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Impact of Bevacizumab-containing Primary Treatment on Outcome of Recurrent Ovarian Cancer: An Italian Study

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Abstract. *Background/Aim: The aim of the study was to assess the outcome of advanced ovarian cancer patients who i) underwent primary surgery followed by carboplatin/paclitaxel–based chemotherapy with or without bevacizumab, ii) were in complete response after chemotherapy, iii) and subsequently recurred. Patients and Methods: The hospital records of 138 complete responders after chemotherapy with (n=58) or without (n=80) bevacizumab were reviewed. Results: Both survival after recurrence and overall survival were related to age (≤61 vs. >61 years, p=0.002 and p=0.0001), performance status (0 vs. ≥1, p=0.002 and p=0.001), histotype (serous vs. non serous, p=0.005 and p=0.01), time to recurrence (≥12 vs. <12 months, p<0.0001 and p<0.0001) and treatment at recurrence (surgery plus chemotherapy vs. chemotherapy, p=0.01 and p=0.004), but not to first–line treatment. Conclusion: This investigation failed to detect a more aggressive behavior of recurrent ovarian cancer after bevacizumab-containing primary treatment.*

Primary debulking surgery followed by three weekly paclitaxel/carboplatin-based chemotherapy is the standard treatment for patients with advanced epithelial ovarian cancer (1-6). Several studies have been performed on the use of weekly dose-dense paclitaxel and carboplatin, intraperitoneal platinum-based chemotherapy, three-cytotoxic drug regimens and maintenance chemotherapy in this clinical setting. A Japanese trial showed a significantly better progression-free survival and overall survival for patients who received dose-dense treatment with carboplatin at an area under the curve (AUC) of 6 mg/ml [AUC 6] on day 1 + 80 mg/m^2 paclitaxel on days 1, 8, and 15 every 3 weeks compared with those treated with conventional carboplatin AUC6 + 180 mg/m^2 paclitaxel on day 1 every 3 weeks for six cycles (7). However, subsequent trials on Caucasian women failed to detect a clinical benefit for a dose-dense weekly regimen (8-11). The meta-analysis of six randomized trials on intraperitoneal chemotherapy in the initial treatment of advanced low-volume epithelial ovarian cancer showed that women who received a component of intraperitoneal chemotherapy had significantly better progression-free survival and overall survival (12). An up-date of the Gynecologic Oncology Group (GOG) 114 and GOG 172 trials revealed that, after a median follow-up of 10.7 years, intraperitoneal therapy was associated with a significant 23% decreased risk of death compared with intravenous chemotherapy (13). However, intraperitoneal chemotherapy, widely accepted in the United States, has been infrequently used in Europe, mainly because of higher toxicity, catheter complications, and clinical trial design issues (14, 15). Moreover, the phase III GOG 252 trial showed that, compared with the intravenous carboplatin reference arm, progression-free survival was not significantly increased with intraperitoneal either cisplatin or carboplatin–based chemotherapy when combined with intravenous bevacizumab (16).

The sequential or concomitant addition of a third cytotoxic agent, such as topotecan, gemcitabine or liposomal doxorubicin to standard paclitaxel/carboplatin-based regimen, as well as the use of maintenance chemotherapy with topotecan or paclitaxel provided no benefit in terms of progression-free survival or overall survival (17-21). Conversely, two randomized phase III trials showed that the addition of concomitant and maintenance bevacizumab to first-

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line paclitaxel/carboplatin-based chemotherapy significantly improved progression-free survival without any significant benefit in overall survival (22, 23). However, a clear, although small, improvement in overall survival appeared to emerge for patients at high-risk of relapse [stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease following primary surgery] in the ICON7 study (24).

Adding bevacizumab to a carboplatin-based doublet, and, respectively, to single-agent non platinum chemotherapy significantly improved progression-free survival of patients with platinum-sensitive and platinum-resistant recurrent epithelial ovarian cancer not previously treated with this antiangiogenic agent, with no significant advantage in terms of overall survival (25-28).

From a theoretic point of view, an antiangiogenic treatment could alter the biological behavior of residual tumor clones and could impact on the clinical course of subsequent recurrent disease, and some preclinical investigations appeared to support this hypothesis (29-31).

This retrospective study compared the pattern of relapse and the outcome of patients with advanced epithelial ovarian cancer who obtained a complete response after surgery followed by carboplatin/paclitaxel–based chemotherapy with or without bevacizumab and who subsequently developed recurrent disease, with the aim to assess whether the relapsed patients after bevacizumab-containing therapy had a worse clinical outcome.

Patients and Methods

This retrospective study was conducted on 138 patients with FIGO stage IIIb-IV epithelial ovarian cancer i) who underwent primary debulking surgery followed by three-weekly intravenous carboplatin/paclitaxel–based chemotherapy with or without bevacizumab for six cycles, ii) who were in complete response at the end of primary treatment, and iii) who subsequently developed recurrent disease at the Departments of Gynecology and Obstetrics of the Universities of Pisa, Brescia, Torino (Mauriziano Hospital), and Milano (Monza) between 2011 and 2017.

The hospital records, including surgical notes, pathological reports, chemotherapy and follow-up data, were collected using a common form with standardized items and a common database.

The choice for a primary debulking surgical approach was individually established on the basis of an accurate evaluation of both the spread of disease at clinical, radiological [chest-abdomen-pelvic computed tomography (CT) scan] and, sometimes, surgical examination and the patient general conditions, after an exhaustive discussion with the patient by a multidisciplinary team.

The tumour stage and histological diagnosis of each case were determined according to the FIGO criteria and the histological typing system of the World Health Organization (WHO), respectively. Tumours were graded as well [G1], moderately [G2], or poorly [G3] differentiated. The baseline characteristics (age, performance status, FIGO stage, histological type, tumour grade, presence or absence of ascites, residual disease after primary debulking surgery, and type of first-line chemotherapy) were reported for each case.

The surgical cytoreduction was defined "optimal" if macroscopically detectable residual disease was ≤1 cm.

The evaluation of the course of disease was based on clinical examination, serum CA125 assay, chest x-ray, abdominal-pelvic ultrasound and CT scan. Additional investigations, i.e. magnetic resonance imaging or positron emission tomography [PET]/CT scan, were performed when appropriate. Complete response was defined as the lack of evidence of disease at clinical and imaging examinations with serum CA125 levels <35 u/ml after the completion of the six cycles of first–line chemotherapy. All the patients were followed-up at regular scheduled intervals with the modalities have been reported in a previous paper (32).

Only the patients with clinical and/or radiological evidence of relapse were included in the present analysis. Asymptomatic patients with rising CA125 levels and negative clinical and imaging examinations who were not still considered to have a recurrent disease, underwent a more stringent follow-up program, and were excluded from the study. Median follow-up of survivors was 54 months (range=13-142 months).

Statistical analysis. SPSS ver.13 Inc Chicago IL was used for computations. The time to recurrence was calculated from the sixth cycle of first-line chemotherapy to the clinical and/or radiological detection of recurrence. The time from the clinical and/or radiological detection of the first recurrence to death or last observation was defined as survival after recurrence. The time from the initial diagnosis to death or last observation was defined as overall survival. The analysed prognostic variables were: age, performance status, FIGO stage, histological type, tumour grade, presence or absence of ascites at presentation, residual disease after primary debulking surgery, first-line chemotherapy (with or without bevacizumab), time to recurrence, number of recurrences, sites of recurrence, and treatment at recurrence. The cumulative probability of survival after recurrence and overall survival were estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables.

Results

Median age of the patients at diagnosis was 61 years (range=38-78 years). Chemotherapy consisted of carboplatin AUC 5-6+175 mg/m^2 paclitaxel every 3 weeks for six cycles in 80 patients (group A) or the same regimen plus 15 mg/kg bevacizumab every 3 weeks added in cycles 2 through 22 (according to the schedule used in GOG 218 trial [22] in 58 patients (Group B).

Tables I and II show patient characteristics at presentation and at recurrence, respectively.

The patients who received bevacizumab had a younger age and a better performance status than those who did not, whereas FIGO stage, histological type, tumor grade, presence or absence of ascites, and debulking status were similar in both groups (Table I). Moreover, the time to recurrence was >12 months in 77.6% of the patients who underwent chemotherapy plus bevacizumab as first-line treatment compared with 61.2% (p=0.04) of those who underwent chemotherapy alone, and recurrence site was single in 72.4% of the former and 50% of the latter (p=0.008) (Table II).

Table I. *Patient characteristics at presentation.*

First line CT	CBDCA+PTX Group A (N=80)		CBDCA+PTX+BEV Group B (N=58)		*p*-Value
Variables	Pts	n	Pts	n	
Age					
≤61 years	41	51.3	40	68.9	0.05
>61 years	39	48.8	18	31.0	
PS					
0	45	56.3	43	74.1	0.03
1-2	35	43.8	15	25.8	
FIGO stage					
IIIb	5	6.3	7	12.1	0.60
IIIc	66	82.5	42	72.4	
IV	9	11.2	9	15.5	
Histotype					
Serous	70	87.5	52	89.6	0.79
Endometrioid	1	1.2	2	3.4	
Clear cell	1	1.2	2	3.4	
Mucinous	0	0	1	1.7	
Undifferentiated	2	2.5	0	0	
Mixed	6	7.5	1	1.7	
Tumour grade					
G2	9	11.3	5	8.6	0.78
G3	71	88.8	53	91.4	
Ascites					
No	35	43.8	25	43.1	1.00
Yes	45	56.2	33	56.9	
RD after PDS					
≤10 mm	69	86.2	52	89.7	0.60
>10 mm	11	13.8	6	10.3	

Table II. *Patient characteristics at first recurrence.*

First line CT	CBDCA+PTX Group A (N=80)		CBDCA+PTX+BEV (Group B) (N=58)		*p*-Value
Variables	Pts	n	Pts	n	
Time to recurrence					
≥12 months	49	61.2	45	77.6	0.0446
<12 months	31	37.7	13	22.4	
Serum CA125 at recurrence					
≤35 U/ml	18	22.5	20	34.5	0.12
>35 U/ml	62	77.5	38	65.5	
N. recurrence site					
Single	40	50.0	42	72.4	0.008
Multiple	40	50.0	16	27.6	
Sites of recurrence					
Abdominal	31	38.7	19	32.7	
Abdominal + other (pelvic, RP, distant)	26	32.5	15	25.9	
Visceral component	57/80	71.2	34/58	58.6	0.14
RP	12	15.0	12	20.7	
Distant	6	7.5	9	15.5	
Distant + RP	5	6.2	3	5.2	
Extra-visceral component only	23/80	28.7	24/58	41.3	0.14
Treatment at recurrence					
CT	67	83.7	46	79.3	
Surgery + CT	10	12.5	9	15.5	
Other	3	3.7	3	5.1	
BEV added to CT	15/77	19.5	2/55	3.6	

CT: Chemotherapy; CBDCA: carboplatin; PTX: paclitaxel; BEV: bevacizumab; n: Number; PS: performance status; G2: moderately differentiated; G3: poorly differentiated; RD: residual disease; PDS: primary debulking surgery; RP: retroperitoneal.

Recurrence rate with only extra-visceral component (retroperitoneal and/or distant) was not significantly different in the patients who received bevacizumab in the first-line therapy and in those who did not (41.3% *versus* 28.7%, p=0.14). Bevacizumab was added to second-line chemotherapy in 19.5% of the women of group A and 3.8% of those of group B, respectively.

The clinical outcome of the patients belonging to group A was as follows: 9 patients (11.2%) had no evidence of disease after a median follow-up of 41 months (range=7-76 months) from the first recurrence and 78 months (range=25-106 months) from the initial diagnosis; 38 patients (47.5%) were alive with disease after a median interval of 28.5 months (range=3-79 months) from the first recurrence and 57 months (range=17-105 months) from the initial diagnosis; 32 patients (40.0%) died of disease after a median time of 20 months (range=1-57 months) from the first recurrence and 41 months (range=19-90 months) from the initial diagnosis; and one (1.2%) died of intercurrent disease with no evidence of tumor after 45 months from the first recurrence and 57 months from the initial diagnosis.

The clinical outcome of the patients belonging to group B was as follows: 6 patients (10.3%) had no evidence of disease at a median follow-up of 19.5 months (range=7-44 months) from the first recurrence and 48.5 months (range=35-95 months) from the initial diagnosis; 30 patients (51.7%) were alive with disease after a median interval of 21 months (range=1-62 months) from the first recurrence and 49 months (range=19-97 months) from the initial diagnosis; 19 patients (32.7%) died of disease after a median time of 19 months (range=1-59 months) from the first recurrence and 40 months (range=11-90 months) from the initial diagnosis; and 3 patients (5.2%) died of intercurrent disease with no evidence of tumor after a median time of 30 months (range=18-31 months) from the first recurrence and 43 months (range=4-50 months) from the initial diagnosis.

In the entire cohort of 138 patients, 2–year and 5–year survival rates after recurrence were and 69.9% and 34.2%, respectively, and 2-year and 5-year overall survival rates were 91.9% and 56.4%, respectively.

Table III. *Variables predictive of survival after recurrence*.

Variables	Patients N.	2-year	5-year	*p*-Value
Age				
<61 years	81	77.6%	49.7%	0.002
≥61 years	57	62.7%	11.1%	
PS				
0	88	76.5%	49.7%	0.002
≥1	50	58.3%	8.6%	
FIGO stage				
IIIb-c	120	69.7%	33.5%	0.940
IV	18	66.7%	44.4%	
Histological type				
Serous	96	77.5%	38.3%	0.005
Not serous	42	50.6%	30.9%	
Tumor grade				
G2	14	62.3%	41.6%	0.990
G3	124	70.9%	33.4%	
Ascites at presentation				
No	60	70.3%	40.5%	0.354
Yes	78	69.9%	27.9%	
First-line CT				
CBDCA+PTX	80	69.4%	39.3%	0.466
CBDCA+PTX+BEV	58	71.0%	19.0%	
RD after PDS				
≤10 mm	121	70.7%	34.9%	0.977
>10 mm	17	64.6%	28.3%	
Time to recurrence				
>12 months	94	82.2%	45.3%	0.0001
≤12 months	44	45.3%	13.7%	
N. recurrences				
Single	89	72.4%	35.0%	0.754
Multiple	49	65.7%	32.6%	
Sites of recurrences				
Visceral sites	91	66.7%	32.7%	0.558
Extra-visceral sites	47	76.3%	37.0%	
Treatment at recurrence				
CT	113	65.7%	24.9%	0.01
Surgery + CT or CT+ surgery	19	94.1%	76.7%	

N: Number; PS: performance status; G2: moderately differentiated; G3: poorly differentiated; CT: chemotherapy; CBDCA: carboplatin; PTX: paclitaxel; BEV: bevacizumab; RD: residual disease; PDS: primary debulking surgery.

Table IV. *Variables predictive of overall survival*.

Variables	Patients N.	2-year	5-year	*p*-Value
Age				
<61 years	81	97.5%	66.3%	0.0001
≥61 years	57	83.9%	41.3%	
PS				
0	88	94.2%	68.4%	0.001
≥1	50	87.8%	34.6%	
FIGO stage				
IIIb-c	120	91.5%	55.8%	0.766
IV	18	94.4%	59.2%	
Histological type				
Serous	96	94.7%	62.3%	0.01
Not serous	42	85.5%	42.3%	
Tumor grade				
G2	14	92.9%	62.5%	0.747
G3	124	91.8%	55.1%	
Ascites at presentation				
No	60	88.3%	64.7%	0.243
Yes	78	94.8%	49.3%	
First- line CT				
CBDCA+PTX	80	93.7%	56.7%	0.609
CBDCA+PTX+BEV	58	89.5%	55.2%	
RD after PDS				
≤10 mm	121	91.7%	55.8%	0.930
>10 mm	17	94.1%	56.2%	
Time to recurrence				
>12 months	94	96.8%	73.0%	0.0001
≤12 months	44	81.2%	15.6%	
N. recurrences				
Single	89	92.0%	54.3%	0.520
Multiple	49	91.8%	58.4%	
Sites of recurrences				
Visceral sites	91	91.0%	56.7%	0.499
Extra-visceral sites	47	93.5%	53.1%	
Treatment at recurrence				
CT	113	91.9%	46.9%	0.004
Surgery + CT or CT+ surgery	19	100.0%	94.4%	

N: Number; PS: performance status; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; CT, chemotherapy; CBDCA: carboplatin; PTX: paclitaxel; BEV: bevacizumab; RD: residual disease; PDS: primary debulking surgery.

As reported in Tables III and IV, survival after recurrence and overall survival were significantly related to patient age (≤61 years *versus* >61 years, $p=0.002$ and $p=0.0001$, respectively), performance (0 *versus* ≥1, $p=0.002$ and $p=0.001$), histological type (serous *versus* non serous, $p=0.005$ and $p=0.01$), time to recurrence (≥12 months *versus* <12 months, $p<0.0001$ for both) and treatment at recurrence (surgery plus chemotherapy *versus* chemotherapy alone, $p=0.01$ and $p=0.004$), but not with FIGO stage, tumor grade, presence or absence of ascites at presentation, residual disease, type of first–line treatment (chemotherapy + bevacizumab *versus* chemotherapy alone) (Figures 1 and 2), number of recurrences, and site of recurrences.

Discussion

Advanced epithelial ovarian cancer patients who receive first-line chemotherapy plus bevacizumab experience a longer progression-free survival than those treated with chemotherapy alone (22, 23). However, bevacizumab could affect the biological behavior of microscopic residual tumor clones. Preclinical studies have suggested an accelerated tumor growth, increased local invasion, and increased distant spread after withdrawal of treatment with antiangiogenic agents (29-31). For instance, Mancuso *et al*. (29) have assessed regrowth of blood vessels in spontaneous RIP-Tag2 tumors and implanted

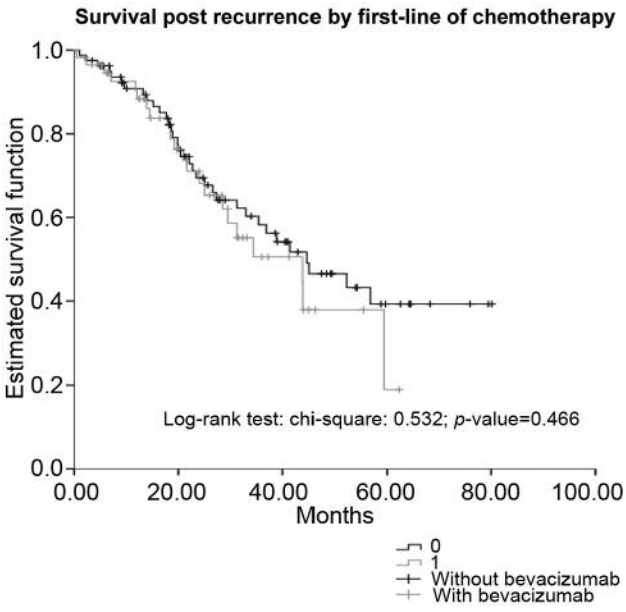

Figure 1. *Survival after recurrence by first-line of chemotherapy.*

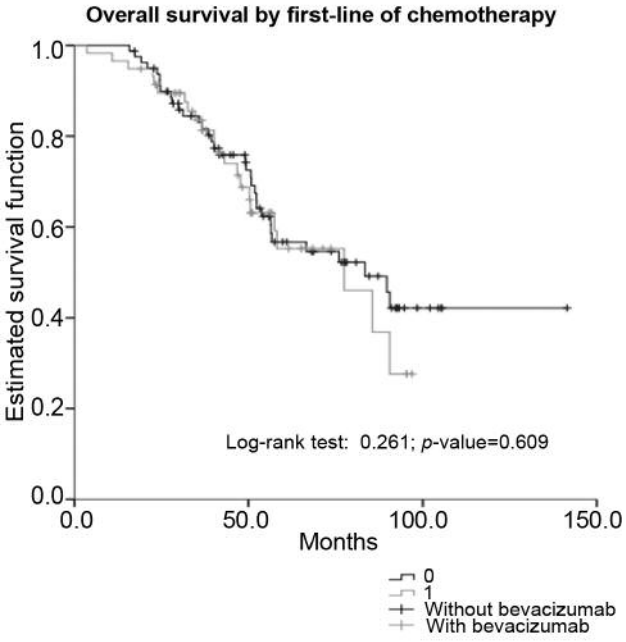

Figure 2. *Overall survival by first-line of chemotherapy.*

Lewis lung carcinomas in mice after blockade of vascular endothelial growth factor receptor signaling by small molecule inhibitors. One day after drug withdrawal, endothelial sprouts grew into empty sleeves of basement membrane and within one week, tumors were fully re-vascularized.

Epithelial ovarian cancer relapses commonly in the pelvis, abdomen, retroperitoneal nodes and pleura, less frequently in the lung and rarely in central nervous system and skin (33-35). A retrospective review of 89 patients with epithelial ovarian cancer treated with bevacizumab alone or in combination with other chemotherapy agents, has shown that the patients who received more than 12 cycles of bevacizumab were more likely to recur in extra-visceral sites (p=0.04), especially in lymph nodes (p=0.0002), compared with those who received ≤12 cycles, thus suggesting that the extended treatment with this antiangiogenic agent might alter the pattern of recurrence (36). Miles *et al*. (37) have performed a pooled analysis of five randomized, placebo-controlled trials enrolling 4,205 patients with breast, colorectal, renal, and pancreatic cancer to assess whether the discontinuation of bevacizumab was associated with accelerated disease progression or increased mortality. They found that the median time from the discontinuation of bevacizumab/placebo as a result of an adverse event to progression or death was 4.0 months [95% confidence interval (CI)=3.4-4.6 months] for bevacizumab and 3 months (95%CI=2.6-3.8 months) for placebo [hazard ratio (HR)= 0.93; 95%CI=0.79-1.10]. When the analysis was expanded to include patients, who stopped treatment for any reason, the median time from discontinuation to death was 10.2 months (95%CI=9.6-10.7) for bevacizumab and 9.3 months (95%CI=8.3-10.0 months) for placebo (HR=0.94; 95%CI=0.86-1.02). Moreover, similar patterns of recurrence were detected in bevacizumab- and placebo-treated patients. Therefore, this retrospective analysis in patients with breast, colorectal, renal and pancreatic cancer failed to show a decreased time to progression, increased mortality, or altered progression pattern after bevacizumab discontinuation.

In our series, survival after recurrence and overall survival were similar in advanced epithelial ovarian cancer patients who received carboplatin/paclitaxel-based chemotherapy plus bevacizumab and in those who received chemotherapy alone as first-line treatment (p=0.466 and p=0.609, respectively), and moreover, the recurrence rate with only extra-visceral component (retroperitoneal and/or distant) was similar in the two groups.

The strengths of the study are represented by the large number of patients, by the length of follow-up and by the description of rate and pattern of recurrence of the two treatment groups. The weaknesses of the investigation are represented by its retrospective nature, by the lack of randomization in the criteria of choice for first-line carboplatin/paclitaxel-based chemotherapy with or without bevacizumab, by the higher incidence of some favorable prognostic variables (younger age, better PS and longer time to recurrence) in patients who received bevacizumab in first-line treatment, and by the addition of bevacizumab to second-line chemotherapy in 3.6% and 19.5%, respectively,

of the patients previously treated and not treated with this antiangiogenic agent. In any case, in agreement with the pooled analysis of Miles *et al*. (37), the present investigation on patients with advanced epithelial ovarian cancer found no significance difference in both the sites of recurrence and the clinical outcome between complete responders who recurred after first-line chemotherapy plus bevacizumab and complete responders who recurred after first-line chemotherapy alone. Therefore, these results failed to detect a more aggressive behavior of recurrent epithelial ovarian cancer after bevacizumab-containing primary treatment.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Study concepts: A.G.; Study design: A.G., F.L., E.S; Recruitment and quality control of data: A.G., A.A.L, S.C., V.Z, A.M.F, M.A.; Data analysis and interpretation: A.G., F.L., E.S., A.A.L., A.M.F; Statistical analysis: A.G., A.A.L, S.C., V.Z.; Manuscript preparation: A.G.; Manuscript editing: All Authors; Manuscript review: All Authors.

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