EJGO European Journal of Gynaecological Oncology

Original Articles

Single-agent bevacizumab for the management of refractory malignant effusions in heavily pretreated patients with recurrent high-grade serous cancers of the ovary, fallopian tube or peritoneum: results from a single institution

W.Y. Chay[1,3], A. Kumar[2], P.J. Hoskins[1], A.V. Tinker[1]

[1]Department of Medical Oncology, British Columbia Cancer Agency, Vancouver
[2]Department of Medical Oncology, British Columbia Cancer Agency, Surrey (Canada)
[3]National Cancer Centre Singapore (Singapore)

Summary

Purpose of Investigation: The authors conducted a retrospective review of single-agent bevacizumab in the management of chemotherapy-refractory malignant effusions in high-grade serous carcinomas (HGSCs). *Material and Methods:* Eligible patients who received single-agent bevacizumab as treatment of refractory malignant effusions were included. The mean paracentesis/thoracentesis interval (MPTI) in days was determined pre- and post-bevacizumab for each patient. Treatment response was defined by a doubling of the MPTI. *Results:* Ten cases were evaluable. Median age was 64 years (47- to 70-years-old). Median number of prior lines of chemotherapy was 6 (range 3-9). The MPTI pre- and post-bevacizumab was 19.6 (3.5-60.5) and 34.8 (5-83) days, respectively. Response rate was 50% (5/10 cases). There was a trend to significance in the difference between the pre- and post-bevacizumab MPTI ($p = 0.26$). Three patients had an extremely long MPTI greater than 60 days between subsequent paracenteses. *Conclusions:* Single agent bevacizumab is useful in the management of symptomatic chemotherapy-refractory malignant effusions in HGSC.

Key words: Ascites; Ovarian cancer; Fallopian tube cancer; Peritoneal cancer; Bevacizumab.

Introduction

Ascites is a frequent clinical problem in patients with recurrent epithelial ovarian, fallopian tube and serous peritoneal cancers (EOC). Thirty percent of patients with platinum resistant/refractory EOC were reported to have malignant ascites in the AURELIA (Avastin Used in Platinum-Resistant Epithelial Ovarian Cancer) study [1]. Ascites causes a wide range of debilitating symptoms such as bloating, pain, dyspnea, nausea, reduced appetite, reduced mobility, and eventual protein malnutrition. The best therapy is to shrink the cancer with chemotherapy. When that goal is no longer possible due to refractory cancer, the physician is then reliant upon physical drainage. However, evacuation of cavity fluids by paracentesis or thoracentesis only provides temporary symptomatic relief, and typically needs to be repeated often with increasing frequencies. These procedures place patients at risk of discomfort, bleeding, infection, and bowel perforation. Finally, they are time consuming, resource intensive, and require a skilled physician and potentially a sonographer, to execute safely. Indwelling catheters are often used as a means to reduce the need for frequent repeated paracenteses. The long term use of these foreign devices pose a potential source of infection for patients. The care of the indwelling catheter is largely dependent on each individual patient who is often not medically trained. Even with best hygiene and nursing practices, patients are often faced with risks of catheter infection requiring hospitalization and removal of the catheter. The presence of an indwelling catheter also increases the risks of loculated effusions. This makes further paracenteses technically difficult and dangerous. Living with a long term drainage catheter also inconveniences the patients. As such, other strategies to "dry up" the effusions would be of great value.

Vascular endothelial growth factor (VEGF) levels are significantly elevated in malignant effusions. VEGF is secreted by tumour cells, and promotes vascular permeability, resulting in extravasation of fluid and proteins into the peritoneum [2, 3]. In a randomized double-blinded, phase II trial of IV aflibercept (a high affinity anti-body against cir-

Revised manuscript accepted for publication October 26, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 6, 2018
doi: 10.12892/ejgo4452.2018

7847050 Canada Inc.
www.irog.net

culating VEGF) in women with recurrent, symptomatic ascites secondary to EOC, benefit was demonstrated by the doubling of the paracentesis interval in the intervention arm from a median of 23 to 55 days (95% CI 10·6-53·1; p = 0.0019) [4]. Development of the drug was not further pursued in this population on account of a high incidence of gastrointestinal perforation (10%) including three deaths in the aflibercept group.

Bevacizumab is a monoclonal antibody against all isoforms of VEGF-A. The potential value of bevacizumab in the management of ascites in current literature is limited. As a single-agent, bevacizumab has been used for the management of refractory malignant ascites in a small series that included nine patients with colorectal, breast, uterine, and ovarian cancers [5]. They were treated with 5 mg/m^2 of intraperitoneal (IP) bevacizumab on a monthly basis, and all experienced resolution of their ascites over the following two months of observation. IP bevacizumab was used in a woman with refractory ovarian high-grade serous carcinomas (HGSCs) with dramatic improvement in ascites control [6]. Intravenous bevacizumab as a single agent for four heavily pretreated patients with refractory ovarian cancer and ascites also resulted in benefit seen for all four patients [7].

The AURELIA phase III study looked at the impact of bevacizumab when added to standard cytotoxics in women with recurrent, platinum resistant EOC. The addition of bevacizumab significantly improved PFS from 3.4 months to 6.7 months [HR: 0.48 (95% CI. 0.38-0.60; unstratified log-rank $p < 0.001$)] [1]. Among the patients with ascites, 2% of those randomized to the bevacizumab arm required paracenteses, while they remained on treatment compared to 17% in the group receiving chemotherapy alone. In the subgroup of patients with ascites, 44 % of those receiving bevacizumab had an improvement in QoL scores, versus only 4.1% in the chemotherapy only arm (CI, 23.9%-55.9%; $p <$ 0.001). The high rate of ascites control by VEGF-targeted therapies, coupled with the QoL improvements support the use of bevacizumab in refractory EOC, in particular for patients with malignant effusions.

The British Columbia Cancer Agency does not routinely fund bevacizumab for women with EOC. However, on compassionate grounds, the present institution has permitted access to bevacizumab for patients with chemotherapy refractory EOC and malignant effusions that needed frequent drainages. The authors report on their provincial experience using single-agent bevacizumab for the management of refractory malignant effusions due to HGSC of ovarian, fallopian tube or peritoneal origin. They quantified the degree of benefit as measured by the doubling of the MPTI pre- and post-bevacizumab.

Materials and Methods

A retrospective chart review was performed on all women who received single-agent bevacizumab for HGSC for ovarian/fallopian tube/primary peritoneal origin at the British Columbia Cancer Agency from January 2007 to the March 2015. Patients were identified from a provincial computerized pharmacy database. Patients were eligible for bevacizumab if they had an ECOG Performance Status of ≤ 3, platinum refractory disease (progression on platinum, or within three months of last platinum treatment), and required frequent para/thoracentesis. Women with prior in-patient management of bowel obstruction or uncontrolled HTN were not eligible for bevacizumab.

The dates of all para/thoracenteses in eligible cases in the three months preceding the initiation of bevacizumab, and while on bevacizumab treatment were recorded. The mean paracentesis/thoracentesis interval (MPTI) in days was calculated using two paracentesis/thoracentesis intervals immediately pre- and one or two paracentesis/thoracentesis intervals post-bevacizumab for each patient. Patients were then noted to have a response to treatment if the MPTI post bevacizumab was two times or greater than the MPTI pre-bevacizumab. A paired t-test was undertaken to determine if there was a difference in the mean MPTI pre and post bevacizumab, assuming significance of $p < 0.05$. The statistical program R version 3.2.0 was used for the data analysis. Institutional research ethics board approval was obtained for this retrospective analysis.

Results

Study population characteristics are shown in Table 1. Fourteen patients in British Columbia received single agent bevacizumab during the specified time period. Four were excluded as they could not be evaluated for response due to not having any post-bevacizumab para/thoracentesis procedures. Among the four excluded patients, the authors were unable to obtain details of followup outside their institution for one of the patients who had been discharged from British Columbia Cancer Agency. Two cases were excluded due to concurrent chemotherapy administration with bevacizumab: oral cyclophosphamide and liposomal doxorubicin respectively. The last case only received bevacizumab over two months and had an interruption in bevacizumab treatment during this period due to subacute intestinal obstruction which resolved. A total of ten cases were eligible for the analysis. Median age was 64 (range 47 to 70) years. The median ECOG performance status was 2 (range 1-3). The median number of prior lines of therapy was 6 (range 3-9).

The most common indication for use of single-agent bevacizumab was for symptomatic ascites requiring repeated paracentesis (n=5). Three other cases had symptomatic pleural effusions requiring repeated thoracocentesis or the insertion of an indwelling PleurX catheter. Two cases had both symptomatic pleural effusions and ascites.

A median of four (range 1-18) cycles of bevacizumab were administered, with the most common dose being 7.5 mg/kg every three weeks (n=5). Other dosing regimens included 7.5 mg/kg given every four weeks (n=4) and 15 mg/kg every three weeks (n = 1). Nine out of ten patients

Table 1. — *Patient characteristics and treatment details.*

N.	Age	Line of tx	Effusion	Bev # cycles	Bev dose	Mean duration between paracentesis (Days)*		Response	Toxicities	Further lines of treatment
						Pre-Bev	Post Bev			
1	66	6	Peritoneal	5	7.5 mg Q28	22.5	28	No	Nil	Liposomal doxorubicin, vinorelbine
2	57	5	Pleural	3	7.5mg Q21	20.3	90	Yes	Empyema	Liposomal doxorubicin
3	47	4	Peritoneal	2	15 mg Q21	7.1	18	Yes	Chylous fluid	Nil
4	68	6	Pleural and peritoneal	2	7.5 mg Q28	60.5	5	No	Nil	Nil
5	65	7	Peritoneal	7	7.5mg/kg Q21	5.1	10.3	Yes	Nil	Nil
6	60	9	Pleural	18	7.5 mg Q21	25.5	66	Yes	Pulmonary embolism	Nil
7	70	6	Peritoneal	5	7.5mg Q28	22.0	8	No	Nil	Capecitabine
8	76	6	Peritoneal	7	7.5mg Q21	14.0	22	No	Loculated ascites	Bevacizumab ongoing
9	52	4	Pleural and peritoneal	1	7.5 mg Q21	14.0	12.3	No	Nil	Gemcitabine
10	63	3	Pleural	2	7.5 mg Q28	3.5	83	Yes	Nil	Liposomal doxorubicin, paclitaxel

**Defined using the two preceding intervals performed most recent to starting bevacizumab and the most recent paracentesis performed after bevacizumab. Tx = treatment.*

received single-agent bevacizumab. One patient received concurrent letrozole. The median duration of treatment with bevacizumab was 12 (range 3-54) weeks.

The mean MPTI increased from 19.6 (range 3.5-60.5) days pre-bevacizumab to 34.8 (range 5-83) days after the initiation of bevacizumab ($p = 0.26$). A 50% response rate was noted (5 of 10 cases, Table 1). Three (30%) patients had a very long mean duration between their subsequent paracenteses of greater than 60 days (subjects 2, 6, and 10). In contrast, the mean duration of paracenteses for these three subjects prior to bevacizumab administration was 20.3, 25.5, and 3.5 days, respectively.

Bevacizumab was well-tolerated with few documented side effects. Blood pressure was well controlled in the eight cases where blood pressure measurements were available. There were no cases of drug discontinuation for uncontrolled hypertension. Details of urinalysis were known for six cases with no cases of proteinuria documented. One out of the ten patients developed a pulmonary embolism requiring anticoagulation. There were no cases of gastro-intestinal perforation, although one case developed intestinal obstruction requiring the discontinuation of bevacizumab. There were no deaths due to bevacizumab toxicity.

The median overall survival after initiation of treatment with bevacizumab was 6.5 (range of 1 to 14) months. Only one patient was alive at the time of data cutoff. Five out of the ten received further treatment after single agent bevacizumab was discontinued. Liposomal doxorubicin was the most commonly used drug (n=3). Other cytotoxics included vinorelbine, capecitabine, gemcitabine, and paclitaxel.

Discussion

Response rates of platinum refractory EOC to standard cytotoxic agents are low, typically < 10% [8]. Symptom management and quality of life remain a priority in the management of these patients and standard chemotherapy does not routinely provide this.

To the present authors' knowledge, this is the largest reported series of selected patients with HGSC ovarian/fallopian tube/peritoneal carcinoma with chemotherapy refractory malignant effusions managed by single-agent bevacizumab. Reports on the role of single-agent bevacizumab specifically for symptomatic ascites from refractory EOC are limited. Two case reports describe a total of five patients, all of whom benefited from single agent bevacizumab, however the magnitude of benefit was not quantified [6, 7]. The present study demonstrated that single-agent bevacizumab given intravenously decreased the frequency of fluid evacuation and in 50% of patients, the time interval between evacuations at least doubles, even in heavily pre-treated patients, including those with chemotherapy-refractory disease. Of interest, three patients experienced a remarkable response to treatment with a mean duration between paracenteses of greater than 60 days after starting bevacizumab.

The present study consisted of very heavily pre-treated patients with borderline performance status. Bevacizumab, despite Health Canada approval, has not had provincial funding and none of the present patients had received it with earlier lines of therapy. Despite this, there were no serious complications, such as bowel perforation, documented. Bevacizumab was either the final or penultimate line of treatment. Even in this heavily pretreated patient, the use of bevacizumab can be safe and efficacious when properly selected. Better results may be possible in fitter patients. Further work, essentially treating more patients, is needed to better identify possible factors predictive of the HGSC subpopulation that benefits from use of bevacizumab.

The present study has several limitations. It is retrospective and small. The authors did not have data regarding the incidence of protein malnutrition, anasarca, and hypoalbuminemia among the study population, although these factors can certainly contribute to the re-accumulation of ascites in this patient population, making it more difficult to ascertain clinical benefit. The incidence of protein malnutrition and hypoalbuminemia is common in heavily pretreated populations and likely to worsen with time as the cancer progresses. Yet patients who received bevacizumab still experienced a longer duration between subsequent paracenteses despite their ongoing poor nutritional status. The present treatment population was selected, as none had had a history of bowel obstruction, and this study only looked at single agent bevacizumab use, without the addition of chemotherapy. Despite this, it suggests that bevacizumab alone can have significant activity against malignant effusions without the toxicity associated with the addition of cytotoxic chemotherapy. Single agent bevacizumab is very well tolerated, having virtually none of the common chemotherapy related side-effects such as nausea, vomiting, alopecia, rashes, and myelosuppression. The side effects of bevacizumab (hypertension, proteinuria, being the most common), seldom lead to a deterioration in quality of life, and can often be well managed. The AURELIA trial clearly demonstrated the benefits of bevacizumab added to chemotherapy on the management of malignant effusions. That trial also demonstrated that chemotherapy alone was not sufficient to manage effusions for the majority of patients randomized to the control arm as patients with platinum resistant disease seldom benefit from subsequent lines of chemotherapy. A post-hoc analysis of the GOG-0218 trial also suggests that the presence of ascites is a predictive factor of benefit from bevacizuamb, although GOG-0218 is a first-line trial of bevacizumab with chemotherapy in treatment of sensitive patients [9]. The heavily pre-treated patient population included in this review had already failed the management of effusions using standard cytotoxics, but a substantial proportion responded to single agent bevacizumab.

Conclusions

In conclusion, this study supports the role of single-agent bevacizumab as effective palliation of symptomatic ascites or pleural effusions in chemotherapy refractory ovarian HGSC.

References

[1] Pujade-Lauraine E., Hilpert F., Weber B., Reuss A., Poveda A., Kristensen G., *et al.*: "Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial". *J. Clin. Oncol.*, 2014, *32*, 1302.

[2] Kraft A., Weindel K., Ochs A., Marth C., Zmija J., Schumacher P., *et al.*: "Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease". *Cancer*, 1999, *85*, 178.

[3] Zebrowski B.K., Liu W., Ramirez K., Akagi Y., Mills G.B., Ellis L.M.: "Markedly elevated levels of vascular endothelial growth factor in malignant ascites". *Ann. Surg. Oncol.*, 1999, *6*, 373.

[4] Gotlieb W.H., Amant F., Advani S., Goswami C., Hirte H., Provencher D., *et al.*: "Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study". *Lancet Oncol.*, 2012, *13*, 154.

[5] El-Shami K., El-Kerm Y.: "Open- label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites". *J. Clin. Oncol.*, 2007, *25*, 9043.a

[6] Hamilton C.A., Maxwell G.L., Chernofsky M.R., Bernstein S.A., Farley J.H., Rose G.S.: "Intraperitoneal bevacizumab for the palliation of malignant ascites in refractory ovarian cancer". *Gynecol. Oncol.*, 2008, *111*, 530,

[7] Numnum T.M., Rocconi R.P., Whitworth J., Barnes M.N.: "The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma". *Gynecol. Oncol.*, 2006, *102*, 425.

[8] Despierre E., Yesilyurt B.T., Lambrechts S., Johnson N., Verheijen R., van der Burg M., *et al.*: "Epithelial ovarian cancer: rationale for changing the one-fits-all standard treatment regimen to subtype-specific treatment". *Int. J. Gynecol. Cancer*, 2014, *24*, 468.

[9] Ferriss J.S., Java J.J., Bookman M.A., Fleming G.F., Monk B.J., Walker J.L., *et al.*: "Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study". *Gynecol. Oncol.*, 2015, *139*, 17.

Corresponding Author:
WEN YEE CHAY, M.D.
National Cancer Centre Singapore
11 Hospital Drive
169610 (Singapore)
e-mail: chay.wen.yee@singhealth.com.sg