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NEO-ADJUVANT VERSUS ADJUVANT USE OF BEVACIZUMAB IN THE MANAGEMENT OF ADVANCED OVARIAN CANCER

N. H. Salah[1*], M. A. Mekkawy[1], H. A. Abou-Taleb[2], M. M. Alaa-Eldin[1], O. A. Nabih[1]

[1]*Clinical Oncology Department Assiut University Hospital Assiut Egypt*
[2]*Department of Obstetrics and Gynecology Assiut University Hospital Assiut Egypt*

Importance: *Ovarian cancer (OC) is the most lethal gynecologic malignancy and is the fifth most common cause of cancer death in women. In June 2018, Bevacizumab was approved by FDA for use with chemotherapy as treatment for women with advanced OC; it is now the most consistently used additional drug in the first-line treatment of OC.* ***Objective:*** *assessing the response, survival, side effects and toxicity of therapy including Bevacizumab in patients who used it as Neoadjuvant line; and those who underwent PDS then adjuvant systemic therapy including Bevacizumab as compared with cases who received only standard post-operative chemotherapy without Bevacizumab.* ***Design:*** *The present study is an interventional prospective case-control study. The study included patients diagnosed with advanced epithelial OC presented to Assiut University hospitals (from June 2018 until April 2021).* ***Setting:*** *Assiut University hospitals (Clinical Oncology Department & Women's Health Hospital outpatient clinics).****Participants:*** *The study included 3 groups of cases:* ***group A:*** *Fifteen patients with clinically* ***resectable tumors****;* ***group B:*** *Seventeen patients with* ***irresectable tumors*** *and* ***control group (C)*** *were 19 cases, were reviewed retrospectively.****Intervention(s): group A:*** *underwent primary surgical resection then received systemic treatment (Adjuvant);* ***group B:*** *were subjected to NACT then underwent assessment for the possibility of surgical resection, after which they continued their adjuvant systemic therapy (Neoadjuvant) and* ***control group (C)*** *received only standard post-operative chemotherapy without Bevacizumab.****Main Outcome(s):*** *Primary outcome: disease free survival (DFS), and overall survival (OS).Secondary outcome: toxicity and side effects of Bevacizumab.* ***Results:*** *There was no significant differences between all study groups as regards characteristics, staging and laboratory data at admission. Comparisons between groups A and B revealed no significant differences as regards DFS, OS, toxicity and side effects.* ***At one-year post-treatment there was a*** *significantly lower CA-125 values in patients who used Bevacizumab (A&B) than those who used conventional chemotherapy (group C): p=0.029. The 3 years OS was 25% for Groups (A&B) and only 5% for Group C.* ***Conclusions and Relevance:*** *Using bevacizumab as adjuvant or as neo adjuvant line improved response to chemotherapy and improved overall survival rates without any significant increase in rate of side effects. Using it as adjuvant and as neo-adjuvant produced comparable success rates: taking in consideration that when bevacizumab was used as neo-adjuvant; this was applied to cases in which surgical assessment stated they are more advanced cases or non-surgically optimal: this means that bevacizumab could convert this group to outcome similar to cases that were considered as "optimal for surgical debulking"; thus adding a considerable advantage to its use in this particular type of patients. Studies with larger number of cases may be needed to confirm our findings*

Keywords: *ovarian cancer; Bevacizumab; advanced; neoadjuvant*

INTRODUCTION

Ovarian cancer (OC) is the most lethal gynecologic malignancy and is the fifth most common cause of cancer death in women. The majority of women with ovarian cancer are diagnosed with advanced-stage disease; only 15% of all cases are diagnosed with local

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*Corresponding author: Nada Hassan salah, E-mail: nada.h.salah88@gmail.com

disease[1]. In the first decade of the 21st century, two randomized trials (GOG 114 and GOG 172) demonstrated that, after optimal tumor resection, women who received combination intravenous/intraperitoneal (IV/IP) cisplatin and paclitaxel had significantly better progression-free survival (PFS: 5.7 and 5.5 months) and overall survival (OS:11.0 and 15.9 months) than those who received IV-only regimens[2,3]. Additionally, the GOG-0218 trial demonstrated that using Bevacizumab in the front-line and maintenance setting improved PFS by 3.8 months compared to conventional every-3-weeks carboplatin and Paclitaxel[4].

Chemotherapy is usually given either only after primary debulking surgery (PDS) or as neoadjuvant chemotherapy (NACT) i.e., before and after interval debulking surgery (IDS). The goal of any cytoreductive surgery is to maximally reduce the disease burden, as doing so is well known to improve patient outcomes[5]. However, recent trials have tried to determine whether patients receiving NACT have better outcomes than those receiving only chemotherapy after PDS.

In June 2018, Bevacizumab was approved by FDA for use with chemotherapy as treatment for women with advanced OC who underwent initial surgical resection. Bevacizumab is now the most consistently used additional drug in the first-line treatment of OC and is now being considered by the US FDA as first-line therapy in the USA[6].

The present study aimed at assessing the response, survival, and toxicity of therapy including Bevacizumab in patients who used it as Neoadjuvant line; and those who underwent PDS then adjuvant systemic therapy including Bevacizumab as compared with OC cases who received only standard post-operative chemotherapy without Bevacizumab.

PATIENTS AND METHODS

The present study is an interventional prospective case-control study. The study included patients diagnosed with advanced epithelial OC presented to Assiut University hospitals (Clinical Oncology Department & Women's Health Hospital outpatient clinics) during the period from June 2018 until April 2021.

The study included 51 patients: 32 study cases diagnosed with advanced epithelial OC presented to Assiut University Hospitals and 19 control cases reviewed retrospectively from patients' files at Clinical Oncology Department. Sample size was calculated at the public health department of Assiut University Faculty of Medicine according to the prevalence of OC cases regionally.

Inclusion criteria were

patients diagnosed with OC FIGO stage II-IV by imaging, tumor markers and/or biopsy, age more than 18 years old, Performance Score 0-2, chemotherapy naïve and have no contraindication to Bevacizumab as: uncontrolled hypertension, bleeding tendency, ischemic events.

Exclusion criteria were

patients previously received chemotherapy or radiotherapy to any part of the abdomen or pelvis, uncontrolled infection, significant cardiovascular disease, patients with active bleeding or conditions associated with high risk of bleeding, and patients with a history of central nervous system (CNS) disease.

A copy of the proposal received approval from The Ethics Review Committee of Assiut University to carry out the present study. Informed consent was obtained from the patients prior to enrolment into the study.

Intervention

Study cases were 32 who received target therapy Bevacizumab added to the standard chemotherapy regimen (Paclitaxel and carboplatin), were further subdivided into two subgroups:

- **Group A:** Fifteen patients with clinically **resectable tumors**; underwent primary surgical resection then received systemic treatment (Adjuvant)
- **Group B:** Seventeen patients with **irresectable tumors** were subjected to NACT then underwent assessment for the possibility of surgical resection, after which they continued their adjuvant systemic therapy (Neoadjuvant).

The control group (C)

were 19 cases, who received only standard post-operative chemotherapy without Bevacizumab, were reviewed retrospectively. The standard chemotherapy regimen received was Paclitaxel (175 mg/m2 of body surface area), followed by carboplatin (area under the curve (AUC) 5). In the patients who developed dose-limiting peripheral neuropathy or hypersensitivity, Paclitaxel was replaced with paclitaxek.

Study cases who received 3 cycles of therapy were followed by mid-cyclic assessment with MRI pelvi-abdomen and serum CA125 level then continued another 3 cycles if there was response to treatment. In case of neoadjuvant treatment, patients underwent surgery after 3 cycles of systemic therapy for possibility of surgical resection, then continued their adjuvant cycles after surgery for another 3 cycles.

Patients were followed up for 2 years, for assessment of survival, and the delayed toxicity, after finishing the planned treatment course, every 3 months.

Outcome

Primary outcome: disease free survival (DFS), and overall survival (OS).

Secondary outcome: toxicity and side effects of Bevacizumab

Statistical Analysis

All statistical calculations was done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data were statistically described in terms of mean ± SD and median (range) when not normally distributed. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using student t test for normally distributed data and Mann Whitney U test for non-normally distributed data. For comparing categorical data, Chi square ($\chi 2$) test was performed. Fisher Exact test was used instead when the expected frequency is less than 5. Kaplan-Meier's method with log rank test was used for overall and progression free survival analysis. P-value is always 2 tailed set significant at 0.05 level.

RESULTS AND DISCUSSION

Results

The pre-treatment clinical and laboratory data characteristics of 51 women with ovarian cancer were shown in **table 1** comparing study groups (A&B) with the control group (C); there was no significant difference between the two compared groups except for the type of primary surgery which was dependent on patients' selection criteria for using a neo-adjuvant line. Comparison between group A and B for the same clinical and laboratory variables were also done but no significant differences was seen.

Treatment protocols in cases of groups A and B who received Bevacizumab is clarified in **Fig. 1**

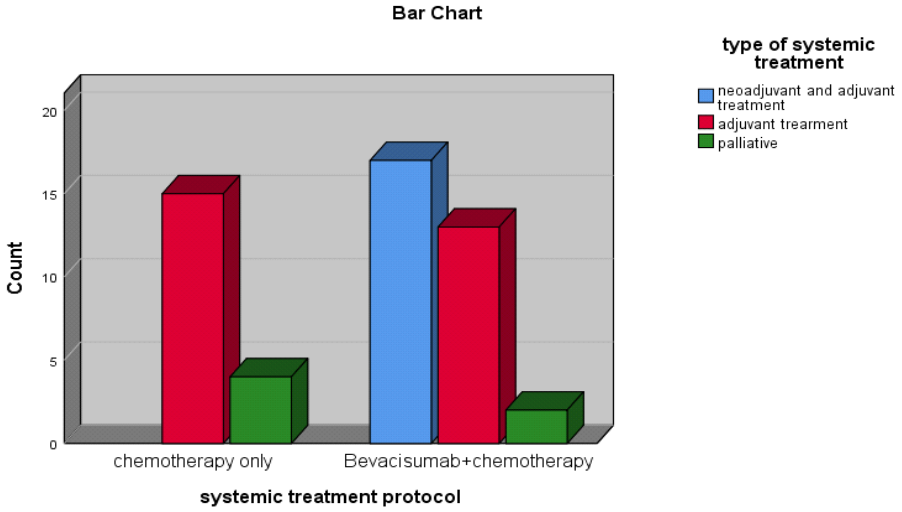

Fig. 1: Treatment protocols among 51 women with ovarian cancers.

Table 1: Comparison of clinical data in study cases (A+B) Vs control group C.

Baseline data	Group A+ B (n=32)		Group C (n=19)		P value
Age (years)					0.839
• Mean ± SD	56.34 ± 10.09		55.74 ± 10.60		
• Range	26 - 74		32 - 69		
Using contraception	12	(37.5)	5	(26.3)	0.413
Type of contraception					0.786
• COCs	6	(50.0)	1	(20.0)	
• IUD	4	(33.3)	3	(60.0)	
• Implants	2	(16.7)	1	(20.0)	
Median parity	4 (2 – 7)		5 (3 – 8)		**0.012**
Smoking	10	(31.3)	3	(15.8)	0.323
Menopausal state					0.370
• Premenstrual	8	(25.0)	7	(36.8)	
• Postmenstrual	24	(75.0)	12	(63.2)	
Positive family history	3	(9.4)	0	(0.0)	0.285
Associated comorbidities	9	(28.1)	7	(36.8)	0.517
• Diabetes	8	(25.0)	4	(21.1)	1
• Hypertension	7	(21.9)	4	(21.1)	1
Clinical presentation					
• Abdominal pain	24	(75.0)	15	(78.9)	1
• Abdominal distension	15	(46.9)	10	(52.6)	0.691
• Vaginal bleeding and/or discharge	1	(3.1)	1	(5.3)	1
• Pelvic pain	3	(9.4)	1	(5.3)	1
• Others					0.129
▪ Accidentally discovered	2	(6.3)	0	(0.0)	
▪ Generalized fatigue	0	(0.0)	2	(10.5)	
1ry surgery (before systemic treatment)					**0.005**
• Radical surgery	9	(28.1)	11	(57.9)	
• Incomplete surgery	5	(15.6)	6	(31.6)	
• Biopsy or cytology only	18	(56.3)	2	(10.5)	
Staging					**0.270**
• FIGO 2A	0	(0.0)	2	(10.5)	
• FIGO 3A	6	(18.8)	4	(21.1)	
• FIGO 3B	6	(18.8)	3	(15.8)	
• FIGO 3C	15	(46.9)	5	(26.3)	
• FIGO 4	5	(15.6)	5	(26.3)	
CA125 (U/ml)					0.959
• Median (range)	741 (0 – 4185)		745 (48 – 3897)		
CEA (ng/ml)					0.665
• Median (range)	2.8 (0.4 – 50.0)		2.7 (0.9 – 110.0)		
CA125/CEA ratio					0.745
• Median (range)	264 (2.4 – 188.2)		319 (1.7 – 2422)		

Quantitative data are presented as median (range). Significance defined by $p < 0.05$.
Group A: cases with adjuvant Bevacizumab; Group B: cases with neo-adjuvant Bevacizumab; Group. C: cases received chemotherapy only.

Comparisons between study groups as regards response and side effects all-over the two years of follow up is shown in details in the following tables. Comparisons between groups A and B had shown no significant difference between the two groups in all items of the comparisons. However, when groups A and B were summated together and compared with group C, the following results were obtained:

In **table 2** during the mid-cyclic follow up, the only significant result was that patients of group (A&B) had significantly more regressive pattern than those of group C.

In **table 3**, the post-cyclic response and side effects were similar with no significant differences between groups (A&B) Vs group C.

The same finding was noted in **table 4;** the 3 months follow up where both types of management had no significant differences in both groups.

When follow up was extended to one-year post-treatment there was a significantly lower CA-125 values in patients who used Bevacizumab (A&B) than those who used conventional chemotherapy (group C); **table 5**.

At 2-years follow up, in **table 6**: peripheral neuropathy was significantly higher in group C; one should notice that artefact resulting from losing most of cases of group C (only one patient continued out of 19: 5%); while in group A&C 8 cases were present out of 32= 25%: a **Fig.** that reflects a fact about survival.

Table 7 shows that comorbidities; hypertension and FIGO staging were associated with significant values as regards overall survival while comorbidities; FIGO staging had the most significant effect on progression free survival.

Table 2: Comparison of Mid cyclic response and side effects among between study cases (A+B) and control cases C.

Mid-cyclic	Group A+ B (n=32)		Group C (n=19)		P value
Mid cyclic CA125 (U/ml)					0.402
• Median (range)	42.0 (3.6 – 981.0)		19.0 (3.3 – 330.0)		
Systemic treatment follow up					**0.019**
• Free	8	(25.0)	11	(57.9)	
• Regressive	24	(75.0)	8	(42.1)	
Systemic treatment side effects					0.726
• No	6	(18.8)	5	(26.3)	
• Yes	26	(81.3)	14	(73.7)	
Hypertension	4	(12.5)	1	(5.3)	0.639
Peripheral neuropathy					0.880
• No	7	(21.9)	5	(26.3)	
• Grade 1	0	(0.0)	0	(0.0)	
• Grade 2	11	(34.4)	5	(26.3)	
• Grade 3	13	(40.6)	9	(47.4)	
• Grade 4	1	(3.1)	0	(0.0)	
Proteinuria	1	(3.1)	1	(5.3)	1
Bleeding per vagina	1	(3.1)	0	(0.0)	1

Quantitative data are presented as median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table 3: Comparison of Post-cyclic response and side effects between study cases A+B and control group C.

Post-cyclic	Group A+ B (n=32)		Group C (n=19)		P value
Mid cyclic CA125 (U/ml)					0.391
• Median (range)	19.5 (1.9 – 403.0)		19.0 (3.1 – 450.0)		
Systemic treatment follow up					1
• Free	19	(59.4)	11	(57.9)	
• Regressive	9	(28.1)	6	(31.6)	
• Stationary	2	(6.3)	1	(5.3)	
• Progressive	2	(6.3)	1	(5.3)	
Systemic treatment side effects					1
• No	3	(9.4)	2	(10.5)	
• Yes	29	(90.6)	17	(89.5)	
Hypertension	2	(6.3)	1	(5.3)	1
Peripheral neuropathy					0.489
• No	2	(6.3)	2	(10.5)	
• Grade 2	16	(50.0)	12	(63.2)	
• Grade 3	14	(43.8)	5	(26.3)	
Proteinuria	2	(6.3)	2	(10.5)	0.623

Quantitative data are presented as median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table 4: Three-months follow up comparison of response and side effects between study groups (A+B) and control group C .

Three months follow up	Group A+ B (n=32)		Group C (n=19)		P value
CA125 (U/ml)					0.327
• Median (range)	14.5 (2.2 – 318.0)		11.0 (3.2 – 542.0)		
Systemic treatment follow up					0.877
• Free	19	(63.3)	11	(61.1)	
• Regressive	2	(6.7)	1	(5.6)	
• Stationary	6	(20.0)	5	(27.8)	
• Progressive	1	(3.3)	1	(5.6)	
• Recurrence	2	(6.7)	0	(0.0)	
Systemic treatment side effects					0.282
• No	8	(26.7)	2	(11.1)	
• Yes	22	(73.3)	16	(88.9)	
Hypertension	1	(3.3)	0	(0.0)	1
Peripheral neuropathy					0.119
• No	9	(30.0)	2	(11.1)	
• Grade 1	0	(0.0)	1	(5.6)	
• Grade 2	12	(40.0)	5	(27.8)	
• Grade 3	9	(30.0)	9	(50.0)	
• Grade 4	0	(0.0)	1	(5.6)	
Proteinuria	2	(6.7)	0	(0.0)	0.521
Stroke	1	(3.3)	0	(0.0)	1

Quantitative data are presented as median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table 5: 12 Months follow up comparison of response and side effects between study groups (A+B) and control group C.

12 months follow up	Group A+ B (n=23)		Group C (n=11)		P value
CA125 (U/ml)					**0.029**
• Median (range)	19.0 (2.0 – 274.0)		124.0 (7.9 – 314.0)		
Systemic treatment follow up					0.566
• Free	11	(57.9)	3	(37.5)	
• Stationary	1	(5.3)	0	(0.0)	
• Progressive	3	(15.8)	1	(12.5)	
• Recurrence	4	(21.1)	4	(50.0)	
Systemic treatment side effects					0.103
• No	12	(63.2)	2	(25.0)	
• Yes	7	(36.8)	6	(75.0)	
Peripheral neuropathy					0.051
• No	12	(63.2)	2	(25.0)	
• Grade 2	6	(31.6)	3	(37.5)	
• Grade 3	1	(5.3)	3	(37.5)	

Quantitative data are presented as median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table 6: Two years follow up comparison of response and side effects between study group A+ B and control group C.

18 months follow up	Group A+ B (n=8)		Group C (n=1)		P value
CA125 (U/ml)					0.444
• Median (range)	3.5 (2.0 – 42.0)		9 (9.0 – 9.0)		
Systemic treatment follow up					----
• Free	8	(100.0)	1	(100.0)	
Peripheral neuropathy					0.222
• No	7	(87.5)	0	(0.0)	
• Grade 1	1	(12.5)	0	(0.0)	
• Grade 3	0	(0.0)	1	(100.0)	

Quantitative data are presented as median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table 7: Overall survival and progression free survival according to clinic-pathological details of the studied ovarian cancer cases (n=51).

	OS (3 years)		PFS (3 years)	
	Estimate ± SE	**P value**	**Estimate ± SE**	**P value**
Age		0.325		0.658
• < 50	76.5 ± 10.3%		18.9 ± 9.8	
• ≥ 50	64.7 ± 8.2%		19.5 ± 7.1	
Using contraception		0.879		0.723
• No	67.6 ± 8.0		16.1 ± 6.6	
• Yes	70.6 ± 11.1		25.3 ± 10.9	
Smoking (active or passive)		0.849		0.445
• No	68.4 ± 7.5		19.7 ± 6.7	
• Yes	65.6 ± 7.7		17.3 ± 11.1	
Menopausal status		0.552		0.954
• Premenopausal	73.3 ± 11.4		14.4 ± 9.4	
• Postmenopausal	66.7 ± 7.9		21.3 ± 7.1	
Family history		0.952		0.375
• Negative	68.7 ± 6.7		18.3 ± 5.8	
• And type of treatment	66.7 ± 27.2		33.3 ± 27.2	
Comorbidities		**0.026**		**0.049**
• No	77.1 ± 7.1		24.8 ± 7.6	
• Yes	50.0 ± 12.5		6.7 ± 6.5	
Diabetes mellitus		0.158		0.341
• No	71.8 ± 7.2		22.2 ± 6.9	
• Yes	58.3 ± 14.2		9.2 ± 8.7	
Hypertension		**0.014**		0.052
• No	77.5 ± 6.6		24.3 ± 7.0	
• Yes	36.4 ± 14.5		0.0 ± 0.0*	
FIGO staging		**0.029**		**0.038**
• 2A	0.0 ± 0.0*		0.0 ± 0.0*	
• 3A	80.0 ± 12.6		10.0 ± 9.5	
• 3B	66.7 ± 15.7		30.0 ± 17.5	
• 3C	85.0 ± 8.0		30.0 ± 10.2	
• 4	40.0 ± 15.5		0.0 ± 0.0*	
Type of treatment		0.160		**0.007**
• Group A + Group B	75.0 ± 7.7		27.2 ± 8.2	
• Group C	57.9 ± 11.3		5.7 ± 5.5	
Adjuvant versus Neo-adjuvant		0.277		0.208
• Group A	66.7 ± 12.2		21.8 ± 11.1	
• Group B	82.4 ± 9.2		31.7 ± 11.7	
CA125 (U/mL)		0.624		0.132
• < 286	75.0 ± 15.3		0.0 ± 0.0*	
• ≥ 286	63.2 ± 7.6		21.1 ± 6.6	

* The follow up was ended before 36 months of follow up.

The same variables OS and PFS are further clarified in **fig. 2 and 3**.

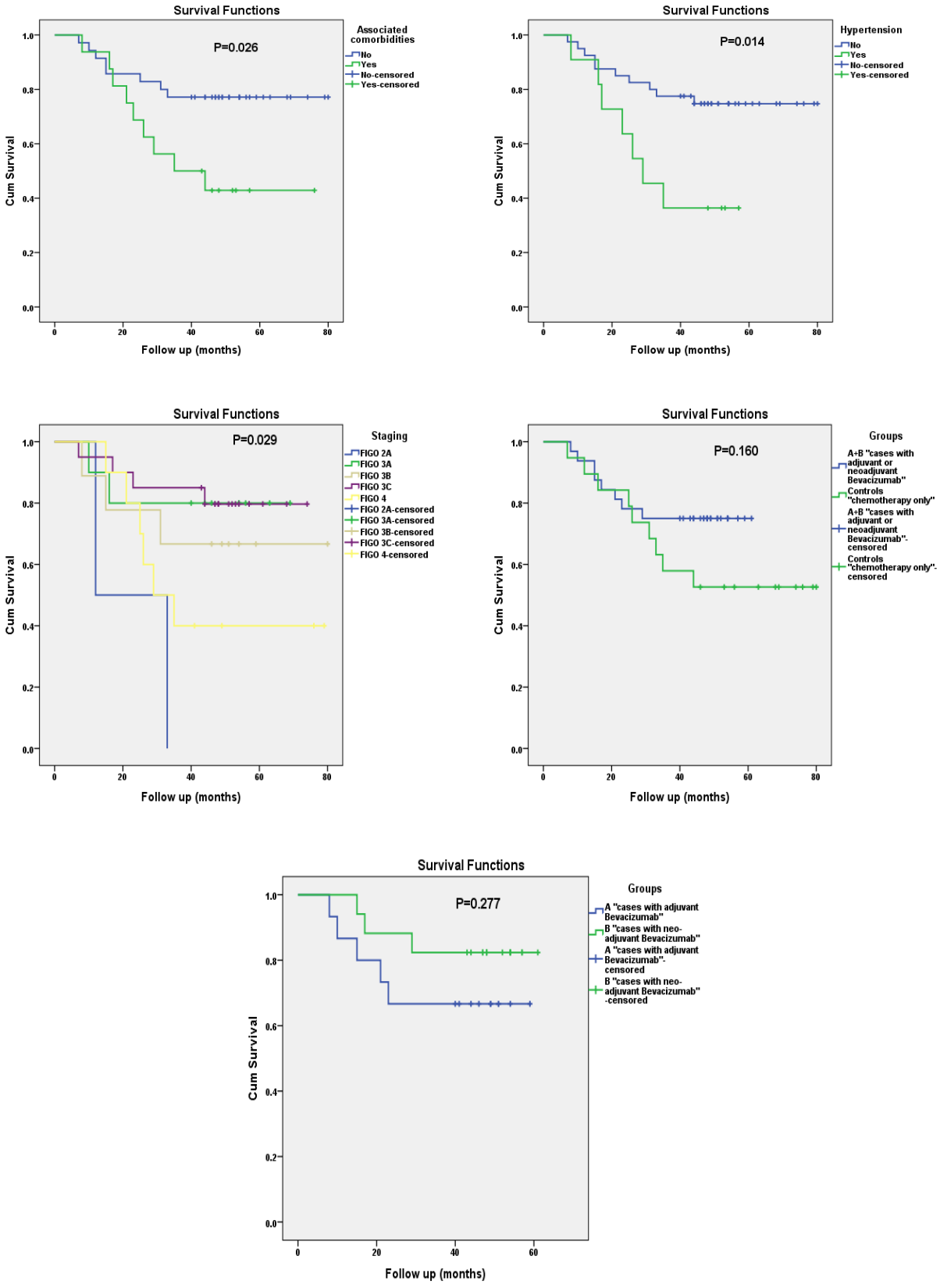

Fig. 2: Overall survival curves according to the clinic-pathological details of the studied ovarian cancer cases.

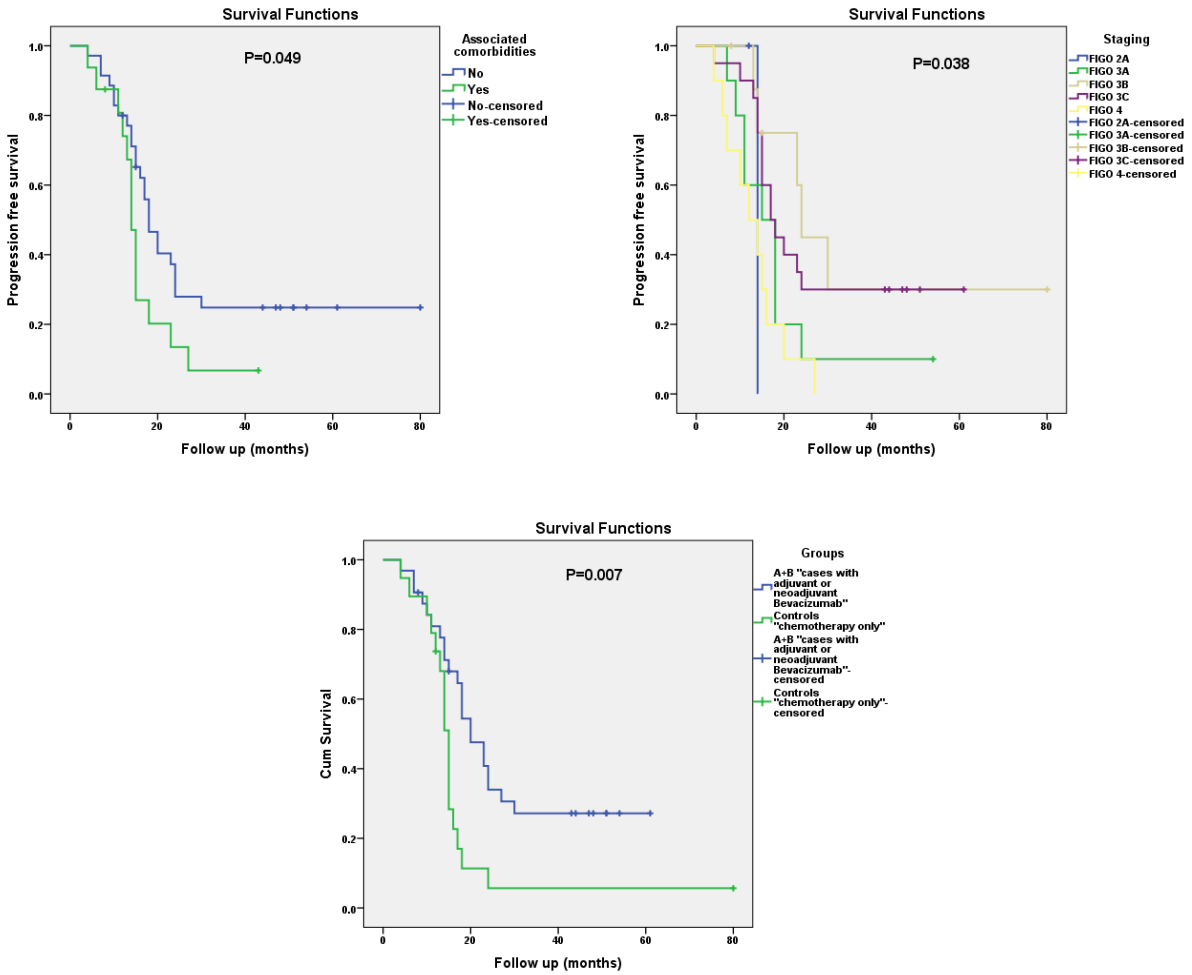

Fig. 3: Progression free survival curves according to the clinic-pathological details of the studied ovarian cancer cases.

Discussion

The majority of women with ovarian cancer are diagnosed with advanced-stage disease. For such patients, surgical resection aided by chemotherapy has been the optimal frontline treatment. Chemotherapy is usually given either adjuvant after primary debulking surgery (PDS) or as neo/adjuvant chemotherapy (NACT) before and after interval debulking surgery (IDS). The goal of any cytoreductive surgery is to resect the disease maximally to improve patient outcomes. However, recent trials have tried to determine whether patients receiving NACT and post-IDS chemotherapy have better outcomes than those receiving only chemotherapy after PDS. In june 2018, Bevacizumab was approved by FDA for use with chemotherapy as treatment for women with advanced ovarian cancers who underwent initial surgical resection after the results of GOG-0218 and ICON7 trials that demonstrated that the use of bevacizumab in the front-line and maintenance setting improved PFS when compared with conventional every-3-weeks carboplatin and paclitaxel, but probably no difference in OS[7].

Our study aimed to assess response, survival, side effects and toxicity of upfront chemotherapy with Bevacizumab in patients having advanced epithelial ovarian cancer, as compared with conventional chemotherapy only.

The study started on June 2018 until April 2021; recruited 51 patients with advanced ovarian cancer, selected from Clinical Oncology Department, Assiut University Hospital and were classified into three groups:

Study cases (32) who received the target therapy Bevacizumab added to the standard chemotherapy regimen,

A- Fifteen patients underwent surgical resection then received systemic treatment with Bevacizumab.
B- Seventeen patients were subjected to neoadjuvant treatment with Bevacizumab then underwent assessment for possibility of surgical resection after which they continued their adjuvant systemic therapy
C- Control cases (19 cases) who received only post-operative standard chemotherapy, were reviewed retrospectively from patients‘ files.

The pre-treatment clinical and laboratory data characteristics of all cases in our study were compared dividing the patients into: study groups (A&B) who received bevacizumab adjuvant or neoadjuvant respectively and the control group (C) who received only adjuvant chemotherapy. Comparison between group A and B for as regards clinical and laboratory variables had shown no significant differences between cases of groups A & B, the only significant variable was the type of primary surgery (either IDS in neoadjuvant cases or PDS in adjuvant cases), also the FIGO stage showed significant difference as most of group B cases were of stage IIIC this is mostly due to the reason that cases who were initially selected as advanced or irresectable and were introduced to the neoadjuvant treatment first while less advanced stages as IIIa were more liable to have optimal cytoreduction by PDS then adjuvant treatment and this agrees with international studies as ***Chi (2006)***[8].

Moreover, the type of primary surgery showed significant difference as none of the patients of group C received neoadjuvant treatment, this agrees with the patients' selection criteria of international literature such as ICON 7 (2015) and GOG218 (2012) clinical trials. Concerning the Baseline laboratory data of the studied ovarian cancer cases who received Bevacizumab, there was a significantly higher level of CA125 median range in the group who received neoadjuvant treatment then IDS (group B) than the adjuvant treatment group (group A) and this might be due to the fact that the group received neoadjuvant treatment were logically more advanced hence, having higher tumor marker levels. Not forgetting the fact that most of our study cases diagnosed in an advanced stage and in older age category which characterizes ovarian cancer type II; many international studies suggest that CA 125 levels are relatively higher in those cases[9,10].

During the mid-cyclic follow up, patients of group (A&B) had significantly more regressive pattern than those of group C, with 100% of group B cases showing regressive course and that indicates very good response to bevacizumab given neoadjuvant with chemotherapy with good safety profile as there was no extra significant side effects, while the post-cyclic response and side effects were similar with no significant differences between groups (A&B) Vs group C: possible explanations for the observed results are that patients with more severe disease or at higher risk of progression usually have rapid cell proliferation and division which appear to be more sensitive to anti-neovascularization agents and are subject to antitumor targeted therapy[11].

We couldn't find significant difference between group A versus group B or in group A+B versus Group C, concerning neither response nor side effects in the three and six months follow up of patients indicating that there is no reported increased side effects with using bevacizumab either neoadjuvant or adjuvant but there is also no difference in patients' short-term outcome, while in the 6 months follow up there was a statistically significant difference between Group (A+B) versus Group C regarding side effects specifically peripheral neuropathy which was more prominent in the chemotherapy only group (group C) and this also showed in the 9, 12 and 18 months follow up.

When follow up was extended to one-year post-treatment there was a significantly lower CA-125 values in patients who used Bevacizumab (A&B) than those who used conventional chemotherapy (group C) and this lowered level of serum CA125 was translated to increased PFS on longer follow up, this may support the fact that CA125 level has a predictive value in cases of advanced ovarian cancers[12]. As agreed by ***Zhang (2018)***[13] which stated that decreasing CA-125 was independently associated with the optimal cytoreduction rate and survival of patients diagnosed with advanced stage HG-SOC and treated with NAC/IDS[13].

Concerning the side effects and safety profile of bevacizumab in our study, there was no significant difference in side effects between bevacizumab/chemotherapy arm and chemotherapy only arm, and this is quite similar to international literature as ***Haunschild and Tewari (2020)***[14] illustrated in 2020 that GOG-0218 and ICON-7 demonstrated a safety profile of bevacizumab similar to other cancers. The most common side effects associated with bevacizumab treatment are hypertension, proteinuria and epistaxis[15]. Other side effects during chemotherapy such as neutropenia, thrombocytopenia, neuropathy and hypersensitivity reactions occurred commonly in both studies but probably not due to bevacizumab. Bevacizumab package labeling has a black box warning for the risk of GI perforation, healing complications and hemorrhage but none of them occurred in any of our study patients. In general, Bevacizumab in well tolerated and in trials of prolonged maintenance exposure to bevacizumab the median time to discontinuation from unacceptable toxicity in 9.9 months[14,16]. In GOG-0218, QOL survey scores were initially lower for the bevacizumab arm but there was no difference in QOL during the maintenance phase[17] (In ICON-7, there was no overall difference in QOL during the study period).

At 2-years follow up, peripheral neuropathy was significantly higher in group C; one should notice that artefact resulting from losing most of cases of group C (only one patient continued out of 19: 5%); while in group A&C 8 cases were present out of 32= 25%, also peripheral neuropathy is common with chemotherapy especially taxanes which agrees with studies as ***Oza (2017)***[16] and ***Haunschild and Tewari (2020)***[14] and most of international literature.

Also our study showed that comorbidities; hypertension and FIGO staging were associated with significant values as regards overall survival while comorbidities; FIGO staging had the most significant effect on progression free survival this partially agrees with another study in Nigeria published in 2021 by ***Okunade (2021)***[18] showed that PFS could be predicted by the age and FIGO stage of the disease, whereas menopausal status was predictive of OS in patients with EOC. Also most of international literature demonstrated that stage is the most significant predictor of survival in advanced ovarian cancers as ***Dinca (2020)***[19] illustrated in January 2020 that FIGO IIIC stage, suboptimal cytoreduction, presence of postoperative complications, inadequate adjuvant treatment and pathological type of clear cell cancer are prognostic factors for overall survival in patients with advanced ovarian cancer, the type of optimal cytoreduction and adjuvant treatment are independent protective factors for overall survival, and the presence of postoperative complications has been shown to be an independent risk factor[19].

Conclusion

Using bevacizumab as adjuvant or as neo adjuvant line seems to improve response to chemotherapy and improves overall survival rates without any significant increase in rate of side effects. On the other hand; comparison between using it as adjuvant and as neo-adjuvant produced comparable success rates: taking in consideration that when bevacizumab was used as neo-adjuvant; this was applied to cases in which surgical assessment stated they are more advanced cases or non-surgically optimal: this means that bevacizumab could convert this group to outcome similar to cases that were considered as “optimal for surgical debulking”; thus adding a considerable advantage to its use in this particular type of patients. Studies with larger number of cases may be needed to confirm our findings.

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العلاج ما قبل الجراحي و بعد الجراحي باستخدام البيفاسيزوماب في علاج اورام المبيض المتقدمة

ندى حسن صلاح[١] – محمد عبد الحكيم مكاوى[١] – هشام احمد أبوطالب[٢] – محمد علاء الدين حسن[١] – علا نبيه عبد الفتاح[١*]

[١]قسم الأورام الإكلينيكية ، مستشفى جامعة أسيوط ، اسيوط ، مصر

[٢]قسم أمراض النساء والتوليد ، مستشفى اسيوط الجامعي، اسيوط ، مصر

سرطان المبيض (OC) هو الورم الخبيث الأكثر فتكا في أمراض النساء. في عام ٢٠١٨، تمت الموافقة على بيفاسيزوماب من قبل إدارة الغذاء والدواء الأمريكية لاستخدامه مع العلاج الكيميائي كعلاج للنساء المصابات بحالات اورام المبيض المتقدمة.

الهدف: تقييم استجابة بيفاسيزوماب وبقائه وسميته في المرضى الذين استخدموه كمساعد جديد أو مساعد مع العلاج الجهازي مقارنة بالحالات التي تلقت العلاج الكيميائي بعد العملية الجراحية فقط.

التصميم: دراسة الحالات والشواهد التدخلية المحتملين. شملت المرضى الذين يعانون من اورام المبيض المقدمة إلى مستشفيات جامعة أسيوط من عام ٢٠١٨ حتى عام ٢٠٢١.

التدخل (التدخلات): المجموعة أ: خضع ١٥ مريضاً للاستئصال الجراحي الأولي ثم تلقوا العلاج المساعد، المجموعة ب: ١٧ مريضاً تلقوا العلاج قبل الجراحي ثم خضعوا للاستئصال الجراحي يليه العلاج المساعد. والمجموعة الضابطة (ج): ١٩ مريضا تلقوا العلاج الكيميائي بعد العملية الجراحية فقط دون بيفاسيزوماب وتمت مراجعتهم بأثر رجعي.

النتيجة الأولية: البقاء على قيد الحياة خالية من الأمراض(DFS) ، والبقاء على قيد الحياة بشكل عام (OS).

النتيجة الثانوية: سمية بيفاسيزوماب

النتائج: كشفت المقارنات بين المجموعتين A و Bعن عدم وجود فروق ذات دلالة إحصائية فيما يتعلق بـ DFS ونظام التشغيل والسمية. في عام واحد بعد العلاج، كانت قيم CA-125 أقل بكثير في المرضى الذين استخدموا بيفاسيزوماب (A & B) مقارنة بالعلاج الكيميائي التقليدي (المجموعة .(C نظام التشغيل لمدة ٣ سنوات كان ٢٥% للمجموعات (أ& ب) و٥% فقط للمجموعة ج.

الاستنتاجات: بيفاسيزوماب تحسين معدل الاستجابة والبقاء على قيد الحياة بشكل عام دون زيادة كبيرة في الآثار الجانبية. أدى استخدامه كمساعد وكمساعد جديد إلى إنتاج معدلات نجاح قابلة للمقارنة: مع الأخذ في الاعتبار أن استخدام ا لمواد المساعدة الجديدة تم تطبيقه على حالات أكثر تقدمًا أو غير قابلة **للعلاج:** وهذا يعني أن بيفاسيزوماب يمكن أن يعطي هذه المجموعة نتيجة مماثلة للحالات القابلة للجراحة في المقام الأول؛ هناك حاجة لدراسات أكبر لتأكيد النتائج التي توصلنا إليها.