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The management of malignant ascites and impact on quality of life outcomes in women with ovarian cancer

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Abstract

Malignant ascites is one of the most common sequela of epithelial ovarian cancer. It causes significant symptoms and can have a detrimental impact on patient quality of life, especially in women with recurrent ovarian cancer. The management of symptomatic ascites consists of both mechanical treatments that aim to drain the peritoneal cavity, and medical therapies that prevent and diminish the development of ascites. Mechanical options include serial paracentesis, peritoneal catheters, and peritoneovenous shunts. Pharmaceutical treatments include diuretics, angiogenesis inhibitors, and other targeted agents. There is a perception, without formal analysis, that intractable ascites is less common in the taxane era of therapy. In this review paper, we highlight current and emerging therapeutic strategies, complications and contraindications, and their effects on patient quality of life.

Keywords

Ascites; Ovarian cancer; Quality of life; Paracentesis; Angiogenesis inhibitor

1. Introduction

Epithelial ovarian cancer is the leading cause of gynecologic cancer-related mortality in the United States, with an estimated 14,240 deaths in 2016 [1]. The majority of new cases present with advanced-stage disease, where initial treatment consists of a combination of cytoreductive surgery and platinum and taxane-based chemotherapy [2]. The natural history for most patients with advanced epithelial ovarian cancer is one of clinical remission after primary therapy. However, long-term cure rates languish between 20–30% and relapse occurs in most patients, who are subsequently exposed to multiple chemotherapeutic agents [3]. Given the high recurrence rate in this population, a focus on quality of life (QOL) through managing symptoms of disease and treatment-related toxicity is paramount.

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In many clinical situations where no clear superior management strategy exists, measuring QOL parameters is essential in the decision-making process in order to provide patient-centered treatment. The Outcomes Working Group of the American Society of Clinical Oncology (ASCO) has emphasized the need for trials to collect QOL and toxicity data [4]. As research standards have progressed, the U.S. Food and Drug Administration (FDA) has called for similar data collection efforts and has strongly recommended that all approval of new anti-cancer New Drug Applications (NDAs) therapies incorporate QOL information in order to provide patient-specific clinical context of the treatment effect (response rate, survival, etc) [5]. Furthermore, some therapeutic interventions may have significant therapeutic impact on symptom relief, thus improving QOL, despite little to no direct anti-tumor effect [6].

One of the most common sequela of epithelial ovarian cancer is the occurrence of malignant ascites, which usually portends an advanced stage and worse prognosis [7]. Ascites manifests as continuous abdominal pressure, increased abdominal girth, pain, nausea, bladder/bowel dysfunction, in addition to diminished pulmonary capacity and dyspnea [8]. These symptoms can significantly impact patients' instrumental activities of daily living. Initially, ascites is managed through the primary treatment of underlying disease, i.e. surgical cytoreduction and platinum/taxane chemotherapy, which typically resolves symptoms [9]. However, patients with multiple recurrences are subjected to several chemotherapeutic regimens and frequently develop chemoresistant disease [10]. This can lead to refractory ascites in up to two thirds of patients and can have debilitating effects on their QOL [11–13].

Peritoneal fluid is normally produced by capillary membranes of the abdominal peritoneum and reabsorbed through lymphatic channels. Indeed approximately one liter of fluid is thought to traverse the peritoneal cavity daily [14]. While no standard definition of ascites exists, accumulation of >500 mL within that cavity is generally accepted as more than physiological variance. Malignant ascites is characterized by the presence of large numbers of tumor and immune/hematopoietic cells, high concentrations of inflammatory cytokines, high protein and lactate dehydrogenase levels, and a low glucose level [15]. In ovarian cancer, malignant ascites occurs due to both increased production of fluid and obstructed efflux through the lymphatic system [16]. This is purported to occur via several pathophysiological mechanisms: The high protein content of ascitic fluid suggests vessel wall compromise. Vascular endothelial growth factor (VEGF) and inflammatory cytokines enhance vessel permeability in the tumor microvasculature and peritoneal surfaces, and have been implicated in “third-spacing” [17]. Along with malignant cells and mesothelial cells, VEGF also produces excessive peritoneal fluid. Micrometastases disrupt normal lymphatic channels and lead to decreased lymphatic resorption [18]. This causes a reduction in the circulating blood volume, which activates the renin-angiotensin-aldosterone pathway, leading to sodium and fluid retention. Additionally, portal hypertension secondary to liver metastases can cause further worsening of ascites [19].

The management of malignant ascites in ovarian cancer consists of both limiting the development of peritoneal fluid accumulation and addressing its outflow. As therapies for recurrent disease rarely lead to a cure, the therapeutic intent should focus on improving

QOL. In this review paper, we discuss current and emerging therapeutic strategies, which include both mechanical and pharmaceutical treatment options.

2. Mechanical treatment

Mechanical treatment options aim to drain the accumulating ascites in patients with ovarian cancer. These include serial paracentesis, tunneled peritoneal catheters, and peritoneovenous shunts (Table 1).

2.1 Paracentesis

Paracentesis is the mainstay of ascites management in ovarian cancer. The majority of patients will feel immediate relief in symptoms, and thus, a quick improvement in QOL [20]. The use of readily available paracentesis kits allows this procedure to be done on an outpatient basis or at the bedside in a hospice setting. Physical and physiological parameters are also improved. In a study of 35 sequential paracenteses on patients with recurrent cancer and symptomatic tense ascites, Gotlieb et al. demonstrated a significant decrease in intraperitoneal pressure, periumbilical girth, pubo-xiphoid length, pulse, systolic blood pressure, and respiratory rate [21]. A prospective study of 44 patients showed a significant improvement in symptoms with the removal of a median of 5L of ascites (range 0.8–15L), without any reported adverse events [22]. Other studies suggest it is safe to remove up to 5L without significantly affecting plasma volume or necessitating fluid replacement [23, 24]. Potential complications associated with paracentesis include hypotension, hypoproteinemias, perforation, intraperitoneal bleeding, peritonitis, and pulmonary embolus [25, 26]. The use of ultrasound guidance helps minimize the risk of bowel perforation. Over time, the ascites can become loculated and difficult to drain from a single site. Repeated large volume paracentesis are associated with a significantly higher incidence of hypotension and may necessitate volume replacement [19]. Compared to other plasma expanders, colloids been found to have a lower rate of circulatory dysfunction, albeit with no improvement in survival [27].

2.2 Peritoneal catheters

Improvement in symptoms tends to be temporary as ascites reaccumulates in most patients, necessitating repeated paracenteses. In a study of 43 patients with malignant ascites, the mean duration of symptomatic relief was 10.4 days (range 4 – 45 days) [28]. The need for multiple office/emergency department visits and recurring abdominal needle accessions can negatively impact patient QOL. Placement of a tunneled peritoneal catheter can be performed in this situation, especially for women with a prolonged life expectancy [26]. It is inserted by interventional radiologists, and allows patients and their families to manage drainage at home [29]. It is also an option for patients who are referred to hospice and expected to require frequent paracenteses. Risks include catheter occlusion, leakage from the catheter site, hypotension, peritonitis, and sepsis [8, 26]. Antibiotic use in the first week after insertion may decrease the risk of infection [30]. Different catheters have been described, including port-a-catheters, dialysis catheters, and PleurX catheters (Denver Biomedical, Golden, CO) [31–34]. Originally developed for pleural drainage, the PleurX catheter is a 15.5 fr silicone catheter with a valve mechanism that prevents flow unless the valve is

aligned correctly [32]. Use of this catheter appears to reduce the risk of sepsis [8, 29]. In a retrospective study of 107 patients, Rosenberg and colleagues showed that the PleurX catheter provided effective palliation with a complication rate similar to that for large volume paracentesis, while preventing the need for frequent trips to the hospital for repeated percutaneous drainage [31].

2.3 Peritoneovenous shunts

An alternative option that avoids multiple paracenteses is a peritoneovenous shunt. It is a tube that allows flow from the peritoneum to the vena cava through a one-way valve mechanism that opens at a specific pressure. While it may be placed surgically, most recent reports describe percutaneous placement by interventional radiologists [35]. The 3 most common types of shunts described are the Leveen, Denver, and Hyde shunts. There is no prospective data comparing the effectiveness of these shunts in malignant ascites, and the Leveen shunt has been discontinued [36]. Complications include shunt occlusion, infection, sepsis, tumor embolization, and disseminated intravascular coagulation [37]. A retrospective study of Denver shunts reported an overall complication rate of 38% [36]. Of additional concern is the possible hematogenous seeding of malignant cells through the shunt. However, despite shunting of very large numbers of tumor cells into the circulation over long periods of time, pathological analysis failed to demonstrate evidence for systemic tumor spread in many patients [38, 39]. Due to the fatal risks of pulmonary edema and embolization after insertion, patients require central hemodynamic monitoring for 24 hours post-procedure [19, 40]. Shunting is contraindicated in patients with less than one month of life expectancy. In addition, those with hemorrhagic, chylous, or loculated ascites would not benefit from the procedure. As shunting may cause hemodilution and fluid overload, advanced renal or heart failure are relative contraindications, as are coagulation disorders and portal hypertension [37]. Given the potential for serious morbidity, mortality, and cost associated with peritoneovenous shunts, tunneled peritoneal catheters may be a better option for patients with ovarian cancer with regards to QOL. However, no randomized trials have compared the two methods.

3. Medical therapy

A significant proportion of women with recurrent ovarian cancer have refractory ascites that is resistant to chemotherapy, necessitating long-term drainage [19]. In addition, those with a history of extensive debulking surgery and multiple recurrences have a high chance of intra-abdominal and pelvic adhesions. This leads to loculated fluid collections and limits the effectiveness of mechanical drainage [41]. Pharmaceutical treatments aim to stop or diminish the development of malignant ascites. Options include diuretics, angiogenesis inhibitors, and immunologic agents (Table 2).

3.1 Diuretics

Although diuretics have been described in the initial management of ascites, there are no prospective randomized trials supporting the use of diuretics as first-line therapy in ovarian cancer patients. The goal of diuretic therapy is a decrease in overall plasma volume. In a review of patients with different malignancies, 43% of patients had symptomatic

improvement with diuretics [19]. It appears they are most effective in women with hepatic metastasis and ascites due to portal hypertension. This is characterized by a serum-ascites albumin gradient (SAAG) of >1.1 g/dL, consistent with the gradient seen in benign ascites due to liver cirrhosis [42]. Conversely, patients with ascites due to peritoneal carcinomatosis with a SAAG of <1.1 g/dL have been shown to have minimal response [43]. The majority of ovarian cancer patients with significant ascites have peritoneal carcinomatosis and may be unlikely to respond to diuretic therapy.

The most commonly studied drugs are spironolactone (potassium-sparing aldosterone antagonist) and furosemide (loop diuretic). The usual diuretic regimen consists of single morning doses of oral spironolactone and furosemide, beginning with 100 mg of the former and 40 mg of the latter, in addition to dietary sodium restriction. With a weight-loss goal of approximately 1 kg/day, the daily doses of spironolactone and furosemide can be increased every 3–5 days to 400 mg and 160 mg, respectively [44]. Close monitoring of electrolyte imbalances is necessary. Although there is no limit to the daily weight loss of patients who have significant edema, a goal of 0.5–1 kg/day once the edema has resolved is prudent. Complications include hypotension, hypovolemia, and renal failure. Hyponatremia (serum sodium <125 mmol/L), a serum creatinine >1.5 mg/dL, infection, and encephalopathy are considered contraindications [45]. There are no direct comparisons of diuretics and mechanical treatment options with regards to QOL endpoints.

3.2 Angiogenesis inhibitors

3.2.1 Bevacizumab—Over the last decade, several innovative approaches for the management of ascites have emerged. Angiogenesis, the process of neovascularization, is essential for tumor growth, and is mediated by the VEGF family of ligands and receptors [46]. Given the role of VEGF in tumor carcinogenesis and the development of malignant ascites (via the enhancement of microvasculature permeability and peritoneal fluid production), antiangiogenic agents have been explored in this setting [47–49]. Bevacizumab is a dimeric monoclonal antibody directed against VEGF that inhibits binding of the normal VEGF ligand to its receptor, and thus angiogenesis and tumor proliferation [50].

The incorporation of bevacizumab as part of a first-line treatment for women with newly diagnosed ovarian cancer has been evaluated in two prospective trials conducted by the Gynecologic Oncology Group (GOG 218) and the International Collaborative on Ovarian Neoplasms (ICON 7) [51–53]. In both trials, the addition of concurrent and maintenance bevacizumab improved progression-free survival (PFS) but not overall survival (OS). Importantly, an unplanned subgroup analysis of GOG 218 demonstrated that treatment with bevacizumab improved PFS and OS specifically in patients with ascites but not in other patients. Women with ascites who received bevacizumab had a median PFS of 15.2 months (95% CI, 14.1–16.2 months) compared to a median of 10.4 months (95% CI, 9.7–11.2 months) for those who did not receive it ($p<0.001$). Similarly, those who received bevacizumab had a higher median OS (43.3 months [95% CI, 40.4–48.3 months] vs 39.9 months [95% CI, 35.7–42.8]; $p=0.035$) [54]. This suggests that ascites may predict the population of women more likely to derive long-term benefit from bevacizumab. On the other hand, it is important to note that in ICON 7, bevacizumab led to more serious (grade

3–4) adverse events (66 vs 56%), including a higher rate of mild to serious (grade 2 or higher) hypertension (18 vs 2%) and gastrointestinal perforation (1.3% vs 0.4%) [52]. A higher rate of adverse events was also seen in GOG 218. Bevacizumab is contraindicated in patients with bleeding or thrombotic disorders, stroke, ischemic cardiac disease or congestive heart failure, uncontrolled hypertension, and a history of gastrointestinal perforation [55]. QOL outcomes were assessed in that trial using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and Quality of Life Questionnaire–Ovarian Cancer Module 28 (QLQ-OV28). The mean global QOL score at 54 weeks after treatment initiation was higher in the standard chemotherapy group than in the bevacizumab group (76.1 [Standard Deviation 18.2] vs 69.7 [19.1] points; difference 6.4 points, 95% CI 3.7–9.0, $p<0.0001$). This difference was not deemed clinically significant by the authors and both groups showed improvement in QOL scores over time. Bevacizumab was associated with statistically significant but clinically small decrements of role functioning, financial worries, attitudes to disease or treatment, hormonal symptoms, and rash (all $p<0.01$) [56]. In a follow-up analysis, global QOL did not differ between those who received standard chemotherapy and those receiving bevacizumab at week 76 (mean score 75.9 [SD 19.3] vs 72.6 [18.9] points, $p=0.43$) [53]. QOL was also assessed in the GOG 218 trial. There was a small QOL difference observed during chemotherapy (lower for the bevacizumab groups), but this did not persist during maintenance bevacizumab [57]. QOL outcomes were not specifically reported for patients with ascites in either trial.

The addition of bevacizumab to chemotherapeutic regimens has also been evaluated at recurrence. The management of patients with advanced ovarian cancer who recur is frequently stratified based on the time duration between the completion of primary platinum-based treatment and the detection of relapse, which is known as the platinum-free interval. Patients with an interval of ≥ 6 months are considered to have platinum-sensitive disease, while those with an interval of <6 months are considered to have platinum-resistant disease. The OCEANS trial (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Antiangiogenic Therapy in Platinum-Sensitive Recurrent Disease) enrolled patients with platinum-sensitive disease, and the AURELIA trial (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) enrolled patients with platinum-resistant disease [58–60]. As in the primary setting, bevacizumab improved PFS but not OS in both trials. Patient-reported outcomes were assessed in the AURELIA trial. Using the EORTC QLQ-OV28 at weeks 8–9, significantly more patients assigned to the bevacizumab plus chemotherapy arm reported a 15% improvement in abdominal/GI symptoms: 34 (21.9%) of 155 patients assigned to bevacizumab versus 15 (9.3%) of 162 patients assigned to chemotherapy alone (difference 12.7% favoring bevacizumab; 95% CI, 4.4–20.9%; $p=0.002$). A planned subgroup analysis included only the 99 women with ascites at baseline, as those patients were expected to have considerable abdominal pain/GI symptoms. This subgroup showed a greater treatment effect with a 15% improvement in 44.0% of the bevacizumab arm versus 4.1% of the chemotherapy-alone arm (difference 39.9%; 95% CI, 23.9%–55.9%; $p=0.001$). QOL scores were also assessed in that study via an alternate instrument. Using the Functional Assessment of Cancer Therapy–Ovarian Cancer symptom index (FOSI), a 15% absolute improvement was achieved at week 8–9 in 14.6% of patients assigned to bevacizumab

versus 3.6% of those assigned to chemotherapy alone (difference 11.0%; 95% CI, 3.7% to 18.2%; $p=0.002$). In the subgroup of patients with ascites at baseline, a 15% improvement was observed in 21.6% versus 2.1%, respectively (difference 19.5%; 95% CI, 6.3% to 32.6%; $p=0.004$). The authors concluded that the pronounced treatment benefit in the predefined subgroup analysis of patients with ascites at baseline was of special interest and clinical importance given the impact of abdominal/GI symptoms on QOL in this population [61].

Although bevacizumab was not introduced specifically to treat ascites in the above-mentioned trials, its use for this purpose has been assessed in smaller studies. In preclinical mouse models of ovarian cancer, VEGF inhibition was associated with a significant decrease in tumor load and ascites accumulation, which paved the way for its clinical assessment [62]. One study assessed four heavily pretreated patients with recurrent ovarian carcinoma who had symptomatic ascites and required frequent therapeutic paracenteses. With a follow-up of 6 months, intravenous bevacizumab use led to symptomatic relief in all patients, with manageable toxicity and no further paracenteses [47]. Intraperitoneal bevacizumab has also been assessed, with promising results [48, 63, 64]. In the largest series, which evaluated nine patients with colorectal, breast, uterine or ovarian cancer, intraperitoneal bevacizumab led to the resolution of refractory ascites in all patients. There was no need for repeat paracenteses over a median follow-up of >2 months, and no reported grade 2–5 adverse events [63]. When added to the survival outcomes from the GOG 218 subgroup analysis and the QOL results from the AURELIA trial, these data suggest that bevacizumab may have an important role in the management of patients with advanced/recurrent ovarian cancer with ascites. To date, a trial using paracentesis need as a primary endpoint has not been conducted with bevacizumab.

3.2.2 Afibercept (VEGF-trap)—Afibercept, also a VEGF ligand inhibitor, is a VEGF receptor (VEGFR) fusion molecule that binds to and inhibits VEGF binding to all VEGFR isoforms [65]. As with bevacizumab, preclinical data found that it prevented tumor growth and ascites formation [66]. A single-arm study by Columbo et al assessed the efficacy and safety of afibercept in 16 patients with chemoresistant ovarian cancer who had previously required at least 3 paracenteses. At an intravenous dose of 4mg/kg every 2 weeks, median time to repeat paracentesis was 76 (95% CI 64–178) days, which was 4.5 times longer than the baseline interval (17 days). Two patients experienced grade 3–4 treatment-related adverse events (hypertension and intestinal perforation) [67]. In a randomized double-blind phase II study, Gotlieb and colleagues randomized a similar population of 55 patients to afibercept 4mg/kg IV every 2 weeks or placebo. Mean time to repeat paracentesis was significantly longer with afibercept than with placebo (55.1 [SE 7.3] vs 23.3 [7.7] days; difference 31.8 days, 95% CI 10.6–53.1; $p=0.0019$). Strikingly, two patients in the afibercept group did not need a repeat paracentesis during 6 months of double-blind treatment. Patients who received afibercept had a higher rate of grade 3–4 dyspnea (20% vs 8%) but a lower rate of grade 3–4 fatigue (13% vs 44%). The frequency of fatal gastrointestinal events was higher with afibercept (three [10%] intestinal perforations) than with placebo (one [4%] intestinal fistula leading to sepsis) [68]. The largest study assessing afibercept randomized 218 patients to either 2mg/kg or 4mg/kg every 2 weeks. Afibercept

did not meet the primary endpoint for response: there was 1 responder of 106 patients (0.9%) in the 2mg/kg cohort and 5 responders of 109 patients (4.6%) in the 4mg/kg cohort. Treatment-related grade 3–4 hypertension was 25.5% and 27.5% in the 2mg/kg and 4mg/kg cohorts, respectively), and 3 patients had a gastrointestinal perforation (1.4%). The frequency or need for paracentesis was not evaluated in this trial [69]. There is no QOL data on the use of aflibercept and no randomized trials have compared bevacizumab and aflibercept in the context of ovarian cancer-related ascites.

3.2.3 Novel agents—Other angiogenesis inhibitors are currently being assessed in phase III trials in the management of ovarian cancer. These include pazopanib and nintedanib, which are orally administered tyrosine kinase inhibitors (TKIs) that block angiogenesis by inhibiting the actions of VEGF and other growth factors (i.e. platelet-derived growth factor) [70]. These agents may hold promise in the management of ascites. Of concern with all antiangiogenic agents is the fact that anti-VEGF resistance may develop. Changes in the tumor microenvironment that result from suppressed angiogenesis (i.e. hypoxia) and other consequences of VEGF inhibition can promote escape and tumor progression [71]. Efforts are needed to understand pathways that are involved in the escape mechanisms. Targeting these pathways may provide further benefit in the treatment of both ovarian cancer and ascites.

4. Immunologic agents

4.1. Catumaxomab

Catumaxomab is a targeted non-antiangiogenic immunological agent that is approved in Europe as intraperitoneal therapy to treat malignant ascites. It is a trifunctional monoclonal antibody that has 2 antigen-binding sites and a functional Fc domain. The antigen-binding sites bind to T-cells through CD3 and to tumor cells through epithelial cellular adhesion molecule (EpCAM) [72]. EpCAM is expressed on the majority of epithelial carcinomas (i.e. ovarian, hepatobiliary, colonic) but not on normal peritoneal cells [73]. Through its T-cell binding site and Fc domain, catumaxomab recruits and activates T-cells and Fc gamma receptor positive cells (macrophages, dendritic cells, and natural killer cells), redirecting them against the EpCAM-positive tumor cells [74]. Several studies have assessed the use of Catumaxomab in heavily pretreated patients with chemotherapy-refractory ovarian cancer and recurrent symptomatic malignant ascites [72, 75–77]. In a single-arm phase II study of 32 patients, the median puncture-free interval was prolonged 2-fold from 12 to 27.5 days. The median time to first therapeutic puncture was prolonged 4-fold from 12 to 52 days. QOL was assessed using the Functional Assessment of Chronic Illness Therapy-Ascites Index (FACIT-AI). Four weeks after the last drug infusion, symptoms had improved in 9 of 13 categories of the FACIT-AI index (anorexia, dyspnea, vomiting, abdominal pain, abdominal distension, early satiety, urinary frequency, constipation, and emotional distress) and worsened in 4 categories (insomnia, mobility, nausea, and fatigue). Nine patients (28%) experienced a treatment-related serious adverse event [75]. In a phase II/III trial, 258 patients with recurrent malignant ascites from an epithelial tumor (129 ovarian) were randomized to paracentesis plus intraperitoneal catumaxomab or paracentesis alone. Among ovarian cancer patients, puncture-free survival time (the primary efficacy endpoint) was

significantly longer in the catumaxomab group (median 52 vs 11 days; $p<0.0001$), as was median time to next paracentesis (71 versus 11 days; $p<0.0001$). In addition, patients treated with catumaxomab had fewer signs and symptoms of ascites than did control patients. Median OS was 110 days for patients who received catumaxomab and 81 days for those who didn't ($p=0.15$). The most commonly reported adverse events were cytokine release-related symptoms (fever, fatigue, nausea, and vomiting) and abdominal pain. Although frequent, the authors concluded that they were manageable and generally reversible [77]. This study led to the approval of catumaxomab by the European Union in 2009 for the intraperitoneal treatment of malignant ascites in EpCAM-positive carcinomas where standard therapy is not available or no longer feasible [78]. Given that it is an immunological agent, it is contraindicated in patients with acute infections, relevant concomitant hematological, cardiovascular, pulmonary, hepatic, renal or endocrine disease [76]. Catumaxomab is not available in the United States and no trials have compared its use to other drug therapies.

4.2. Imalumab

Imalumab (Bax69) is a new agent with potential immunomodulating activity that is currently under investigation. It is a human, recombinant monoclonal antibody against macrophage migration inhibitory factor that also has anti-inflammatory and antineoplastic actions. In a phase I study of patients with advanced solid tumors, it was well tolerated and showed single agent antitumor activity in heavily pretreated individuals [79]. It is currently being evaluated in a phase 1/2a two-arm dose-escalation study in subjects with malignant ascites and ovarian cancer. The primary outcomes are the occurrence of dose-limiting toxicity and the ratio of puncture free survival over puncture-free interval at baseline [80].

5. Expert commentary and five-year view

Malignant ascites affects a significant proportion of women with advanced and recurrent ovarian cancer. It frequently becomes the most pertinent issue in these patients and can have a detrimental effect on their QOL. We have highlighted different management strategies in this review. While mechanical options deal with the efflux of ascites, pharmaceutical treatments help prevent and diminish its influx. Symptom relief has to be weighed against potentially life-threatening adverse events associated with certain therapies. The risk of morbidity, including intestinal perforation, should be considered, and treatment should be individualized. Future studies looking at novel modalities to manage ascites should not only evaluate efficacy, but concomitantly assess their impact on patient-reported outcomes. Given that recurrent ovarian cancer is rarely curable, a focus on QOL is imperative in this population.

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Table 1

Mechanical treatment options

Treatment	Mechanism	Complications	Contraindications	Comment
Paracentesis	Mechanical drainage through one-time abdominal puncture	Hypotension, hypoproteinaemia, perforation, intraperitoneal bleeding, peritonitis, and pulmonary embolus	Loculated ascites	-First-line treatment -Fast resolution in symptoms but usually temporary with need for repeated medical visits
Peritoneal catheter	Implantable catheter for daily intermittent drainage	Hypotension, peritonitis, sepsis, catheter occlusion, and leakage from catheter site	Loculated ascites	-Prevent need for repeated paracentesis -Indicated in patients with prolonged life expectancy or those referred to hospice who need regular drainage
Peritoneovenous shunt	Tube that allows flow from peritoneum to vena cava through a one-way valve mechanism that opens at a specific pressure	Shunt occlusion, infection, sepsis, tumor embolization, pulmonary edema, and disseminated intravascular coagulation	-Loculated, hemorrhagic, or chylous ascites -Advanced renal failure, heart failure, coagulation disorders and portal hypertension -Patients with less than one month of life expectancy	High cost with potential for serious morbidity and mortality

Table 2

Medical treatment options

Treatment	Mechanism	Complications	Contraindications	Comment
Diuretics	Overall plasma volume reduction through increased urine production	Hypotension, hypovolemia, and renal failure	Hyponatremia, serum creatinine >1.5 mg/dL, infection, and encephalopathy	Ascites due to peritoneal carcinomatosis (majority of ovarian cancer patients) may be unlikely to respond to diuretic therapy
Angiogenesis inhibitors				
a. Bevacizumab	Monoclonal antibody directed against Vascular endothelial growth factor (VEGF) that inhibits binding of the normal VEGF ligand to its receptor	Grade 3–4 hypertension and gastrointestinal perforation	-Bleeding or thrombotic disorders, stroke, ischemic cardiac disease or congestive heart failure, and uncontrolled hypertension -History of gastrointestinal perforation	-Improved progression-free and overall survival specifically in patients with ascites in first-line setting -In small studies, effective in reducing ascites-related symptoms when given intravenously or intraperitoneally
b. Aflibercept	VEGF receptor (VEGFR) fusion molecule that binds to and inhibits VEGF-binding to all classes of VEGFR	Grade 3–4 hypertension, gastrointestinal perforation, and dyspnea	Same as bevacizumab	No randomized trials have compared bevacizumab and aflibercept in context of ovarian cancer-related ascites
c. Pazopanib/Nintedanib	Tyrosine kinase inhibitors that block the actions of VEGF and other growth factors			Currently under investigation in phase III trials in patients in ovarian cancer
Immunologic agents				
a. Catumaxomab	Trifunctional monoclonal antibody with 2 antigen-binding sites and a functional Fc domain that activates an immune response by binding to T-cells, macrophages, and dendritic cells, and redirecting them against tumor cells	Cytokine release-related symptoms (fever, fatigue, nausea, and vomiting) and abdominal pain	Acute infection, concomitant hematological, cardiovascular, pulmonary, hepatic, renal or endocrine disease	Not available in the United States
b. Imalumab	Human, recombinant monoclonal antibody against macrophage migration inhibitory factor that has immunomodulating, anti-inflammatory, and antineoplastic actions			Currently under investigation in a phase 1/2a trial in patients with ovarian cancer