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Impact of bevacizumab containing first line chemotherapy on recurrent disease in epithelial ovarian cancer: A case-control study

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HIGHLIGHTS

- Incorporation of bevacizumab into upfront regimens prolongs PFI in AOC patients.
- However, it is associated with wider presentation of relapse, and lower rate of complete SCS.
- TTP to second line chemotherapy was shorter in women with platinum-sensitive relapse initially treated with bevacizumab.

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ABSTRACT

Objective. To evaluate the timing and pattern of relapse, and duration of response to second line chemotherapy in advanced ovarian cancer (AOC) patients treated with first line carboplatin-paclitaxel chemotherapy with or without bevacizumab.

Patients and methods. This is a case-control study including 222 AOC patients. Seventy-four women treated with first line carboplatin-paclitaxel-bevacizumab chemotherapy (Cases) were matched based on laparoscopic predictive index value, and residual tumor at first surgery with 148 AOC patients treated with carboplatin-paclitaxel. Distribution of pattern of relapse, and response to second line chemotherapy was compared between the two groups. Time to Progression (TTP) for second line chemotherapy was also analyzed for study purpose.

Results. Median platinum-free interval (PFI) was 16 months (range 2–65) in Cases, compared with 9 months (1–83) in Controls (p-value = 0.001). Twenty patients (51.3%) among Cases showed recurrence in multiple anatomic sites, compared with 31 (31.9%) in the Control group (p-value = 0.035). Peritoneal recurrence occurred as diffuse in 30 Cases (96.8%), and 60 Controls (82.2%; p-value = 0.046). Secondary cytoreductive surgery (SCS) was successfully completed in 53.5% of Controls compared to 10.0% of Cases (p-value = 0.016). In women with fully platinum-sensitive relapse, response rate to second line chemotherapy was 85.2% in Controls, compared to 38.4% in Cases (p-value = 0.002). Finally, Cases showed a shorter TTP, compared to Controls (5 months vs 8 months; p-value = 0.041).

Conclusions. Incorporation of bevacizumab into upfront regimens prolongs PFI in AOC patients, but is associated with wider presentation of relapse, lower rate of complete SCS, and shorter TTP to second line chemotherapy in women with platinum-sensitive disease.

1. Introduction

In the past decade, the results of two pivotal randomized phase III clinical trials demonstrated a significant improvement of progression-free survival (PFS), in patients with advanced ovarian cancer (AOC) receiving bevacizumab as part of first line treatment [1,2]. Based on these data, in December 2011, Avastin received European regulatory approval for use in combination with carboplatin-paclitaxel as upfront chemotherapy regimen in OC patients with advanced disease.

The observed prolongation of PFS should be considered a relevant therapeutic achievement, since it delays the onset of physical symptoms associated with progressive disease, as well as the need to start a second-line chemotherapy. Furthermore, the prolongation of PFS may

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in principle increase the chance of response to further platinum-based treatments [3], thus offering a potential long-term benefit.

However, in this encouraging scenario, it is reasonable to hypothesize that the incorporation of bevacizumab into first-line treatment may exert an additional selective pressure on OC cells, with a potentially relevant impact on the natural history of this malignancy. This hypothesis is also supported by recently published retrospective data, which demonstrated a higher rate of lung and pleural recurrence in AOC patients receiving bevacizumab as part of primary treatment [4], thus suggesting that more efforts should be done to definitely clarify how bevacizumab will change the clinical features of OC. Furthermore, despite initial promising results [5,6], it remains to be validated an effective signature able to properly identify at diagnosis those AOC patients who may real benefit from first line bevacizumab-based chemotherapy.

For these reasons, we focused our attention on the impact of upfront bevacizumab containing regimens on recurrent disease, analyzing the timing and pattern of relapse, as well as the rate and duration of response to second line chemotherapy in a single-Institutional case control study including AOC patients treated with first line carboplatin-paclitaxel chemotherapy with or without bevacizumab.

2. Patients and methods

2.1. Study groups

The investigational arm (Cases) included 74 patients with AOC admitted at the Gynaecologic Oncology Unit of the Catholic University of Rome and Campobasso between March 2010 and February 2013 treated, after joint evaluation with the oncologists' team, with the following regimen: carboplatin 5 AUC/paclitaxel 175 mg per square meter of body-surface area/bevacizumab 15 mg/Kg every three weeks, followed by maintenance therapy with bevacizumab 15 mg/Kg until disease progression or for a maximum of 15 months.

The Control arm included a consecutive series of 148 AOC patients, admitted at our Institution between January 2010 and December 2012, treated with carboplatin 5 AUC/paclitaxel 175 mg per square meter of body-surface area every three weeks.

In both groups, patients were selected for primary debulking surgery (PDS), or neoadjuvant chemotherapy based on our Institutional laparoscopy-based algorithm [7], and to avoid imbalance between the two groups in term of initial disease extension and clinical features the Cases were matched with the Controls according to the laparoscopic predictive index value [7,8], and residual tumor at first surgery, using Stata software version 11.0 (Stata Corp, College station, TX). Furthermore, to maximize the power of the study, Cases and Controls were matched in a 1:2 ratio.

All women gave a written informed consent for their data to be collected and analyzed for scientific purpose. The Institutional Review Board approved the study.

2.2. Clinical data

For all patients included in the final analysis, data regarding timing, pattern, and treatment details at the time of relapse were prospectively recorded, and retrospectively analyzed for study purpose. In particular, the timing of recurrent disease was evaluated using the PFI defined as the time elapsed between the date of completion of platinum-based first line chemotherapy and recurrence. The pattern of relapse was classified as *peritoneal*, *parenchymal*, and *lymph-nodal* based on the site of disease [9]. Furthermore, we defined the type of recurrence as *single* in presence of only one anatomic site involved, or *multiple* when relapse diffusion occurred in more than one site. Finally, the extension of intraperitoneal recurrence was classified as *localized* in presence of no more than three nodules, or *diffused* when a wider disease spread was observed [9].

All patients showing platinum-sensitive recurrent disease were submitted to FDG-PET/CT scan, and staging-laparoscopy, to assess the chance of optimal secondary cytoreduction (SCS) [10,11]. All patients judged as suitable for optimal SCS received an attempt of surgical debulking.

Patients showing platinum-sensitive recurrent disease received second-line platinum-based chemotherapy; on the other hand, women showing platinum-resistant relapse were treated with non-platinum agents including weekly paclitaxel, pegylated liposomal doxorubicin, and gemcitabine. The group of cases developing recurrence with a PFI between 6, and 12 months were triaged to receive platinum versus non-platinum regimens, based on a case-specific decision making process. Clinical response to second line chemotherapy was assigned according to RECIST criteria [12], and the response has been classified as complete (CR)/partial (PR), or stable (SD)/progressive (PD). In order to fully evaluate the efficacy of second line treatment, we analyzed in our study also the Time to Progression (TTP), which was defined as the time from beginning of second line chemotherapy to further progressive disease. Data analysis regarding overall survival was not attempted due to the duration of follow-up period.

2.3. Statistical analysis

Differences between Cases and Controls in term of clinico-pathological features at diagnosis, and at the time of relapse were analyzed using the Pearson Chi-square exact test and Kruskall-Wallis test, as appropriate. Medians and life tables were computed using the product limit estimate by Kaplan–Meier method [13], and the log-rank test was used to assess the statistical significance [14]. Cox's regression model with stepwise variable selection [15] was used to analyse the role of clinical-pathological parameters, and treatment details as predictors of TTP for second line chemotherapy. All statistical calculations were performed using the Stata software version 11.0 (Stata Corp, College station, TX).

3. Results

3.1. Clinico-pathological features at diagnosis

As a consequence of matching process, no differences were observed between Cases and Controls in term of disease extension at diagnosis evaluated as laparoscopic predictive index value, and residual tumor at first surgery (Table 1). Around 90% of AOC patients showed high-grade serous histology, and FIGO Stage IIIC at initial diagnosis, without differences between the two groups (Table 1). Median CA125 levels were 792 IU (range 10–7654) in the overall population, with similar levels in Cases and Controls (p-value = 0.607). Median age at diagnosis of women treated with first line bevacizumab-containing chemotherapy was 54 years (range 26–76), which appears slightly lower compared with Controls (median 59, range 29–86; p-value = 0.069).

3.2. Timing of recurrent disease

After a median follow-up of 32 months (Cases 25 months, Controls 32 months; p-value = 0.785), we observed recurrent disease in 39 Cases (52.7%), and 116 Controls (78.4%; p-value = 0.001; Fig. 1). Median PFI was 16 months (range 2–65) in Cases, compared with 9 months (4–83) in the Control group (p-value = 0.001; Fig. 2). AOC patients initially treated with PDS showed a median PFI of 10 months (1–83) in Controls, compared with 19 months (2–65) in Cases (p-value = 0.001, Table 2). Similarly, in the group of women treated with upfront NACT followed by interval debulking surgery, we observed a longer PFI in patients treated with bevacizumab (10 months) compared with Controls (7 months; p-value = 0.032; Table 2). The distribution of relapse according with PFI in the two groups has been reported in Table 2. In particular, we observed platinum-resistant relapse in 45