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A SINGLE-INSTITUTION EXPERIENCE OF BEVACIZUMAB-BASED THERAPY IN HEAVILY PRETREATED EPITHELIAL OVARIAN AND OTHER MULLERIAN CARCINOMAS

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ABSTRACT*

Background: Vascular endothelial growth factor α (VEGFα) mediated angiogenesis is an important prognostic factor in advanced and relapsed Mullerian tract cancers (MTC) such as ovarian (OC), fallopian tube (FTC), type II endometrial (EC-II), and peritoneal papillary-serous carcinomas (PPSC). Recently, bevacizumab (Bev) is the only commercially available VEGFα blocker. Single agent Bev has been found to be as active as any salvage chemotherapy (CTx) in platinum-resistant OC. Despite its unequivocal merits in recurrent disease, the current approval of Bev covers only primary advanced MTCs. We herein summarize our single-institution experience with Bev based systemic therapy (Tx) in patients (pts) with heavily pretreated recurrent MTCs.
Methods: Since 2006, a total of 78 intensively pretreated MTC pts (OC, n=69; 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 45 pts (57.7%) being platinum-resistant. Pts had received a median of 4 (range 1-10) prior CTx. In all pts, Bev based systemic Tx was given, including Bev monotherapy (group A, n= 19), Bev + metronomic CTx (group B, n=38), and Bev + conventionally dosed CTx (Group C, n=21). In all pts, Bev was administered at either 10 mg/kg BW q2w or 15 mg/kg BW q3w. Adverse effects were classified according to the CTCAE 4.0 scale. TTP was calculated from the start of Bev until progression, OS was calculated from the start of Bev until death of any case or loss to follow up.
Results: The most common adverse effects associated with Bev based Tx were hypertension, proteinuria, headache, inflammation/infection, epistaxis, and subileus. Hypertension which often required adequate treatment was limiting in only case, as also were renal toxicity, bowel obstruction, and infection. In the entire population, median TTP was 29.9 wks and median OS was 55.1 wks with no significant difference between platinum-resistant and –sensitive pts. In regard to both TTP and OS, there was a non-significant trend favoring group A (36.0/66.4 wks) and B (29.9/61.6 wks) vs group C (20.3/36.0 wks).
Conclusion: Bev based Tx was active and generally well tolerated in this hard-to-treat population of pts with recurrent MTC. Both TTP and OS were equal or even superior to any conventional Ctx used in this setting. Moreover, clinical Platinum-resistance did not predict a worse clinical outcome. Although this is not a randomized trial, we conclude, that Bev should be preferably given either as single agent or alongside with metronomic CTx in pts with intensively pretreated MTCs. Further clinical trials of Bev in recurrent MTCs are strongly recommended.

*this paper represents an updated version of the abstract submitted

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 78 intensively pretreated pts with MTC (OC, n=69; 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 45 pts (57.7%) 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 22 pts (28.2%) had an initial Karnofsky performance status (KPS) below 70%. In all pts, Bev based systemic Tx was given, including Bev monotherapy (group A, n= 19), Bev + metronomic CTx (group B, n=38), and Bev + conventionally dosed CTx (Group C, n=21). 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 CTCAE 4.0 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, epistaxis, and constipation/subileus. Hematologic side effects like neutropenia, 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 CTCAE grade 2. Hypertension which often required adequate treatment was limiting in only case as were nephrotoxicity, bowel obstruction, and infection occurring in either one additional individual. Thus, 4 (5,1%) of Bev-based treatments had to be terminated due to Tx related side effects which were mainly attributable to Bev in 3 cases. Adverse effects are summarized in Table 2.
Tx efficacy is illustrated in Table 3. In the entire population treated, a total of 6 pts experienced complete response (CR) whereas 27 showed partial remission (PR) accounting for an objective response rate (ORR) of 42.3%. Additing another 18 pts with disease stabilization (SD), the overall rate of benefit was 65.4%. Differences between treatment groups did not reach statistical significance. The overall TTP was 29.9 weeks (wks), and OS was 55.1 wks, respectively. Although pts out of group A (36.1/66.4 wks) or B (29.9/61.6 wks) seemed to do better than those out of group B (20.3/36.0 wks) in terms of both TTP and OS, this trend did not reach statistical significance. Detailed survival analyses are shown in Figure 1. Interestingly, clinical platinum resistance did not adversely influence response rates or survival, neither TTP nor OS (Fig. 1 B,F). It should be noted however, that pts presenting with a low KPS (i. e. 50-60%) had a significantly poorer chance to experience long-lasting TTP, or OS (36.4 vs 67.7 and 9.3 vs 35.0 wks, p<0.0001) as shown in Fig. 1 D, H..

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Table 1: Patients´characteristics

Age	
Median	57.5 J.
Range	29-79 J.
Karnofsky performance status	**n**
90-100%	17
70-80%	39
50-60%	22
Diagnosis	**n**
Ovarian Carcinoma	69
Fallopian Tube Carcinoma	2
Peritoneal Papillary-Serous Carcinoma	3
Type II Endometrial Carcinoma	4
Clinical platinum sensitivity	**n**
Sensitive	33
Resistant	45
No. of prior chemotherapies	**n**
1-2	17
3-4	29
5-6	16
> 6	16
Median	*4*
Range	*1-10*
Bevacizumab-based regimen	**n**
Bevacizumab monotherapy	19
Combinations with metronomic therapy	38
alkylating agents (cyclophosphamide; trofosfamide)	*32*
others (etoposide, cyclophosphamide+capecitabine)	*6*
Combinations with conventional chemotherapy	21
pegylated liposomal doxorubicin	*7*
other single agents (capecitabine; gemcitabine; paclitaxel; topotecan)	*4*
paclitaxel-combinations (with mitoxantrone)	*2*
gemcitabine-based combinations (with treosulfan or mitomcin C)	*8*

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

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

Table 3: Efficacy of bevacizumab-based therapy

	Pt-resistant	Pt-sensitive	Group A	Group B	Group C	Total
CR	5	1	2	2	2	**6**
PR	16	11	7	14	6	**27**
SD	8	10	4	19	5	**18**
PD	16	11	6	13	8	**27**
ORR	46.7%	36.4%	47.4%	42.1%	38.1%.	**42.3%**
RWB	64.4%	67.6%	68.4%	65.9%	61.9%	**65.4%**
TTP (median)	29.9 wks	31.0 wks	36.0 wks	29.9 wks	20.3 wks	**29.9 wks**
OS (median)	52.1 wks	55.1 wks	66.4 wks	61.6 wks	36.0 wks	**55.1 wks**

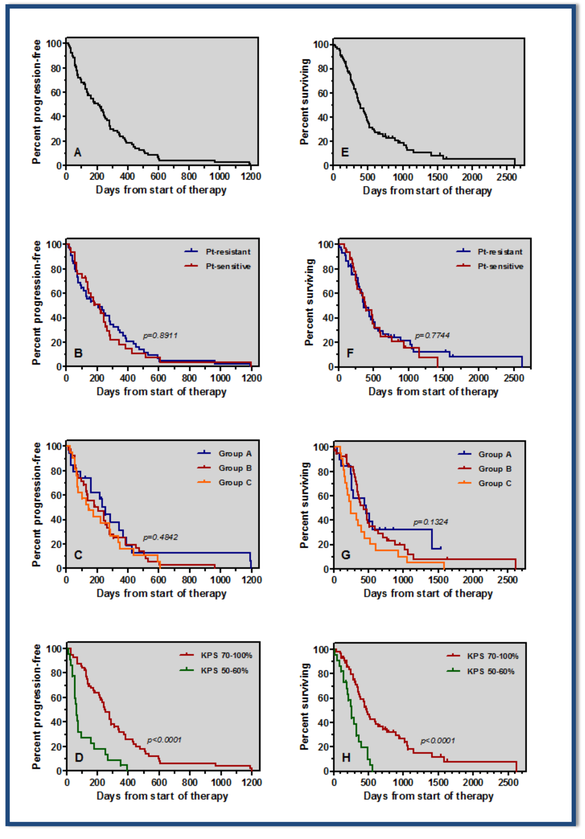

Figure 1: Survival after bevacizumab-based therapy. A-D: progression-free survival; E-H: overall survival; A, E: entire population treated; B, F: survival related to clinical platinum sensitivity; C, G: survival related to treatment of groups A, B, and C; D, H: survival related to performance status

CONCLUSIONS

- Bevacizumab-based salvage therapy was feasible in patients with heavily pretreated advanced epithelial ovarian and other Mullerian carcinomas such as fallopian tube cancer, peritoneal papillary-serous carcinoma, and type II endometrial cancer
- In the treated population 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 while being on therapy despite their intensive pretreatment.
- Bevacizumab-based salvage therapy was effective in patients with heavily pretreated patients with epithelial ovarian cancer and other advanced Mullerian carcinomas.
- Clinical platinum-resistance did not result in an impaired likelihood of both response and survival
- 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 ovarian cancer and other Mullerian carcinomas irrespectively of their clinical platinum resistance status.
- When used as salvage therapy in heavily pretreated patients, bevacizumab should be preferably given as monotherapy or combined with metronomic therapy.