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Research Report

Retrospective analysis of bevacizumab-induced arthralgia and clinical outcomes in ovarian cancer patients. Single center experience

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ABSTRACT

Background: Joint manifestations are ill-defined adverse events that were frequently reported of bevacizumab in ovarian cancer patients. The aim of this study is to describe the incidence and severity of joint manifestations among bevacizumab treated patients as well as their relation to clinical outcomes.
Methods: Medical charts of all ovarian cancer patients that received bevacizumab from 2012 through 2017 were reviewed. Joint manifestations were staged. Kaplan-Meier Survival curves were generated; survival differences were estimated.
Results: 76 Patients diagnosed with stage III or IV ovarian cancer were included. 23 patients (30.3%) developed joint manifestations, 12 of them had Grade I, 4 Grade II and 7 Grade III. Only 3 patients developed arthritis. In 8 cases (34.8%) one joint was affected and in the remaining 15, multiple sites. Median number of bevacizumab cycles to arthralgia development was 7. 3 patients were managed with corticosteroids or methotrexate, all had grade 3 AEs. The remaining received common analgesics. Median duration of the AE was 4.8 months. 7 patients discontinued bevacizumab due to AE. In all but 3 patients AE was finally resolved. Median number of bevacizumab cycles received, frequency of treatment completion or treatment discontinuation due to disease progression did not differ significantly among patients that developed joint manifestations or not. Median PFS and median OS did not differ statistical significantly.
Conclusion: Joint manifestations are common AEs in bevacizumab treated ovarian cancer patients and led to treatment discontinuation in 9% of the patients. However, this has not adversely affected the clinical outcome of the patients. Further research is needed for the appropriate management of these patients.

1. Introduction

Ovarian cancer is the fourth most common cause of cancer related deaths in women (Perren et al., 2011). Standard treatment for women with advanced disease is debulking surgery followed by platinum – based chemotherapy, most commonly paclitaxel and carboplatin (Perren et al., 2011; Burger et al., 2011). The monoclonal anti-VEGF antibody bevacizumab was the first targeted therapy approved for use in advanced ovarian cancer (Perren et al., 2011; Burger et al., 2011). The addition of the antiangiogenic agent bevacizumab to carboplatin plus paclitaxel, followed by bevacizumab alone provided benefit to the time until disease progression and currently is a treatment option in patients with newly diagnosed advanced ovarian cancer (Colombo et al., 2019; Karam et al., 2017; Tewari et al., 2019; Oza et al., 2015).

Bevacizumab is a recombinant humanized monoclonal antibody directed against human vascular endothelial growth factor (VEGF). Bevacizumab inhibits VEGF signaling by blocking the binding of VEGF to its receptors and reduces tumor growth by suppressing angiogenesis in tumor tissues (Goodheart et al., 2005; Hollingsworth et al., 1995; Paley et al., 1997). Vascular endothelial growth factor (VEGF) and angiogenesis are important promoters of ovarian cancer progression (Goodheart et al., 2005; Hollingsworth et al., 1995; Paley et al., 1997; Gasparini et al., 1996; Alvarez et al., 1999). Both correlate directly with the extent of disease and inversely with progression-free survival

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(Goodheart et al., 2005; Hollingsworth et al., 1995; Paley et al., 1997) and overall survival (Hollingsworth et al., 1995; Gasparini et al., 1996; Alvarez et al., 1999; Shen et al., 2000; Duncan et al., 2008), often independently of known prognostic factors (Gasparini et al., 1996; Shen et al., 2000; Duncan et al., 2008).

Clinical development and real-world clinical practice have demonstrated the adverse events of bevacizumab. Some of them are considered as class effects and are directly related to drug's mechanism of action including gastrointestinal perforation, hypertension, proteinuria and thrombo-embolism. These adverse events are well characterized in the various neoplasms that bevacizumab has been approved and specific guidance for their management as well as joint manifestations. Joint manifestations are ill-defined adverse events (AE) that were frequently reported in the registrational trials of bevacizumab in ovarian cancer patients (Aghajanian et al., 2015). Arthralgia is a non-inflammatory pain of joints. Many cancer patients suffer from this problem during their cancer treatment. Vascular endothelial growth factor (VEGF) plays a major role in the pathophysiology of joint pain and therefore, anti-VEGF therapies are in particular associated with this complication. Arthralgia is defined as joint pain, stiffness or aching in the joints (Langenberg et al., 2011; Garcia et al., 2008).

Under this perspective, we hypothesized that joint manifestations are underreported adverse events in ovarian cancer patients receiving bevacizumab in the frontline setting and their occurrence could affect treatment and survival due to either premature treatment discontinuation or in the contrary due to serving as an indicator of treatment efficacy by creating an on-target off-tumor adverse event. Therefore, we undertook a retrospective analysis of patients treated in our institution with bevacizumab for advanced ovarian cancer. Our study aimed at describing the frequency and severity of joint manifestations in this population and identify possible implications in their survival.

2. Patients and Methods

Medical charts of patients that received bevacizumab as part of their first line treatment in our institution from 2012 through 2017 were reviewed. Patients with a diagnosis of International Federation of Gynecology and Obstetrics (FIGO) Stage III/IV epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer based on the findings at initial debulking surgery who were scheduled to receive first-line chemotherapy, or patients with Stage III/IV epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer by cytological diagnosis or histological and imaging diagnosis who had undergone interval debulking surgery after neoadjuvant chemotherapy and were scheduled to receive postoperative chemotherapy were included. The study has been approved by the Institutional Ethics Committee and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent for their participation. Demographic, clinicopahological characteristics, data regarding bevacizumab administration, adverse events and their management as well as survival data were recorded.

2.1. Statistical analysis

Continuous variables were summarized with the use of descriptive statistical measures [median and percentiles (25th, 75th)] and categorical variables were displayed as frequency tables (N, %). Number of bevacizumab cycles included also those cycles that the medication was co-administered with chemotherapy. Joint manifestations, more specifically Joint Pain (Arthralgia) and Arthritis were assessed and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.1. Overall Survival (OS) was defined as the time between the start of chemotherapy and the date of death from any cause. Progression-free Survival (PFS) was defined as the time between the start of chemotherapy and the date of progression. Alive patients were censored at the date of last contact. Kaplan-Meier estimates were used to describe and visualize the effect of categorical variables on OS and PFS. Log-rank tests were used to explore the prognostic value of categorical variables on clinical outcomes. The association of these factors with PFS and OS was assessed through HRs and their 95% confidence intervals estimated from univariate Cox proportional hazards models. All statistical analyses were performed using the SPSS software.

3. Results

3.1. Study population

Between 2012 and 2017, 76 women were included in our analysis. The clinicopathological characteristics of these patients are presented in Table 1. In details, the median age was 56.15 years and all patients had an ECOG performance status of 0 or 1. The majority of patients had FIGO stage IIIc (82.9% – 63 patients) or stage IV disease (10.5% – 8 patients). The rest patients had stage IIIa (1.3% – 1 patient) and 5.3% (4 patients) had IIIb disease. 86.8% (66 patients) had a serous histologic type, 3.9% (3 patients) had endometrioid histologic type, 3.9% (3 patients) clear cell and 5.3% (4 patients) had adenocarcinoma NOS histologic type. From these patients 72.4% (55 patients) underwent Primary debulking surgery whereas 27.6% (21 patients) were operated after neoadjuvant treatment (Interval debulking Surgery). Concerning BRCA mutation 13.2% (10 out of 76) of the patients were BRCA1/2 mutant, 40.8% (31 patients) were BRCA1/2 wild type and there was 46.1% (35 patients) that were not tested.

3.2. Bevacizumab-related study manifestations

Twenty-three patients (30.3%) developed joint manifestations, 12 (52.2%) of them had Grade I, 4 (17.4%) had Grade II and 7 (30.4) had Grade III symptoms. In our cohort, only 4 out of the 23 patients developed joint manifestations while receiving bevacizumab along with chemotherapy (17.4%). In the remaining cases, the adverse event appeared at least one cycle after chemotherapy completion, allowing for a clear association with bevacizumab administration. In all cases adverse event was deemed related to treatment with bevacizumab. All patients that developed arthritis had Grade 3 severity. In eight cases (34.8%) one joint was affected and in the remaining 15 patients (65.2%), multiple sites were affected. Three of the patients were managed with corticosteroids or methotrexate. All of them had grade 3 AEs. The remaining patients received common analgesics (26.1% – 6

Table 1
Clinicopathological characteristics of the patients.

Characteristics	Median, n (%)	
Age	56,15 (76, 100%)	
	n	**(%)**
Stage		
Ic	2	2.6%
IIIa	1	13%
IIIb	4	5.3%
IIIc	61	80.3%
IV	8	10.5%
Histology		
Serous	66	86.8%
Endometrioid	3	3.9%
Clear cell	3	3.9%
Adenocarcinoma NOS	4	5.3%
Surgery		
Primary debulking	55	72.4%
Interval debulking	21	27.6%
BRCA1/2 mutations		
Presence	10	13.2%
Absence	31	40.8%
Unknown	35	46.1%

patients) or NSAID (34.8% – 8 patients). Six patients (26.1%) received no treatment at all. The median duration of the AE was 4.8 months (0.7–28.9 months). Seven patients discontinued bevacizumab due to AE. In all but 3 patients AE was finally resolved, including 6 out of 7 cases that terminated bevacizumab. The characteristics of joint manifestations are presented in Table 2.

3.3. Joint manifestations and survival analysis

The median number of bevacizumab cycles that women developed arthralgia was 7. Median number of bevacizumab cycles received, frequency of treatment completion or treatment discontinuation due to disease progression did not differ significantly among patients that developed joint manifestations or not. In addition, the presence of BRCA1/2 mutations was not related to the onset of AE (Fig. 1). Median PFS did not differ statistical significantly between patients that developed AE and the remaining patients (25.4 vs 22.7 months) (Fig. 2)

4. Discussion

Bevacizumab is an established treatment option in ovarian cancer patients. Administration of bevacizumab has been related to various adverse events as demonstrated by randomized trials and real-world data (Perren et al., 2011; Burger et al., 2011). More severe of them include gastrointestinal perforation and thrombo-embolic events and lead to permanent drug discontinuation. In addition, mild drug-related adverse events as are joint manifestations have been reported in a significant percentage of patients with ovarian cancer treated with bevacizumab (Aghajanian et al., 2015). Joint manifestations are ill-defined adverse events (AE) but could compromise quality of life and impair tolerance of bevacizumab administration.

Our study confirms joint manifestations as a common adverse event among ovarian cancer patients receiving bevacizumab. Symptoms were though mild in the majority of patients. However, in the era of targeted therapies, long lasting mild adverse events could also affect compliance with treatment and lead to treatment discontinuation (Langenberg et al., 2011; Garcia et al., 2008). This is specifically important for bevacizumab administration since results from clinical trials suggest that the therapeutic effect in ovarian cancer patients rapidly declines post treatment discontinuation (Langenberg et al., 2011). On that basis, longer exposure to bevacizumab was tested as a part of a phase III trial that did not though meet its primary efficacy endpoint (Pfisterer et al., 2021). In a recently published cohort of ovarian cancer patients receiving bevacizumab, arthralgia was reported in almost 40% of patients. In that case, development of arthralgia was correlated with decreased progression-free survival, though its significance was not confirmed in the multivariate analysis. In our study, we evaluated all joint manifestations reported including arthralgia and arthritis. We did not detect any adverse impact of these symptoms in the duration of treatment with bevacizumab. Also, survival – both progression free and overall – was similar between patients with joint manifestations and those without symptoms. Therefore, it is likely that development of arthralgia during bevacizumab treatment do not impair survival.

Table 2
Characteristics of joint manifestations in the cohort of patients.

Characteristics	n	(%)
Presence of joint manifestations		
No	53	69.7%
Yes	23	30.3%
Type of joint manifestations		
Arthralgia	20	87%
Arthritis	3	13%
Adverse event Grading		
Grade 1	12	52.2%
Grade 2	4	17.4%
Grade 3	7	30.4%
Location of adverse event		
One joint	8	34.8%
Multiple joints	15	65.2%
Adverse event management		
No treatment	6	26.1%
Common analgesics	6	26.1%
NSAIDs	8	34.8%
Steroids/methotrexate	3	13.0%
Adverse event outcome		
Recovered	19	82.6%
Ongoing	4	17.4%

On the other hand, joint manifestations induced by bevacizumab could be an on-target, off-tumour effect of the drug. Analogous cases have been suggested for several targeted agents. Hypertension is a common adverse event for all anti-VEGF medications. Hypertension induced by VEGF-TKIs has been associated with favourable outcome in patients with metastatic kidney cancer. Vascular endothelial growth factor (VEGF) is implicated in the pathophysiology of pain and joint pain in particular (Nagai et al., 2014). More specifically, VEGF exerts neuroprotective effects (Sondell et al., 2000) and VEGF inhibition may cause degeneration of motor neurons (Oosthuyse et al., 2001) and painful sensory neuropathy by inhibiting the VEGFR2 (Verheyen et al., 2012; Beazley-Long et al., 2013). Both VEGFR tyrosine kinase inhibitors and anti-VEGF antibodies affect negatively dorsal root ganglion neurons in and HDAC6-dependent manner (Verheyen et al., 2012). Due to the neuroprotective effects of VEGF, it is postulated that long term exposure to anti-VEGF agents may also affect other types of neurons as well. Indeed, severe optic neuropathies have been recorded in glioblastoma patients treated with bevacizumab (Sherman et al., 2009). It should be noted though, that antiangiogenic treatment may have protective effect in the pain related to pre-existing osteoarthritis by a different mechanism. It is considered that increased VEGF levels in the synovial fluid are related to painful osteoarthritis and disease development (Bonnet and Walsh, 2005). Angiogenesis induced by chronic inflammation in osteoarthritis may mediate neo-innervation that contributes to joint pain experience (Mayer et al., 1999). Thus, bevacizumab has been tested successfully in preclinical models as a treatment of osteoarthritis. Under this perspective, the exact mechanism that bevacizumab may induce joint manifestations in ovarian cancer patients remain vague and it cannot be truly considered an off-tumour effect of the drug.

Finally, in our cohort of patients, joint manifestations were reported at a median number of seven administrations of bevacizumab. This implies that for the majority of the patients the onset of the adverse event was detected after frontline chemotherapy completion. This as well as the median duration of the symptoms are in accordance with previous published study (Ventriglia et al., 2021). A possible explanation could be that joint manifestations are a late onset adverse event of bevacizumab. On the other hand, bone, joint and muscle pains are frequently encountered during chemotherapy administration and are usually attributed by treating physicians to cytotoxic drugs or possible G-CSF administration. This underlies the possibility that early onset joint manifestation possibly attributed to bevacizumab could be underreported during a retrospective collection of data. This is confirmed also by a prospective analysis of joint pain during bevacizumab treatment in various neoplasms. Monotherapy of bevacizumab for more than 5 months was significantly associated with the appearance of this adverse event in this study (Vauléon et al., 2021).

Our study has several limitations. First of all, it is subjected to all biases attributed to the retrospective collection of the data. Also, it is a single center analysis. However, this ensures the homogeneity of treatment in these patients in a reference center for gynecological malignancies. Also, the number of patients may be limited, but it is analogous to those published in previous corresponding trials. Finally, co-administration of chemotherapy with bevacizumab during the initial phase of frontline treatment of these patients may have obscured reporting of joint manifestation that were attributed to bevacizumab treatment during this period. Our study has strengths too. We evaluated

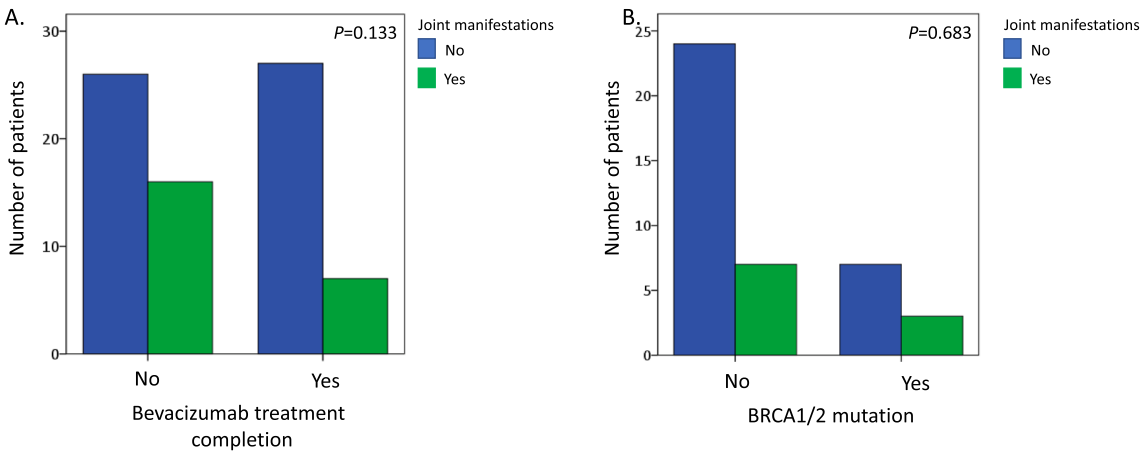
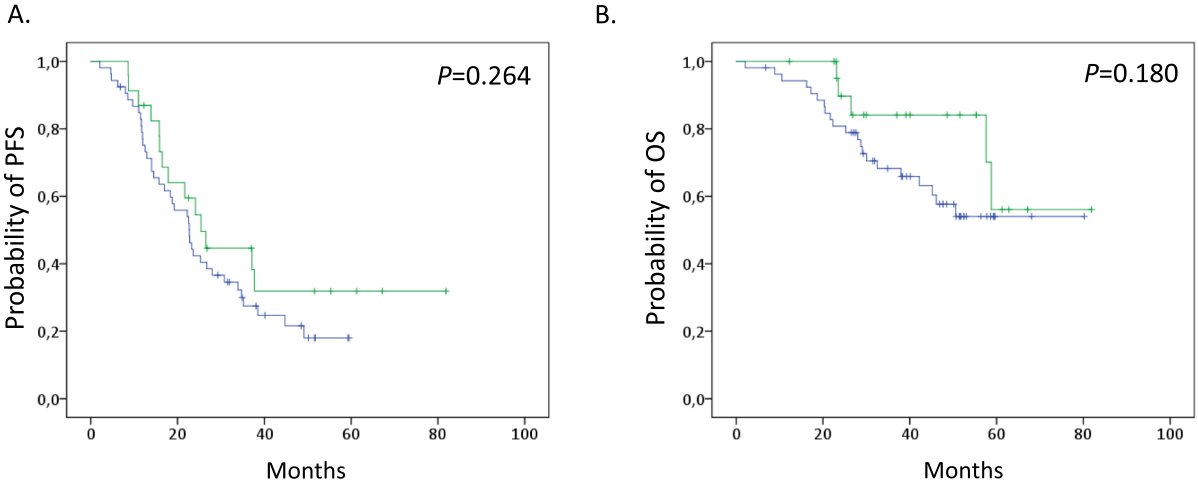


Fig. 1. A. Joint manifestations and completion of treatment. B. Joint manifestations and presence of BRCA1/2 mutations.



	Joint manifestations	
	No	Yes
Events (N/%)	40/53 [75.5%]	14/23 [61.9%]
mPFS	22.7	25.4

	Joint manifestations	
	No	Yes
Events (N/%)	21/53 [39.6%]	5/23 [21.7%]
mOS	NR	NR

Fig. 2. A. Joint manifestations and progression free survival (PFS). B. Joint manifestations and overall survival (OS).

all types of joint manifestations that could be attributed to bevacizumab administration, according to CTCAE criteria for the grading of adverse events. In addition, we have a long follow-up of the patients allowing for the association of these adverse events not only with PFS but with OS as well. Finally, we have described in detail the clinical course of these events allowing for proper management of these patients in the future.

In conclusions, our study confirms that joint manifestations are a common problem among women receiving bevacizumab maintenance treatment for ovarian cancer. We have shown that proper management leads to treatment discontinuation to only a limited number of cases. It is also reassuring that treatment interruption or premature discontinuation does not adversely affect survival in these patients. Physicians are aware of these low intensity and quite bothersome adverse events of bevacizumab and studies like ours provide information to guide therapeutic decisions in the future.

CRediT authorship contribution statement

Maria Kaparelou: Methodology, Resources, Data curation, Writing – original draft. **Michalis Liontos:** Methodology, Data curation, Writing – original draft. **Pelagia Katsimbri:** Methodology, Resources, Data curation, Writing – review & editing. **Aggeliki Andrikopoulou:** Data curation, Writing – review & editing. **Alikistis Papatheodoridi:** Writing – review & editing. **Anastasios Kyriazoglou:** Data curation, Writing – review & editing. **Aristotelis Bamias:** Methodology, Resources, Supervision, Writing – review & editing. **Flora Zagouri:** Resources, Supervision, Project administration, Writing – review & editing. **Meletios Athanasios Dimopoulos:** Resources, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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