BEVACIZUMAB IN PATIENTS WITH HEAVILY PRETREATED OVARIAN AND OTHER MULLERIAN CANCERS: A SINGLE-INSTITUTION EXPERIENCE

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ABSTRACT

Objective: Bevacizumab (Bev) is as active as any salvage chemotherapy (CTx) in patients (pts) with recurrent ovarian cancer (OC) and other Mullerian carcinomas (MTC). We hereby report on our single-institution experiences with Bev-based systemic therapy (Tx) in pts with heavily pretreated MTCs.
Methods: A total of intensively pretreated MTC pts (ovarian: n=63; fallopian tube: n=2; type II endometrial: n=4; peritoneal: n=3) who did not qualify to be recruited onto a clinical trial have been included in this analysis. Pts had received a median of 4 (range 2-10) prior CTxs, 42 were Platinum- resistant. Bev (10 mg/kg q2w or 15 mg/kg q3w was given as asingle agent (group A, n=13), with metronomic CTx (group B, n=39), or combined with conventional CTx (group C, n=20).
Results: Most common Bev related side effects were hypertension, proteinuria, headache, infection, epistaxis, and subileus which were not Tx limiting except in 2 pts. Median TTP was 25.7 wks and median OS was 55.1 wks with no difference between Pt-resistant and Pt-sensitive pts. In regard to TTP, there was a non-significant trend favoring group A (32.9 wks) and B (29.6 wks) vs group C (19.2 wks). Regarding OS, group B pts (67.7 wks) did significantly better than group C pts (35.4 wks, p=0.02).
Conclusions: Bev-based Tx was active and well tolerated in pts with heavily pretreated MTCs. Clinical Pt-resistance did not predict a worse clinical outcome. However, Bev should be preferrably given as single agent or combined with metronomic CTx.

INTRODUCTION

Angiogenesis is an important prognostic factor in ovarian carcinoma (OC) and other Mullerian tract cancers (MTCs) such as fallopian tube carcinoma (FTC), peritoneal papillary-serous carcinoma (PPSC), or type II endometrial carcinoma (EC-II). Vascular endothelial growth factor α (VEGFα) plays a crucial role in tumor angiogenesis related to MTCs. Bevacizumab (Bev) is a humanized monoclonal antibody (MAb) inhibiting angiogenesis by direct binding to VEGFα. Currently, Bev is approved for the treatment of primary advanced stage OC, FTC, and PPSC in addition to platinum-based chemotherapy (CTx). Most recently, Bev has been demonstrated to add substantial activity to conventional CTx in randomized trials run in both platinum-sensitive and platinum-resistant relapsed MTCs. In platinum-refractory OC, Bev can be regarded as active as any single chemotherapeutic agent used in this setting. Bev has also been combined successfully with metronomic CTx such as low dose oral cyclophosphamide (CPA). Nevertheless, the role of Bev in intensively pretreated MTCs has still to be defined inasmuch as limited clinical experience exists so far elucidating the optimal regimen for this drug to be used in. This paper presents a retrospective analysis Bev based salvage therapy in patients (pts) with heavily pretreated OC, FTC, PPSC, and EC-II.

METHODS

Since 2006, a total of 72 intensively pretreated pts with MTC (OC, n=63; FTC, n=2; EC-II, n=4; PPSC, n=3) who did not qualify for recruitment into a controlled clinical trial were included in this study with 42 pts (58.3%) being platinum-resistant in regard to the *Markman* criteria. Pts had received a median of 4 (range 1-10) prior CTx. It should be noted that 20 pts (27.8%) had an initial Karnofsky performance status (KPS) below 70%. In all pts, Bev based systemic Tx was given, including Bev monotherapy (group A, n= 17), Bev + metronomic CTx (group B, n=35), and Bev + conventionally dosed CTx (Group C, n=20). Bev was administered at either 10 mg/kg BW q2w or 15 mg/kg BW q3w. Patients´ characteristics are summarized in Table 1 which also gives an overview of the different regimens used in this study.
Adverse effects were classified according to the NCI-CTC scale. Response to Tx was determined by using the RECIST 1.0 criteria and reevaluated by RECIST 1.1 in all pts with bidimensionally measurable lesions. In pts presenting with evaluable disease only, response to Tx was recorded in regard to the *Rustin* criteria. The time to progression (TTP) was calculated from the start of Bev based Tx until progression or death, OS was calculated from the start of Bev based Tx until death of any case or loss to follow-up.

RESULTS

Adverse reactions associated with Bev based Tx were hypertension, proteinuria, infection, and constipation/subileus. Hematologic side effects like granulocytopenia, anemia, or thrombocytopenia were mainly attributable to simultaneously administered CTx as were alopecia, hand-foot syndrome, or neurologic dysfunctions. In general, Tx was well tolerated. Although side effects occurred frequently, they rarely exceeded NCI-CTC grade 2. Hypertension which often required adequate treatment was not limiting in any case as was not any other of the aforementioned toxicities except proteinuria and infection in either one case. Adverse effects are summarized in Table 2.
Tx efficacy is illustrated in Table 3. In the entire population treated, a total of 5 pts experienced complete remission (CR) whereas 25 showed partial remission (PR) accounting for an objective response rate (ORR) of 41.7%. Additing another 18 pts with disease stabilization (SD), the overall rate of benefit was 66.7%. Differences between treatment groups did not reach statistical significance. The overall TTP was 25.7 weeks (wks) and the OS was 55 wks. Differences in TTP between group C and group A or B lacked statistical significance. In contrast, the OS of group B pts (67.7 wks) was significantly better than that of group C pts with 35.4 wks (p=0.02). Detailed survival analyses are shown in Figure 1. Interestingly, clinical platinum sensitivity did not influence TTP and OS, as well. It should be noticed however, that pts presenting with a low KPS (i. e. 50-60%) had significantly poorer chance to experience long-lasting TTP, or OS (p<0.0001).

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Table 1: Patients´characteristics

Age	
Median	57 J.
Range	29-78 J.
Karnofsky performance status	**n**
90-100%	14
70-80%	38
50-60%	20
Diagnosis	**n**
Ovarian Carcinoma	63
Fallopian Tube Carcinoma	2
Peritoneal Papillary-Serous Carcinoma	3
Type II Endometrial Carcinoma	4
Clinical platinum sensitivity	**n**
Sensitive	30
Resistant	42
No. of prior chemotherapies	**n**
1-2	15
3-4	26
5-6	15
>6	16
Median	*4*
Range	*1-10*
Bevacizumab-based regimen	**n**
Bevacizumab monotherapy	17
Combinations with metronomic therapy	35
alkylating agents (cyclophosphamide; trofosfamide)	*31*
others (capecitabine; etoposide; combinations	*4*
Combinations with conventional chemotherapy	20
pegylated liposomal doxorubicin	*7*
other single agents (capecitabine; gemcitabine; paclitaxel; topotecan)	*4*
paclitaxel-based combinations (with mitoxantrone)	*2*
gemcitabine-based combinations (with trosulfan or mitomcin C)	*7*

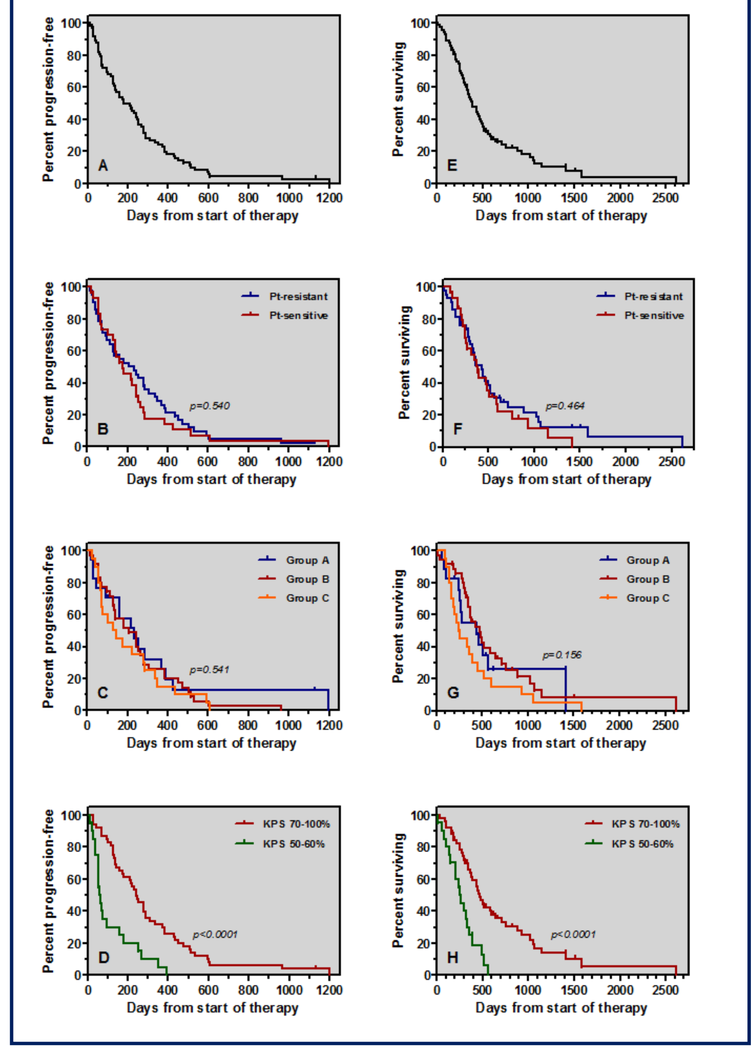

Figure 1: Survival after bevacizumab-based therapy. A-D: progression-free survival; E-H: overall survival; A, E: entire population treated; B, F: survival related to clinical platinum sensitivity; C, G: survival related to treatment of groups A, B, and C; D, H: survival related to performance status

Table 2: Toxicity associated with bevacizumab-based therapy.
*adverse effects which are likely to be related to bevacizumab

Toxicity	Any grade	G3	G4
Hematologic			
Neutropenia	12	5	-
Anemia	13	2	-
Thrombocytopenia	6	1	-
Fever*	5	1	1
Infection*	16	2	1
Non-hematologic			
Alopecia	11	5	-
Hypertension*	25	5	-
Hand-foot syndrome	7	-	-
Gastrointestinal			
Nause/Vomiting	7	-	-
Constipation/Subileus*	8	1	-
Diarrhea *	4	-	-
Proteinuria*	23	3	1
Sensory polyneuropathy	5	-	-
Headache*	6	1	-
Bleeding*	4	-	-

Table 3: Efficacy of bevacizumab-based therapy

	Group A	Group B	Group C	Total
CR	2	2	1	5
PR	6	13	6	25
SD	3	10	5	18
PD	6	10	8	24
ORR	47.1%	42.9%	35.0%.	41.7%
RWB	64.7%	71.4%	60.0%	66.7%
TTP (median)	32.9 wks	29.6 wks	19.2 wks	25.7 wks
		P=0.02		
OS (median)	63.0 wks	67.7 wks	35.4 wks	55.1 wks

CONCLUSIONS

- Bevacizumab-based salvage therapy was feasible in patients with heavily pretreated advanced Mullerian carcinomas
- In the treated papulation of patients, bevacizumab-based therapy was generally well tolerated.
- Toxicity was managable even in relatively frail patients with a low initial performance status.
- Bevacizumab-related side effects were not therapy-limiting with very few exceptions. In particular, intestinal perforations were not observed in this group of patients despite their intensive pretreatment.
- Bevacizumab-based salvage therapy was effective in patients with heavily pretreated patients with advanced Mullerian carcinomas.
- Combinations of bevacizumab and conventional chemotherapy did not offer any advantages over bevacizumab monotherapy or bevacizumab-based metronomic therapy in the population studied.
- Due to the managable toxocity profile, bevacizumab-based therapy can be given to relatively frail patients although they have a significantly poorer chance to experience long-term responses.
- Bevacizumab-based therapy appears to be a valuable option for the salvage therapy of heavily pretreated patients with Mullerian carcinomas irrespectively of their clinical platinum resistance status.
- When used as salvage therapy in heavily pretreated patients, bevacizumab should be preferrably given as monotherapy or combined with metronomic therapy