years and < 70 years, ECOG performance status of 0 - 2 and adequate coagulation values, liver and renal functions. The excluded patients who had received anti-cancer drugs before, history of bowel obstruction related to the underlying disease, prior radiotherapy to the pelvis or abdomen, surgery within 4 weeks before starting the study, history or evidence of thrombotic or hemorrhagic disorders, un-controlled hypertension and active cardio-vascular disease.

All the patients provided a written informed consent before enrollment in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and local laws and regulations of our country.

Randomization and treatment

Randomization was done by a direct calling of the patients by telephone with stratification according to Gynecologic Cancer Intergroup (GCIG), International Federation of Gynecology and Obstetrics (FIGO) stage and planning of an interval (≥ 4 weeks) between surgery and start of chemotherapy. Patients were randomly distributed with a 1:1 ratio to receive paclitaxel (175 mg per square meter of body-surface area) and carboplatin (area under the curve; AUC= 5), given every 21 days and repeated for 6 cycles (standard chemotherapy group; CT group). The other group took the same protocol with addition of bevacizumab drug (7.5 mg/kilogram of body weight), concurrently given every 21 days and repeated for 6 cycles (BEV-CT). Bevacizumab dose reduction was not permitted. Chemotherapy dose modification guidelines were consistent with standard clinical practice. Patients in the BEV-CT group received standard-of-care treatment (without bevacizumab) at progression. Bevacizumab was discontinued in patients with any grade of GI perforation.

Assessment

Assessments were done at the same time points in both groups. Patients were clinically assessed with measurements of cancer antigen 125 (CA-125) before each cycle of chemotherapy, repeated every 6 weeks in the first year 1, then every 3 months during the second year. In cases with disease progression, these assessments were repeated every 6 months. At baseline, after randomization computed tomography or magnetic resonance imaging was done, every 6 months until disease progression. All assessments were reviewed by the same investigator, who did not know the treatment assignments. Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Treatment outcome and statistical analysis

The main outcomes of interest were PFS, OS and toxicities in both groups. PFS was estimated from the start of randomization to the start

of any indicator of a disease progression or death, whichever happened first; patients' data that had no disease progression were censored as of the date of their last follow-up. Sensitivity analyses were done in which the data of patients who had no disease progression were censored at the date of last imaging evaluation. Disease progression was considered according to the Response Evaluation Criteria in Solid Tumors (RECIST)¹⁹ recommendations depending on clinical or symptomatic, radiologic indicators of disease progression and did not include asymptomatic progression on the basis of CA-125 measurements. OS was measured from the start of randomization to the occurring of death from any cause; data of patients who still alive were censored at the date of the patient was last documented to be alive.

The principle analysis was conducted for measuring the difference in the distribution of PFS and OS between the two groups using of an un-stratified log-rank test. Other planned analyses were used including a log-rank test that stratified for factors used for randomization and flexible parametric survival models²⁰ to smooth survival curves and measure the survival differences with the use of all the collected survival data. Safety analyses included the patients who had administered at least one cycle treatment of the planned protocol. All P values were considered two-sided.

Results

Patients

Both treatment groups were well balanced according to the baseline patients' characteristics. Their median age was 47.5 & 47.7 years for CT & BEV-CT groups, respectively. All patients of the CT group (100%) had an ECOG performance status of 0 & 1, while 14 patients (93.33%) were in the BEV-CT group. Other baseline patient's characteristics including histology & grade at diagnosis, FIGO staging and presence of ascites are summarized in (Table 1).

Efficacy and survival

The cut-off date for the primary analysis was December 2015. In the CT group, the median duration of follow-up was 20.0 months versus 24 months in the BEV-CT group estimating a median follow-up of 23.4 months. It was found that disease progression and deaths had occurred in 50% of patients (n=15; 9 in CT group & 6 in BEV-CT group) during their follow up. The median PFS was found 18.2 months in CT group versus 21.8 months in the BEV-CT group. Our study met its main objective, showing a significant improvement in PFS with the addition of bevacizumab to the standard chemotherapy in ovarian cancer patients using Kaplan-Meier curve ($P = 0.043$) (Figure 1). It was found that the median OS in the CT group was 22.8 months while 24.0 months in the BEV-CT group and this was statistically in-significant ($P = 0.143$) (Figure 2).

Toxicity

It was noticed that both hypertension (grade ≥ 2) and proteinuria were higher in the BEV-CT group. One patient (6.67%) in the BEV-CT group had Grade ≥ 2 GI perforation while none in patients received CT alone. There were smore adverse events (e.g., vomiting, diarrhea and abdominal pain) in CT group than BEV-CT group while thromboembolic events, bleeding and peripheral neuropathy were more in the BEV-CT group. Grade 3 thrombocytopenia had equal incidence in both groups while grade 3 neutropenia and anemia were more in the CT group (Figure 3).

Table 1 Baseline Patients Characteristics in Both Groups

Character	CT group (n = 15)	BEV-CT group (n = 15)
Age (years): Median (range)	47.5 (30 - 69)	47.7 (31 - 65)
Histology at diagnosis: Serous adenocarcinoma	13 (86.67)	14 (93.33)
Endometrioid	2 (13.33)	1 (6.67)
Histologic grade at diagnosis:		
1	2 (13.33)	1 (6.67)
2	3 (20.0)	3 (20.0)
3	10 (66.67)	11 (73.33)
Stage: 2	8 (53.33)	7 (46.67)
3	7 (46.67)	8 (53.33)
ECOG performance status:		
0	11 (73.33)	13 (86.67)
1	4 (26.67)	1 (6.67)
2	0 (0.0)	1 (6.67)
Ascites	4 (26.67)	5 (33.33)

Data (other than age) are presented as number (%). ECOG, Eastern Cooperative Oncology Group.

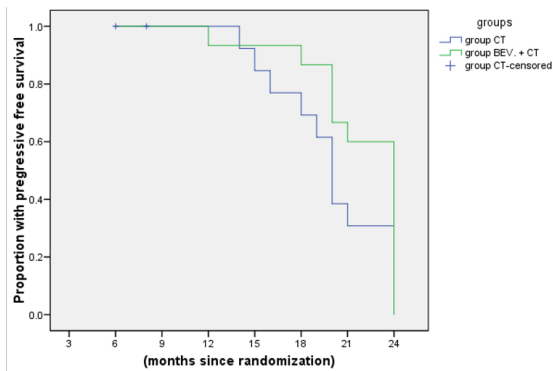


Figure 1 Progression free survival (PFS) curve.

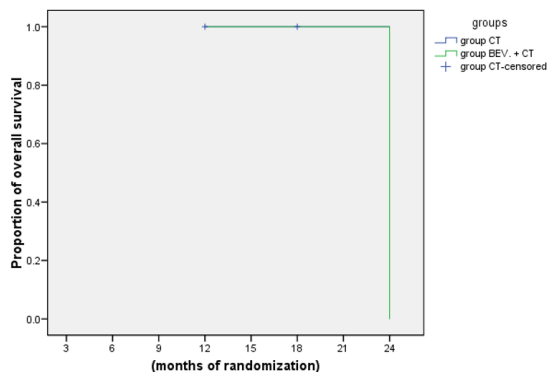


Figure 2 Overall survival (OA) curve.

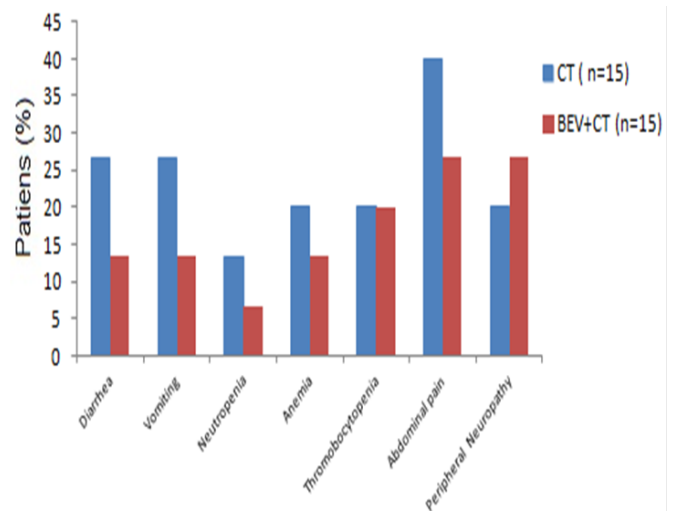


Figure 3 Adverse events of both groups.

In the CT group, there were 2 deaths (13.33%) that were not related mainly to disease progression and were resulting from infection with neutropenia, while in the BEV-CT group there were no any deaths (Table 2). In this study, nine patients had ascites at baseline; four patients (26.67%) were found in the CT group and had been underwent to paracentesis during the study treatment while five patients (33.33%) received BEV-CT (only 2 patients underwent to paracentesis after starting treatment).

Table 2 Adverse Events in Both Groups

Adverse Events	CT group (n = 15) Number (%)	BEV-CT group (n = 15) Number (%)
Hypertension grade ≥ 2	1 (6.67)	4 (26.67)
Proteinuria	0 (0.0)	1 (6.67)
GI perforation grade ≥ 2	0 (0.0)	1 (6.66)
Bleeding	1 (6.67)	3 (20.0)
Venous thromboembolic events	2 (13.33)	4 (26.67)
Congestive heart failure	0 (0.0)	1 (6.67)
Death	2 (13.33)	0 (0.0)

GI, gastrointestinal.

Discussion

Angiogenesis was found contributing to solid-tumor growth and metastasis.⁹ EOC cell lines were found frequently expressing the VEGF.¹⁰ High serum VEGF levels correlated with a higher risk of death or recurrence in ovarian cancer.¹¹ Bevacizumab is a recombinant monoclonal antibody against VEGF. The activity of single-agent bevacizumab and the ability to combine it with chemotherapy in recurrent ovarian cancer led to studies exploring its use as a front-line therapy. This prospective study was planned to assess adding the bevacizumab to the adjuvant chemotherapy (paclitaxel and carboplatin) as a first-line treatment of EOC as regard OS, PFS and toxicities. Our study showed a significant difference of PFS in BEV-CT group compared with CT group ($p = 0.043$) and this was consistent with Micha et al. and Penson et al.^{21,22} They showed that the addition of bevacizumab to front-line chemotherapy is feasible and well tolerated with encouraging activity with significant PFS in the BEV-CT group. On the other hand, the Gynecologic Oncology Group (GOG-0218) trial showed no significant difference in PFS, meanwhile it became significantly improved when bevacizumab was maintained as a single agent.

However, it is important to note that no significant improvement in OS has been reported between the two groups in this study ($P = 0.143$) and this result was consistent with Micha et al., Penson et al., GOG-0218 trial, International Collaboration on Ovarian Neoplasms (ICON7) and Ovarian Cancer Study Comparing Efficacy and Safety of Recurrent Disease (OCEANS).^{21–25}

In the present study, grade 2 hypertension and proteinuria were more common with bevacizumab than with chemotherapy alone. These reported adverse events were consistent with Perren et al.²⁴ whose trial led to the approval by the European Commission of bevacizumab in combination with the standard chemotherapy (carboplatin and paclitaxel) as a front-line treatment for women with advanced ovarian cancer. This was consistent with the safety profile of bevacizumab-containing therapy in previously reported trials in ovarian cancer.^{26, 27} The adverse events possibly related to tumor burden, because these effects are related to cumulative toxicities of carboplatin and paclitaxel, respectively, and also to the increased chemotherapy exposure in the BEV-CT group. However bevacizumab increased the range of adverse events including bowel perforation and hypertension, it did not affect the chemotherapy administration.²⁶ All

these data provide a great evidence for the role of bevacizumab in ovarian cancer treatment. However, a drawback of all these studies was the further reduced ability to detect an OS benefit.

Conclusion

Bevacizumab has demonstrated a significant efficacy benefit in combination with adjuvant standard chemotherapy for ovarian cancer as a first-line treatment. The present study concluded that adding of bevacizumab to the standard chemotherapy gives meaningful improvement of PFS in ovarian cancer patients. However, there was in-significant difference in OS. The safety profile of bevacizumab was as expected in this study. Most AEs recovered over time and no new safety events were noticed. However, more efforts to identify biomarkers with potential predictive and prognostic values in EOC patients treated with bevacizumab are important in selection of patients for therapy and they are recommended to be a subject of ongoing researches.

Acknowledgment

None.

Conflicts of interest

None.

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