Gynecologic Oncology 161 (2021) 374–381

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

REZOLVE (ANZGOG-1101): A phase 2 trial of intraperitoneal bevacizumab to treat symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer

Katrin M. Sjoquist [a,*], David Espinoza [a], Linda Mileshkin [b], Sumitra Ananda [b,g,h,i], Catherine Shannon [c], Sonia Yip [a], Jeffrey Goh [d], David Bowtell [b,j], Michelle Harrison [e], Michael L. Friedlander [f]

[a] National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Australia
[b] Peter MacCallum Cancer Centre, Melbourne, Australia
[c] Mater Cancer Care Centre, South Brisbane, Australia
[d] Icon Cancer Centre, Brisbane, Australia
[e] Chris O'Brien Lifehouse, Sydney, Australia
[f] Prince of Wales Hospital, Sydney, Australia
[g] Western Health, Furlong Road, St Albans, Australia
[h] Epworth Freemasons Hospital, East Melbourne, Australia
[i] Department of Medicine, Western Health, University of Melbourne, Melbourne, Australia
[j] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia

HIGHLIGHTS

- Malignant ascites is an important cause of morbidity for cancer patients, including those with recurrent ovarian cancer.
- Limited treatment options exist to manage ascites in patients with chemo-resistant cancers who are receiving best supportive care.
- This study investigated the effect of intraperitoneal injections of low-dose bevacizumab on ascites formation in patients.
- Intraperitoneal bevacizumab was safe, active, and warrants further study as a palliative intervention.

ARTICLE INFO

Article history:
Received 5 November 2020
Accepted 2 February 2021
Available online 23 February 2021

Keywords:
Ovarian cancer
VEGF inhibitors
Intraperitoneal therapy
Ascites
Palliative care

ABSTRACT

Background. The primary aim of this study was to evaluate the activity of intraperitoneal bevacizumab (IP-bev) in delaying re-accumulation of malignant ascites in women with chemotherapy-resistant epithelial ovarian cancer (CR-EOC) who have ceased chemotherapy. Secondary outcomes were safety and quality of life.

Methods. Women with CR-EOC and malignant ascites that reaccumulated within 28 days of their last paracentesis (P-1) were administered IP-bev 5 mg/kg following their first therapeutic paracentesis on study (P0). Additional doses of IP-bev were allowed at each subsequent paracentesis (P1, P2, etc) provided the interval from the last dose was 42 days or greater (median time from first to second therapeutic ascitic drainage).

Results. 24 participants (median age 67 years [range 38–86]; median 4.5 lines prior systemic treatment [range 1–12]; ECOG performance status of 0 in 1, 1 in 8, and 2–3 in 15) were recruited. The doses of IP-bev administered were 1 in 13 participants, 2 in 5, 3 in 2, 4 in 1, and 5 in 1. The proportion with a TTP of >42 days using competing risk analysis was 77% (95% CI 58–92). Median time from P0 to P1 or death was 48 days (range 8–248). Median paracentesis-free interval (P0–P1 or death) was 4.29-fold (95% CI 2.4–5.8) higher following a first dose of IP-bev compared with the time between paracenteses prior to study entry (P-1–P0).

Conclusion. IP-bev was safe, active, and warrants further study as a palliative intervention for recurrent ascites in CR-EOC patients receiving best supportive care.

1. Introduction

Malignant ascites is common and an important cause of morbidity for patients in the last months of life with a variety of cancer types, including recurrent ovarian and other gynaecological cancers, as well as

* Corresponding author at: NHMRC Clinical Trials Centre, University of Sydney, Australia Locked Bag 77, Camperdown, NSW 1450, Australia.
E-mail address: katrin.sjoquist@ctc.usyd.edu.au (K.M. Sjoquist).

https://doi.org/10.1016/j.ygyno.2021.02.002

breast, colorectal, gastric and pancreatic cancers. Malignant ascites has a major impact on quality of life. Symptoms include abdominal pain, abdominal distension, nausea, anorexia, dyspnoea, vomiting and fatigue. Malignant ascites is a negative prognostic factor for overall survival [1]. The mean survival duration is only about 20 weeks after the diagnosis of malignant ascites, but there is significant variation in survival between patients with different tumour types. The survival of patients with malignant ascites from ovarian cancer has been reported to be as high as 30–35 weeks [2], but this likely includes patients with chemotherapy-sensitive cancers and is shorter in patients with chemotherapy-resistant epithelial ovarian cancer (CR-EOC).

There are limited treatment options to manage ascites in patients with chemo-resistant cancers who are receiving best supportive care. Malignant ascites is commonly unresponsive to diuretics [2,3] and patients frequently require multiple admissions or visits to hospital for ultrasound-guided peritoneal drainage of ascites to palliate symptoms in their last few months of life. Repeated frequent drainage of large volumes of ascites can contribute to cancer cachexia, as ascitic fluid contains high concentrations of protein, fat-soluble vitamins and carotenoids, which are depleted by the removal of ascites [4,5]. Furthermore, insertion of drains can be painful for patients, and over time loculation of ascites can occur, which makes drainage very difficult [6]. Simpler, less burdensome treatments in this patient population are worth further investigation.

Vascular endothelial growth factor (VEGF) plays a pivotal role in the development of malignant ascites by increasing vascular permeability [7–9]. Bevacizumab (bev) is a humanised monoclonal antibody that recognises and binds to all major isoforms of human VEGF-A and prevents VEGF from interacting with its receptors, thereby inhibiting downstream activation of its signalling pathways [10]. bevacizumab has been reported to have single-agent activity when administered as 15 mg/kg every three weeks intravenously; 15% platinum resistant cancers [11] and 21% following 1 or 2 prior lines of treatment regardless of platinum sensitivity [12]. A significant number of grade 3 or 4 adverse events, including gastrointestinal perforation in 11.4% of participants were noted in the platinum resistant setting.

In Bevacizumab is widely used to treat patients with advanced ovarian cancer in combination with chemotherapy, as well as in maintenance treatment following chemotherapy in both the first-line [13,14] and recurrent settings (platinum-sensitive [15] and platinum-resistant [16]), and has regulatory approval in many countries. However, it is expensive and is not approved or funded to treat patients with recurrent ovarian cancer in Australia. We were particularly interested in evaluating the role of bevacizumab in controlling symptomatic ascites in patients with CR-EOC who were no longer receiving chemotherapy.

The terminal half-life of intravenous (IV) bevacizumab is 21 days (range 11–50 days) [17]. Repeated IV administration of bevacizumab at doses of 15 mg/kg every three weeks has been described in case reports as reducing the frequency of paracentesis for patients with CR-EOC [19]. The terminal half-life of IP-bev is not known, but IP-bev has been reported to be resorbed and circulate for around six weeks [18] and hence require less frequent administration. However, there are theoretical advantages of administration directly into the abdominal cavity [20]; IP administration allows direct exposure to the active agent, and potentially limits systemic exposure and resulting toxicities [21].

When this trial was initially conceived there was limited evidence of the safety and activity of the IP route of administration of bevacizumab [19] [22]. However, a promising pilot study reported by El Shami et al. [23] evaluated the safety and efficacy of IP administration of bevacizumab at 5 mg/kg in nine participants with a variety of solid tumours. The investigators reported that malignant ascites resolved without re-accumulation or repeat paracentesis in 9/9 participants after a single intraperitoneal dose of bevacizumab over a median observation period of over two months. An Italian group also reported a patient with ovarian cancer who had complete resolution of ascites after a low dose of IP-bev [24]. They reported an increase in the proportion and function of CD 8 effector T cells and a reduction in circulating T regulatory cells, and hypothesised that IP administration of bevacizumab induces intraperitoneal immune activation and may be an alternative explanation for its apparent efficacy after a single dose. Concerns existed about increased risk of bowel perforation based on results from early Phase II trials [25] and retrospective series of patients with recurrent ovarian cancer [26]. Subsequently, the IP use of bevacizumab has been investigated in a randomised Phase III trial in the first-line setting in combination with platinum-based chemotherapy [27]. There was no evidence of a significant increase in perforations, although this population would be at lower risk.

We hypothesised that with appropriate patient selection a single IP administration of low-dose bevacizumab would be safe and reduce the formation or delay the re-accumulation of malignant ascites and palliate symptomatic patients with malignant ascites.

2. Methods

The REZOLVE study (ANZGOG 11–01) was a single arm Phase II study conducted in six academic medical centres in Australia with experience in treating gynaecologic malignancies and intraperitoneal administration of chemotherapy. The study was coordinated by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, in collaboration with the Australian New Zealand Gynaecological Oncology Group (ANZGOG). The study was performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans and the Declaration of Helsinki. Ethical approval was obtained at all participating sites and all participants provided signed, written informed consent. The study was prospectively registered (ACTRN12611000801910).

Eligible women had CR-EOC and symptomatic malignant ascites that recurred within 28 days of their last paracentesis (P-1). Participants were required to have platinum resistant/refractory recurrent epithelial ovarian cancer, peritoneal cancer, or fallopian tube cancer and cytologically confirmed malignant ascites requiring therapeutic ascitic drainage for symptomatic management; be aged 18 years or over; not receive or plan to receive additional systemic anticancer treatment for the duration of study treatment; have an estimated survival of 12 weeks or more; functional levels at ECOG 0–3; and have provided written informed consent. Participants with any of the following were excluded: pulmonary emboli or deep vein thrombosis unless on anticoagulation and no thrombotic episode in the preceding six weeks; known bleeding diathesis, or history of active bleeding including known gastric ulceration within 60 days; uncontrolled hypertension or unstable cardiac disease; previous episode of ascites due to non-malignant causes, for example hepatic failure, portal venous obstruction; concurrent illness, including severe infection that may jeopardise the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety or limit their ability to comply with protocol; pregnancy, lactation, or inadequate contraception; known hypersensitivity to or serious reaction resulting from any components of bevacizumab, Chinese hamster ovary cell products or other recombinant human or humanised antibodies; having received anti-VEGF therapy within the last three months.

In addition, exclusion criteria pertaining to a high risk of bowel perforation required participants to have none of the following: history of bowel obstruction within six months prior to study entry; CT scan that demonstrates involvement of bowel by tumour; symptoms to suggest impending bowel obstruction; prior whole abdominal radiotherapy; active or non-healing intra-abdominal fistulae or history of fistulae within previous 60 days; major surgery within the preceding six weeks.

2.1. Study treatment

Participants had IP-bev 5 mg/kg instilled at the end of their first therapeutic paracentesis on study (P0) via the temporary indwelling catheter used for drainage of ascites. The drainage catheter was recommended to be inserted under ultrasound guidance and removed following administration of IP-bev. Additional doses of IP-bev were allowed at each subsequent paracentesis (P1, P2 etc) if the interval from the last dose was 42 days or more. All treatments considered palliative/supportive in nature were allowed, with the exception of systemic anticancer therapy. The primary objective was to evaluate the activity of intraperitoneal bevacizumab to reduce the formation or delay the re-accumulation of malignant ascites (median time from first to second therapeutic ascitic drainage). Serial samples of blood and ascites were collected for translational studies. We selected a time to repeat paracentesis (TTP) of at least 42 days as a meaningful benefit based on the results of the El Shami study [23] and the case reports [25,27]. Demonstrating a median TTP of at least 42 days would provide sufficient evidence of activity to warrant further investigation.

2.2. IP dosing and administration

Dosing was based on pre-drainage weight, with bevacizumab given at a dose of 5 mg/kg diluted in 100 mL normal saline. Following therapeutic paracentesis according to local protocol, Bevacizumab 5 mg/kg was then administered as an intraperitoneal infusion in 100 ml saline followed by a further 400 mL saline over a total of 30–60 min via the same intraperitoneal catheter/drain.

Patient-reported outcomes were evaluated at baseline, prior to, and at three-weekly intervals following each therapeutic paracentesis. Three validated questionnaires were administered; the European Organization for Research and Treatment of Cancer (EORTC) Core questionnaire (QLQ-C30, [28]), the Ovarian Specific 28-item questionnaire (OV28, [29]), the MOST (Measure of Ovarian Cancer Symptoms and Treatment Concerns) [30]. Information about health-related resource utilisation during the study period including, but not limited to, visits to emergency departments, general practitioners and other outpatient facilities and inpatient bed days was also collected.

2.3. Sample size and statistical methods

We hypothesised that 50% of participants would have a TTP of at least 42 days following a single dose of IP-bev. Thus, the primary endpoint was the proportion of participants remaining alive who did not require repeat paracentesis at 42 days. A clinically worthwhile median TTP of at least 42 days is equivalent to at least 50% of participants being paracentesis-free at six weeks (42 days). An initial sample size of 16 participants would have 80% power with 95% confidence to exclude a (less clinically interesting) rate of 20% in favour of a clinically meaningful rate of 54% of participants being paracentesis-free at six weeks.

No formal interim analyses were planned, but study safety was closely monitored by the trial management committee, with particular attention to Grade 3/4 toxicities, especially bowel perforations. A prespecified threshold of one or more participants experiencing bowel perforations, or > 2 participants experiencing Grade 3 or 4 toxicities probably or definitely attributable to the intraperitoneal administration of bevacizumab was set, at which point modification of the protocol or ceasing recruitment was to be considered. If events attributed to bevacizumab occurred in two or fewer of the first 16 participants, and six or more of the first 16 participants were paracentesis-free at six weeks (42 days), then accrual was planned to continue to a maximum of 30 participants to achieve more precise estimates.

Time-to-event outcomes were summarised using cumulative incidence curves, with patients who died of any cause prior to therapeutic draining considered as a competing risk. The proportion of participants not requiring repeat therapeutic drainage, those experiencing Grade 3/4 toxicities and those with bowel perforations were described by their estimates and the 95% confidence intervals. Items from the quality of life questionnaires were used to derive numerical scales in accordance with the scoring manuals and/or conventions for each instrument and the results were summarised as means and standard deviations. Exact conditional logistic regression was used to explore the relationship of key prognostic variables to overall survival (Better: OS >8 weeks from registration versus Poor: OS ≤8 weeks).

3. Results

A total of 24 participants were recruited from December 2013 until December 2017. Of these, 22 received at least one dose of bevacizumab and 10 of the 22 participants had a repeat paracentesis. Participant characteristics are shown in Table 1. The median age was 67 years (range 38–86). Participants had received a median of 4.5 lines of prior systemic treatment (range 1–12). ECOG performance status was 0–1 in nine participants, and 2–3 in 15. The numbers of doses of IP-bev administered were 1 in 13 participants, 2 in 5, 3 in 2, 4 in 1, and 5 in 1.

Fig. 1 demonstrates the timing of paracenteses per participant, completion of quality of life assessments and survival. The time from the first pre-study drainage (P-1) to first on-study drainage with IP-bev (P0) is also included (purple shading). The median time from P0 to P1 or death (puncture-free survival) was 48 days (range 8–248 days). The median paracentesis-free interval (PFI) (P0 to P1 or death) was 4.30 (95% CI 2.4–5.8) times higher following the first dose of IP-bev compared with the time between paracenteses prior to study entry (P-1 to P0). The proportion free of paracentesis at 42 days using competing risk analysis was 77% (95% CI 58–92). The median ratio of PFI or death to PFI prior to study (P1 to P0:P0 to P-1) was 4.30 (95% CI 2.40–5.75). The median overall survival was 78 days (95% CI, 47–139), shown in Fig. 2.

The median time from the second drainage to the third drainage or death was 77 days. Median P2–P1 (or death) to P1–P0 ratio was 1.08 (95% CI 0.7–1.38). One participant received five taps, with a median PFI of 119 days with IP-bev, having had an initial pre-study PFI of 22 days. There were few adverse events, with all serious adverse events consistent with the known safety profile. Table 2 outlines the worst grade of toxicity events recorded per participant, using NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0). There was a strong correlation between the total number of adverse events experienced on study and time to death (Spearman correlation

Table 1
Patient demographics.

Characteristic	Category	n (%)
Age (years)	67 (median)	range (38–86)
ECOG performance status	0	1 (4)
	1	8 (33)
	2–3	15 (64)
Prior systemic treatment	4.5 lines (median)	range (0−12)
Number of drainages prior to study entry	1.75 (mean) 1.03 (SD)	range (1–5)
Doses IP-bev administered	1	13
	2	5
	3	2
	4	1
	5	1
Clinical chemistry	**Median**	**Range**
Albumin, g/L	28	19–39
CRP, mg/L	62	6–221
Ca125, IU/ml	2274	35–9223

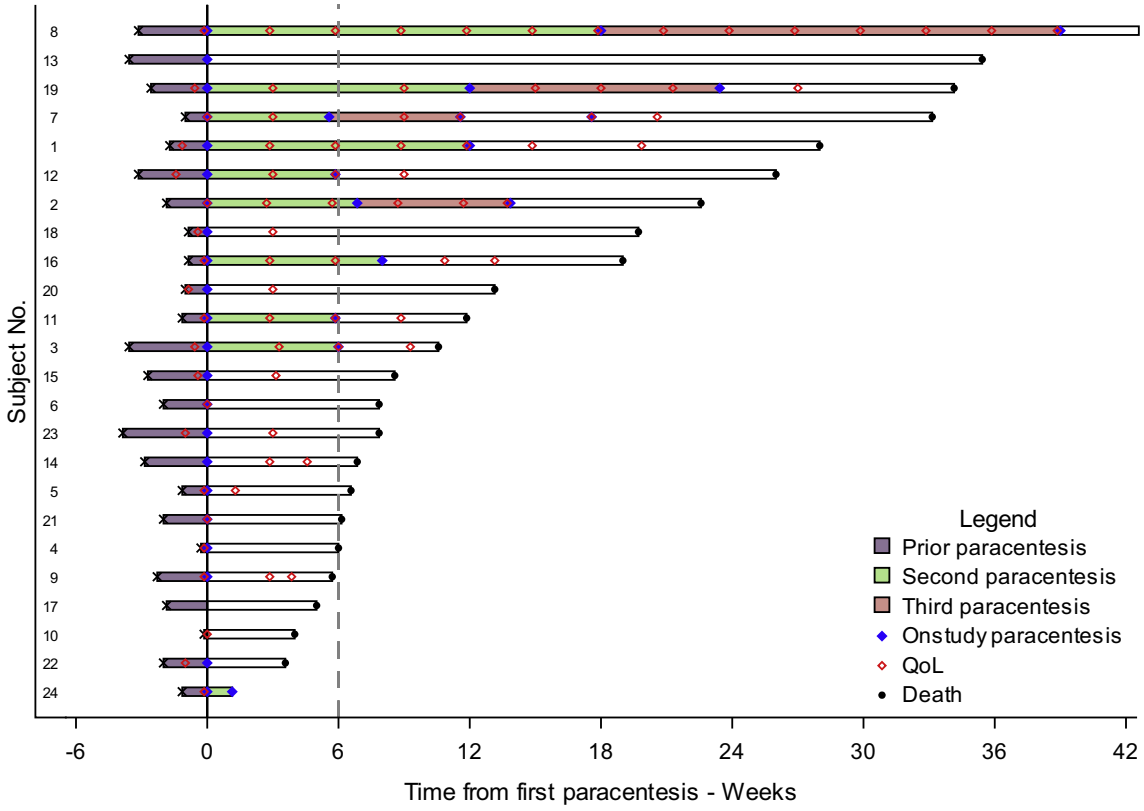

Fig. 1. Time to paracentesis.

0.72916). No relationship existed between number of adverse events and lines of prior chemotherapy, PFI or the number of drains inserted prior to study entry.

3.1. Patient-reported outcomes

22/24 (91.6%) of participants completed baseline quality of life assessments, and 13 (81.25%), eight (88.9%), seven (100%) and five (100%) eligible participants completed these assessments at subsequent visits. Baseline quality of life was poor, with high symptom burden in this population, shown in Fig. 3. Concerns in this patient population included symptoms attributable to cancer, as well as toxicities from previous treatments. More than half of participants reported at least moderate abdominal symptoms at baseline (Fig. 3), reflected in mean scores of 57.2/100 (SD 16.8) and 59.5/100 (SD 24.5) for abdominal/GI symptoms domains on QLQ-OV28 and MosT respectively. Participants

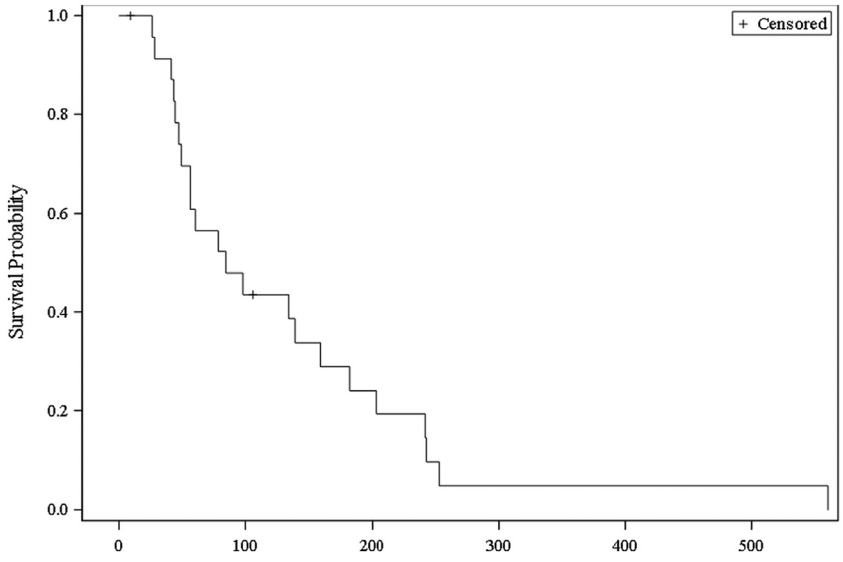

Fig. 2. Overall survival.

Table 2
Adverse events (regardless of attribution).

Frequency	Grade 3	Grade 4	Total
Abdominal pain	1	0	1
Acute on chronic renal failure	0	1	1
Anaemia	1	0	1
Ascites	2	0	2
Bilirubin increased	1	0	1
Colonic perforation	1	0	1
Fatigue	2	0	2
Gastroparesis	1	0	1
Headache	1	0	1
Pleural effusion	1	0	1
Pneumonia	1	0	1
Vomiting	1	0	1
Worst grade abdominal distension	4	0	4
Worst grade nausea	2	0	2
Worst grade abdominal pain	3	1	4
Worst grade hypertension	1	0	1
Worst grade small intestinal obstruction	3	0	3
Anaemia	1	0	1
Fatigue	1	0	1
Vomiting	1	0	1
Total	29	2	31

who completed baseline and subsequent quality of life assessment at three weeks reported a significant reduction in these symptoms of −26.1 (−42.0, −10.2) $n = 11$, $p = 0.0078$ and − 32.2 (−58.3, −6.1) $p = 0.0313$, $n = 9$. Fig. 4 outlines individual symptom scores assessed by the OV-28 abdominal symptoms domain for participants who completed at least two serial quality of life assessments. Higher scores indicate greater symptom burden.

No correlation was found between known or postulated prognostic factors at baseline, including lines of prior chemotherapy, symptom burden or performance status outlined in (Table 3), and early deterioration (< 8 weeks).

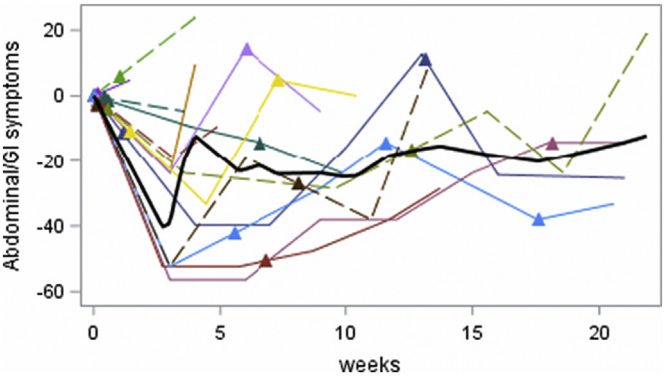

Fig. 4. Change in abdominal/GI symptoms assessed by OV-28. Legend: Triangles represent timing of taps, coloured lines = individual patient scores, black line = fitted LOESS curve. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Health resource utilisation

Participants in this population accessed significant amounts of health care resources in their final months of life; of the 16 who provided this information, 14 reported at least one overnight hospitalisation (range 1–4), lasting a median three (IQR 2, 5.5) nights per admission. 10/17 (58.8%) had contact with palliative care team members, with between one and 30 contacts reported. Only 1/24 (4.2%) participants reported using alternative medicines or practitioners.

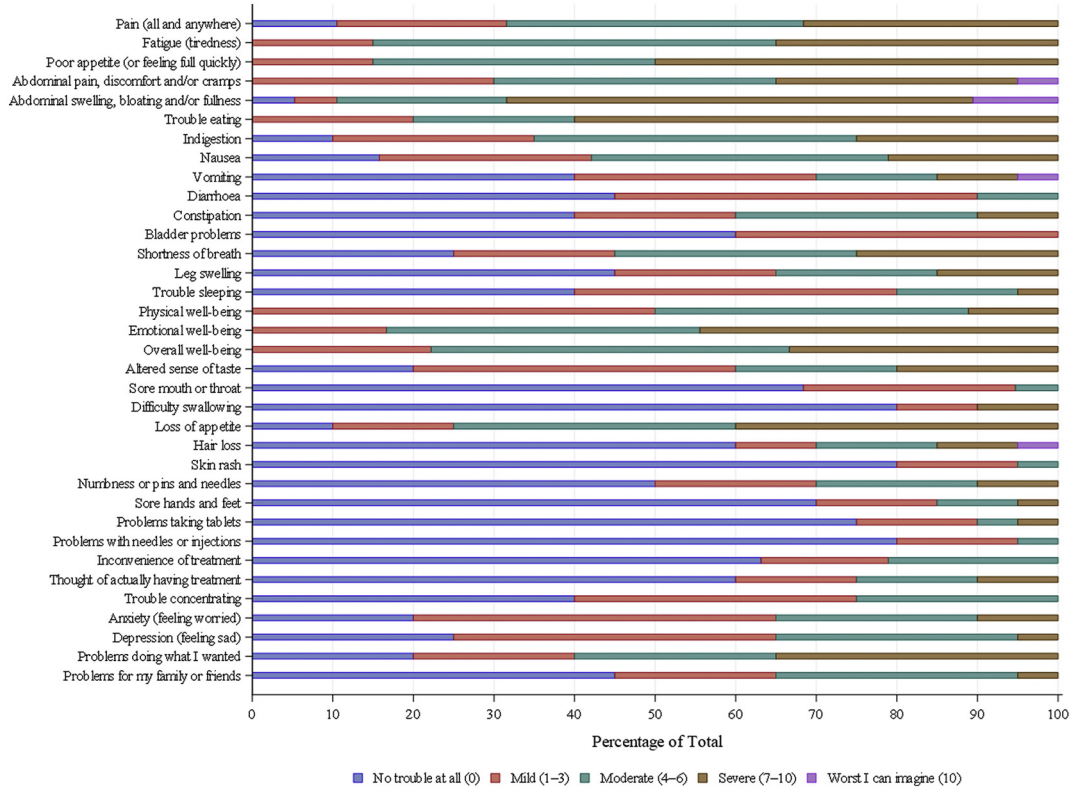

Fig. 3. Baseline patient reported symptoms and concerns assessed by MOST.

Table 3
Association of OS (>8 v ≤ 8 weeks) to baseline variables.

Variable	Level	>8wks ($N = 13$)	≤8wks ($N = 10$)	OR (95% CI)*	*P*-value (Exact)*
No. of lines of previous chemotherapy	1 to ≤4.5	6 (46%)	5 (50%)	1.16 (0.17–8.14)	1.0000
	4.5 to ≤12	7 (54%)	5 (50%)		
Number of previous ascites drainage	1 to ≤1	6 (46%)	6 (60%)	1.71 (0.25–12.83)	0.8134
	1 to ≤5	7 (54%)	4 (40%)		
Age at registration	38.00 to ≤67.01	5 (38%)	6 (60%)	2.31 (0.34–17.94)	0.5469
	67.01 to ≤85.55	8 (62%)	4 (40%)		
Platelets	255 to ≤368	9 (69%)	3 (30%)	0.21 (0.02–1.51)	0.1471
	368 to ≤650	4 (31%)	7 (70%)		
Haemoglobin	74 to ≤109	6 (46%)	7 (70%)	2.60 (0.37–23.08)	0.4742
	109 to ≤131	7 (54%)	3 (30%)		
While blood cell count	2.4 to ≤7.1	7 (54%)	5 (50%)	0.86 (0.12–5.97)	1.0000
	7.1 to ≤15.1	6 (46%)	5 (50%)		
Neutrophil count	1.5 to ≤5.75	6 (46%)	5 (50%)	1.16 (0.17–8.14)	1.0000
	5.75 to ≤13.4	7 (54%)	5 (50%)		
Albumin	19 to ≤28	6 (46%)	6 (60%)	1.71 (0.25–12.83)	0.8134
	28 to ≤39	7 (54%)	4 (40%)		
CRP	6 to ≤42	6 (50%)	6 (60%)	1.47 (0.21–11.36)	0.9700
	42 to ≤221	6 (50%)	4 (40%)		
CA125	35 to ≤1100	7 (58%)	4 (40%)	0.49 (0.06–3.49)	0.6699
	1100 to ≤9223	5 (42%)	6 (60%)		
ECOG	0 to ≤2	12 (92%)	7 (70%)	0.21 (0.00–3.19)	0.3998
	2 to ≤3	1 (8%)	3 (30%)		
Loculated ascites	Yes	3 (27%)	3 (43%)	0.52 (0.04–5.79)	0.8552
	No	8 (73%)	4 (57%)		
Estimated fluid volume	500 mL–2 L	3 (25%)	1 (14%)	0.52 (0.01–8.42)	1.0000
	>2 L	9 (75%)	6 (86%)		

Note: * Estimates from exact conditional logistic regression analysis.

4. Discussion

We demonstrated that IP-bev is active in patients with CR-EOC and symptomatic ascites, and leads to a 4.3 (95% CI 2.4–5.8)-fold increase in the median PFI (P0 to P1 or death) following a first dose of IP-bev compared to the time between paracenteses prior to study entry (P-1 to P0). All participants had ceased palliative chemotherapy at study entry and were receiving best supportive care, which included therapeutic paracenteses for symptomatic ascites. This is the first prospective study to demonstrate the safety and activity of single-agent IP low-dose bevacizumab in patients with chemotherapy-resistant ovarian cancer with symptomatic ascites and end-stage disease. Notably, none of the participants on this study received concurrent anticancer therapy during the study period, and all had demonstrated recurrence of symptomatic ascites within four weeks of therapeutic paracentesis on at least one occasion prior to study entry.

The treatment was safe, with bowel perforation and other potential safety events of concern below the prespecified safety threshold. The majority of adverse events overlapped with, or were attributable to, disease progression in a cohort of patients with a very poor prognosis and high symptom burden. While the inclusion criteria specified a clinician estimated survival of greater than 12 weeks, 10/22 (45%) died within eight weeks, reflecting how difficult it can be to predict survival in these patients. The proportion of patients who died without requiring a second paracentesis limits conclusions regarding the median paracentesis free interval in this group.

When this study was initiated, no prospective trials investigating IP-bev to control ascites in patients with chemotherapy-resistant ovarian cancer had been undertaken. Subsequently, a study was reported that investigated IP-bev 300 mg in combination with IP cisplatin 40 mg/m^2 given second-weekly for six weeks, together with intravenous carboplatin and paclitaxel in the first-line setting [27]. No significant increase in adverse events was noted from the addition of IP-bev, although the trial population was very different to our study. While this study suggested a reduction in ascites from the addition of IP-bev, all participants were also treated with platinum-based chemotherapy. In contrast, our trial focused on intermittent administration of single agent low-dose bevacizumab in chemotherapy-resistant participants with a larger disease burden, who were being treated to control symptoms and delay the accumulation of ascites and the need for frequent paracenteses. Our highly selected patient population made recruitment more challenging but was important to understand safety and activity in this palliative setting.

Our patient population was representative of typical patients with CR-EOC and symptomatic malignant ascites. The symptoms reported by participants using validated outcome measures were consistent with those reported by patients with platinum-resistant ovarian cancer, with a high proportion of symptoms attributable to ascites. Safe, active treatments that palliate symptoms from ascites with minimal morbidity are of particular value in this setting, given that diuretics are ineffectual and the only effective treatment available is therapeutic paracentesis. For patients already undergoing a paracentesis there is minimal

inconvenience, with the only additional treatment time being a short infusion of bevacizumab following drainage of ascites. The depot effect and prolonged concentrations of bevacizumab within the peritoneal cavity is an effective and well-tolerated treatment for patients with chemotherapy-resistant ovarian cancers and symptomatic malignant ascites who have no other treatment options available. The findings of this study may be applicable to patients with recurrent ascites secondary to other malignancies and is worthy of further study given how common ascites is in the final months of life with many cancers.

There are currently no approved treatments for palliation of malignant ascites. Catumaxomab, a monoclonal antibody against EpCAM and CD3 [31] was investigated as a treatment for malignant ascites and was administered as an intraperitoneal (IP) infusion on Days 0, 3, 7, and 10. The puncture-free survival time was significantly longer in the catumaxomab group (median 46 days) than the control group (median 11 days), as was the median time to next paracentesis (77 versus 13 days), suggesting that this was a potentially effective palliative treatment. However, there were significant side-effects related to cytokine release and it was withdrawn by the company.

The cost of bevacizumab represents a potential barrier in some healthcare settings. The cost of each infusion on study was approximately AUD 1600/vial plus administrating costs, with most participants requiring a maximum of 1 × 400 mL vial per infusion. Although no formal cost evaluation was undertaken, at an average total of AUD 2000 per infusion, this represents good value in our healthcare setting when weighed against the ability to reduce or avoid the complications, inconvenience and costs of ascitic drains or indwelling catheters.

Not all participants benefited from IP-bev. Limited exploration of predictors of benefit was possible in this small sample size. The ability to predict who will deteriorate quickly could help avoid futile interventions in this group. In this small cohort, prognostic factors identified in other settings [32] were not associated with deterioration within eight weeks. Exploratory analyses for potential predictive biomarkers including VEGF pathway factors in blood and ascites are underway and will be presented separately.

5. Conclusion

Bevacizumab given by the IP route following drainage of malignant ascites in symptomatic women with chemotherapy-resistant ovarian, fallopian tube or primary peritoneal cancer is active, with an acceptable safety profile. It is potentially more convenient than repeated IV administration, as it is administered directly into the peritoneal cavity following therapeutic paracentesis. Further study as a palliative intervention for patients with symptomatic ascites for cancers other than ovarian cancer, and potentially also malignant pleural effusions, is warranted.

Funding

DB reports grants from Roche-Genentech, AstraZeneca, and BeiGene, as well as personal fees from Exo Therapeutics, outside the submitted work. MLF reports grants from AstraZeneca and Novartis; personal fees from MSD, GSK, Novartis, Takeda and Lilly, and other funding from Abbvie, outside the submitted work. LM reports other funding from Roche, outside the submitted work. KMS reports grants from Cancer Australia and the Ovarian Cancer Research Foundation during the conduct of the study; personal fees from Amgen, Servier, Merck, MSD and CDD, outside the submitted work. SY reports grants from Cancer Australia and the Ovarian Cancer Research Foundation during the conduct of the study. All other authors have no conflicts of interest to declare.

Author contributions

KMS: conceptualization, Data curation; Funding acquisition; Writing - original draft; Writing - review & editing; DE, data analysis, Writing - review & editing, supervision; LM, Data curation, Funding acquisition, Writing - review & editing, supervision; SA, Data curation, Writing - review & editing; CS, Data curation, Writing - review & editing, supervision; SY, Funding acquisition, Writing - review & editing; JG, Data curation, Writing - review & editing; MH: supervision; Writing - review & editing; MLF: conceptualization, Data curation, Funding acquisition, Writing - original draft; Writing - review & editing, supervision

Declaration of Competing Interest

None.

Acknowledgements

The trial was supported by grant funding from Cancer Australia (1067589, 1050134) and the Ovarian Cancer Research Foundation. The investigators would like to thank all participants and their families for their support of the study.

References

[1] J.S. Ferriss, J.J. Java, M.A. Bookman, G.F. Fleming, B.J. Monk, J.L. Walker, 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. 139 (1) (2015) 17–22.
[2] S. Kobold, S. Hegewisch-Becker, K. Oechsle, K. Jordan, C. Bokemeyer, D. Atanackovic, Intraperitoneal VEGF inhibition using bevacizumab: a potential approach for the symptomatic treatment of malignant ascites? Oncologist. 14 (12) (2009) 1242–1251.
[3] R.S. Suidan, C.C. Sun, S.N. Westin, R.L. Coleman, G.B. Mills, L.A. Meyer, The management of malignant ascites and impact on quality of life outcomes in women with ovarian cancer, Expert Rev. Qua. Life Cancer Care 1 (3) (2016) 231–238.
[4] Z. Hilal, G.A. Rezniczek, R. Klenke, A. Dogan, C.B. Tempfer, Nutritional status, cachexia, and anorexia in women with peritoneal metastasis and intraperitoneal chemotherapy: a longitudinal analysis, J. 28 (6) (2017), e80, .
[5] F.J. Schweigert, J. Raila, J. Sehouli, U. Buscher, Accumulation of selected carotenoids, alpha -tocopherol and retinol in human ovarian carcinoma Ascitic fluid, Ann. Nutr. Metab. 48 (4) (2004) 241–245.
[6] V. Rudralingam, C. Footitt, B. Layton, Ascites matters, Ultrasound. 25 (2) (2017) 69–79.
[7] V. Loizzi, V. Del Vecchio, G. Gargano, M. De Liso, A. Kardashi, E. Naglieri, et al., Biological pathways involved in tumor angiogenesis and bevacizumab based anti-Angiogenic therapy with special references to ovarian Cancer, Int. 18 (9) (2017) 14.
[8] H. Zhao, X. Li, D. Chen, J. Cai, Y. Fu, H. Kang, et al., Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial, Med. Oncol. 32 (2) (2015) 292.
[9] S.L. Sangisetty, T.J. Miner, Malignant ascites: a review of prognostic factors, pathophysiology and therapeutic measures, World J. Gastroin. Surg. 4 (2012).
[10] T. Shih, C. Lindley, Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies, Clin. Ther. 28 (11) (2006) 1779–1802.
[11] S.A. Cannistra, U.A. Matulonis, R.T. Penson, J. Hambleton, J. Dupont, H. Mackey, et al., Phase II study of bevacizumab in patients with platinum-resistant ovarian Cancer or peritoneal serous Cancer, J. Clin. Oncol. 25 (33) (2007) 5180–5186.
[12] R.A. Burger, M.W. Sill, B.J. Monk, B.E. Greer, J.I. Sorosky, Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian Cancer or primary peritoneal Cancer: a gynecologic oncology group study, J. Clin. Oncol. 25 (33) (2007) 5165–5171.
[13] R.A. Burger, M.F. Brady, M.A. Bookman, G.F. Fleming, B.J. Monk, H. Huang, et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer, N. Engl. J. Med. 365 (26) (2011) 2473–2483.
[14] T.J. Perren, A.M. Swart, J. Pfisterer, J.A. Ledermann, E. Pujade-Lauraine, G. Kristensen, et al., A phase 3 trial of bevacizumab in ovarian cancer, N. Engl. J. Med. 365 (26) (2011) 2484–2496.
[15] C. Aghajanian, S.V. Blank, B.A. Goff, P.L. Judson, M.G. Teneriello, A. Husain, et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, J. Clin. Oncol. 30 (17) (2012) 2039–2045, https://doi.org/10.1200/jco.2012.42.0505.
[16] E. Pujade-Lauraine, F. Hilpert, B. Weber, A. Reuss, A. Poveda, G. Kristensen, et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian Cancer: the AURELIA open-label randomized phase III trial, J. Clin. Oncol. 32 (13) (2014) 1302–1308.
[17] Ltd RP, Bevacizumab Product Information, Roche Australia website, 2010 accessed August 18th 2010.
[18] D. Ignjatovic, K. Aasland, M. Pettersen, S. Sund, Y. Chen, M. Spasojevic, et al., Intra-abdominal administration of bevacizumab diminishes intra-peritoneal adhesions, Am. J. Surg. 200 (2) (2010) 270–275.
[19] T.M. Numnum, R.P. Rocconi, J. Whitworth, M.N. Barnes, The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma, Gynecol. Oncol. 102 (3) (2006) 425–428.
[20] M. Markman, Intraperitoneal antineoplastic drug delivery: rationale and results, Lancet Oncol. 4 (5) (2003) 277–283.

[21] P. Jacquet, P.H. Sugarbaker, Peritoneal-plasma Barrier. Peritoneal Carcinomatosis: Principles of Management, Springer, 1996 53–63.
[22] C.A. Hamilton, G.L. Maxwell, M.R. Chernofsky, S.A. Bernstein, J.H. Farley, G.S. Rose, Intraperitoneal bevacizumab for the palliation of malignant ascites in refractory ovarian cancer, Gynecol. Oncol. 111 (3) (2008) 530–532.
[23] K. El-Shami, A. Elsaid, Y. El-Kerm, Open-label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites, J. Clin. Oncol. (Meeting Abstracts) 25 (18_suppl) (2007) 9043.
[24] F. Bellati, C. Napoletano, I. Ruscito, M. Pastore, M. Pernice, M. Antonilli, et al., Complete remission of ovarian cancer induced intractable malignant ascites with intraperitoneal bevacizumab. Immunological observations and a literature review, Investig. New Drugs 28 (6) (2010) 887–894.
[25] S.A. Cannistra, U.A. Matulonis, R.T. Penson, J. Hambleton, J. Dupont, H. Mackey, et al., Phase II study of bevacizumab in patients with platinum-resistant ovarian Cancer or peritoneal serous Cancer, J. Clin. Oncol. 25 (33) (2007) 5180–5186.
[26] J.P. Diaz, W.P. Tew, O. Zivanovic, J. Konner, P.J. Sabbatini, L.A. dos Santos, et al., Incidence and management of bevacizumab-associated gastrointestinal perforations in patients with recurrent ovarian carcinoma, Gynecol. Oncol. 116 (3) (2010) 335–339.
[27] H. Zhao, X. Li, D. Chen, J. Cai, Y. Fu, H. Kang, et al., Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial, Med. Oncol. 32 (2) (2015) 37.
[28] N.K. Aaronson, S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N.J. Duez, et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, J. Natl. Cancer Inst. 85 (5) (1993) 365–376.
[29] E. Greimel, A. Bottomley, A. Cull, A.C. Waldenstrom, J. Arraras, L. Chauvenet, et al., An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer, Eur. J. Cancer 39 (10) (2003) 1402–1408.
[30] M.T. King, M.R. Stockler, P. Butow, R. O'Connell, M. Voysey, A.M. Oza, et al., Development of the measure of ovarian symptoms and treatment concerns: aiming for optimal measurement of patient-reported symptom benefit with chemotherapy for symptomatic ovarian cancer, Int. J. Gynecol. Cancer 24 (5) (2014) 865–873.
[31] M.M. Heiss, P. Murawa, P. Koralewski, E. Kutarska, O.O. Kolesnik, V.V. Ivanchenko, et al., The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial, Int. J. Cancer 127 (9) (2010) 2209–2221.
[32] F.T. Roncolato, E. Gibbs, C.K. Lee, R. Asher, L.C. Davies, V.J. Gebski, et al., Quality of life predicts overall survival in women with platinum-resistant ovarian cancer: an AURELIA substudy, Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 28 (8) (2017) 1849–1855.