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# BEVACIZUMAB-BASED THERAPY IN PATIENTS WITH INTENSIVELY PRETREATED EPITHELIAL OVARIAN AND OTHER MULLERIAN TRACT CARCINOMAS:A SINGLE-INSTITUTION EXPERIENCE

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## BACKGROUND

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** |

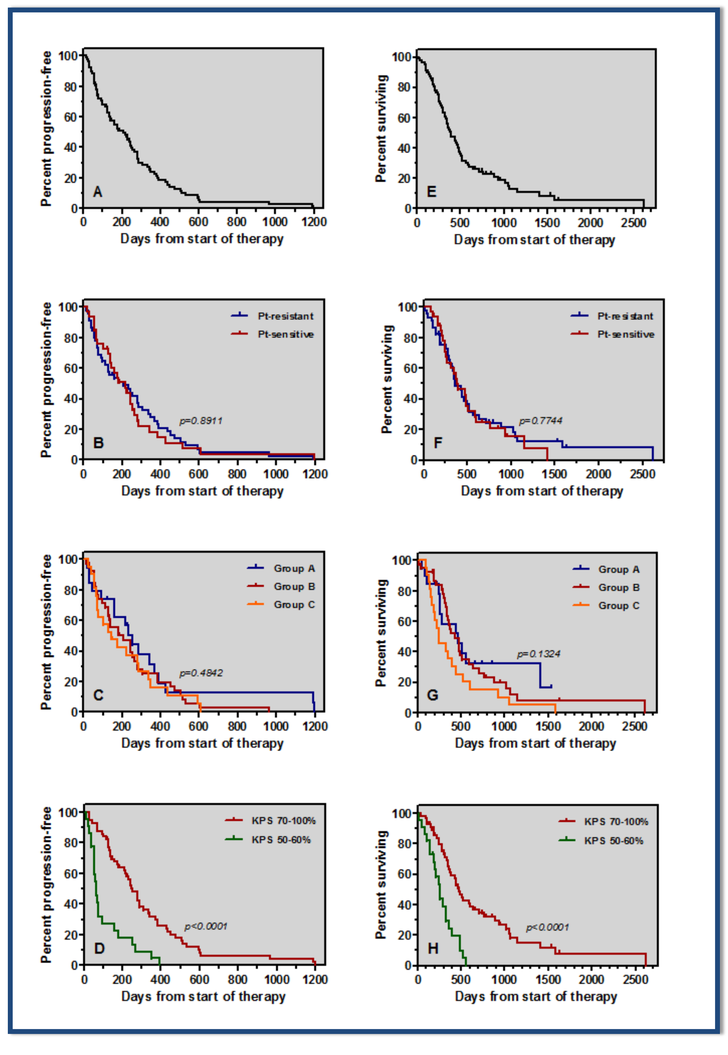


**Figure 1:** Survival after bevacizumab-based therapy. A-D: progression-free survival; E-H: overall survival; A, E: entire population treated; B, F: survival related to clinical platinum sensitivity; C, G: survival related to treatment of groups A, B, and C; D, H: survival related to performance status

## 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.