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Narrative review of malignant ascites: epidemiology, pathophysiology, assessment, and treatment

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Background and Objective: Malignant ascites (MA) is common in patients with advanced cancer, and about 60% of patients with MA experience distressing symptoms. In addition, MA has been identified as a poor prognostic factor, therefore, making the management of MA an important issue. We aimed to review literature describing MA provide a narrative synthesis of relevant studies.

Methods: A literature search of articles published between 1971 and May 2023 was performed in PubMed, and Cochrane library using the words "ascites/malignant ascites" and the theme of each section. Authors independently selected the articles used and summarized. Finally, this manuscript was obtained consensus through discussed among all authors.

Key Content and Findings: The pathophysiological mechanism of ascites formation involves increased vascular permeability and impaired fluid drainage through the lymphatic system, which explain the occurrence of peritoneal carcinomatosis, portal hypertension due to liver tumors, liver cirrhosis in the background of hepatocellular carcinoma, and Budd-Chiari syndrome caused by tumor occlusion of the hepatic vein. The efficacy and safety of various treatments and procedures have been investigated previously; however, no treatment guidelines have been established yet. Diuretics and paracentesis are often selected as the first lines of treatment. Intraperitoneal drug administration (catumaxomab, bevacizumab, aflibercept, hyperthermic intraperitoneal chemotherapy, triamcinolone), indwelling peritoneal catheters, peritoneovenous shunting, and cell-free and concentrated ascites reinfusion therapy are commonly used to manage refractory ascites. A new device for this purpose is alfapump, which transfers ascites fluid from the peritoneum into the urinary bladder. In addition, thoracic epidural analgesia may be effective for managing ascites-related symptoms.

Conclusions: Despite these options, no standard treatment for MA has been established yet because few trials have been conducted in this area. There are many issues to be investigated, and future research and treatment development are expected.

Keywords: Malignant ascites (MA); paracentesis; indwelling peritoneal catheter; peritoneovenous shunting (PVS)

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Introduction

Malignant ascites (MA) is a common condition in patients with cancer that significantly decreases quality of life (QOL). In addition, MA is associated with poor prognosis due to a variety of factors that contribute to treatment refractoriness and difficulty achieving symptom relief. Currently, there are few established guidelines for MA treatment, with no high-quality evidence based on large prospective studies. In this review article, we summarize MA in terms of its epidemiology, pathogenesis, assessment methods, and treatment, including medications and procedures, and discuss future research agendas. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-554/rc).

Methods

A literature search of articles published was performed using PubMed and Cochrane library in whole period, which was between 1971 and May 2023. The database search was conducted using the words as follows: "ascites" or "malignant ascites" were always included, and the words "epidemiology", "pathophysiology", "diagnosis", "symptoms", "treatment", "diuretics", "abdominal paracentesis", "intraperitoneal administration" with the words of catumaxomab, bevacizumab, ziv-aflibercept, hyperthermic intraperitoneal chemotherapy (HIPEC) and triamcinolone, "indwelling peritoneal catheter", "peritoneovenous shunting (PVS)", "cell-free and concentrated ascites reinfusion therapy (CART)", "alfapump" and "thoracic epidural analgesia" were added. The articles to be collected included any study designs and those in English. Selection of the articles used was conducted each author independently, and each author prepared summaries of the collected articles. And then, the consensus about the manuscript was obtained through the discussion and comments from all authors. A summary of the search strategy is provided in *Table 1*.

Results

Epidemiology

MA is defined as the pathologic accumulation of fluid in the abdominal cavity caused by a malignant tumor. It leads to various clinical symptoms and a decline in patients' QOL. MA accounts for about 10% of all cases of ascites (1,2). It is most frequently associated with ovarian cancer, while gastric, uterine, breast, colorectal, and pancreatic cancers together account for 80% of cases (3-5). Twenty percent of patients with ascites were not diagnosed where the primary tumor was, and 3–7% of patients with MA secondary to gastric cancer had ascites at the time of initial diagnosis (6). More than one-third of patients with ovarian cancer had ascites at initial diagnosis, and almost all had ascites at recurrence (7).

MA has been identified as a poor prognostic factor. The median survival of patients with ascites was shown to be 5–7 months (4,8,9), and only 11% survived for longer than 6 months (9). Those with ovarian cancer had better survival than those with other cancers, with a mean overall survival of 32 weeks (8). Patients with ascites of unknown origin or secondary to gastrointestinal cancers had the worst survival. In addition, liver metastasis, reduced oral intake, low serum albumin, low serum total protein, high inflammation, renal dysfunction, dyspnea, delirium, edema, and fatigue were associated with poor prognosis of those with MA (4,10).

Pathophysiology

The peritoneal cavity normally contains 50–100 mL of serous peritoneal fluid that is rich in protein (40 g/L) (11,12). This fluid is physiologically produced by mesothelial cells on a continuous basis and then reabsorbed through the peritoneal surface (13). Peritoneal capillaries facilitate the exchange of various molecules and cells between the peritoneum and plasma. The peritoneal fluid is released into the peritoneal cavity through lymphatic apertures (named "stomata") that are present on the serosal membrane, and about two-thirds of this fluid is ordinarily absorbed via lymphatic vessels near the diaphragm. The fluid then flows through the mediastinal lymphatic vessels and right thoracic duct, and eventually empties into the right subclavian vein (11). This mechanism of fluid production and absorption is influenced by portal hypertension, sodium balance, and vascular permeability.

Ascites results from an imbalance between peritoneal fluid production and absorption (14) that is caused by increased vascular permeability and impaired fluid drainage through the lymphatic system (15). It is classified as a transudate or exudate according to its protein concentration. This determination is usually made using the serum-ascites albumin gradient (SAAG) or ascitic fluid total protein (AFTP). Transudative ascites is defined as SAAG ≥1.1 g/dL and/or AFTP <25 g/L, while exudative ascites is

Table 1 The search strategy summary

Items	Specification
Date of search	1/May/2023
Databases and other sources searched	PubMed, Cochrane library
Search terms used	[Ascites]/[Malignant ascites] and titles of each content
Timeframe	1971 to May 2023
Inclusion criteria	Any study, English language
Selection process	It was conducted independently

defined as SAAG <1.1 g/dL and/or AFTP ≥25 g/dL (16,17). The pathogenesis of ascites is complicated and is often multifactorial, the aforementioned-classification systems are useful for identifying the etiology of ascites. Transudative ascites results from portal hypertension, which is usually caused by cirrhosis, heart failure, or nephrotic syndrome. In contrast, exudative ascites is generally caused by inflammation or malignancy (18,19). However, MA can be either transudative or exudative depending on its cause. The primary etiologies of MA are as follows: (I) peritoneal carcinomatosis, (II) portal hypertension due to liver tumors (regardless of whether they are primary or metastases), (III) liver cirrhosis against a background of hepatocellular carcinoma, and (IV) Budd-Chiari syndrome caused by tumor occlusion of hepatic veins. A previous report by Runyon *et al.* found that the most common cause of MA (in 53% of cases) was peritoneal carcinomatosis (20), and it was categorized as exudative ascites in this context. Portal hypertension and Budd-Chiari syndrome are both due to obstruction of the critical venous system in the liver. MA in these settings takes the form of transudative ascites, and the pathogenetic mechanisms involved are like those seen in cirrhosis (21,22).

The lymphatic vascular system is essential for fluid drainage. Lymphatic vessels are abundant in the peritoneal membrane, and their obstruction by tumor cells has been suggested to result in ascites formation. However, MA can occur even if no tumor has been detected clinically. In such cases, ascites frequently exhibits a high protein concentration that is thought to be related to changes in peritoneal permeability caused by components of the tumor microenvironment, such as cytokines and chemokines (23). Some studies of ovarian cancer have suggested that the prognosis of patients with MA is influenced by these components (24,25). Tumor-induced chemokines and inflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor, and vascular endothelial growth factor (VEGF) have been detected in ascites, and high levels of these cytokines were associated with poor prognosis (24,25). In contrast, another study by Ito *et al.* found that high levels of anti-inflammatory cytokines such as IL-10 were associated with longer survival (26).

Vascular permeability is also important for the formation of ascites. The previous studies showed that vascular permeability was affected by inflammatory cytokines such as IL-1, IL-6, and IL-8, all of which are abundant in MA (23,27), as well as by VEGF, matrix metalloproteinases (MMPs), and various other chemokines (11,23). VEGF can increase vascular permeability more than histamine (28). In a variety of tumors, malignant cells overexpress VEGF, and MA is rich in VEGF. VEGF was found in 49% to 96% in malignant cells of patients with MA (28-30). VEGF downregulates claudin-5, which forms tight junctions in the peritoneal epithelium. This downregulation is suggested to be one mechanism underlying the VEGF-induced enhancement of vessel permeability (31). Another is the tyrosine phosphorylation of cadherin-catenin complexes, as this decreases junctional strength (31,32). MMPs are overexpressed in a variety of malignancies, including ovarian, colorectal, gastric, and breast cancers, and they play a role in tumor invasion and metastasis (33). In ovarian cancer, the secretion and activation of VEGF and MMPs were reported to be interrelated; in particular, MMP9 contributed to ascites formation via VEGF activation (34).

Assessment and differential diagnosis of ascites

There are many causes of ascites besides malignancy, including liver cirrhosis, renal failure, congestive heart failure, nephrosis, and pancreatitis (1). The most common cause is cirrhosis (80%), while MA accounts for 10% of all cases (1). To differentiate malignant from benign ascites, it

is useful to perform cytological and biochemical analyses of ascites fluid. MA is usually cytologically positive, has a high protein concentration, and exhibits SAAG <1.1 g/dL (35-37). However, these tests are not always sufficiently accurate. In a retrospective analysis of 62 patients with pancreatic cancer, only 36 (58%) had positive ascites cytology, and all of most (82%) had SAAG >1 g/dL (38,39). Therefore, multiple abdominal punctures may be necessary to confirm the presence of malignant cells when it is clinically difficult to differentiate between benign and MA.

The appearance of ascites, i.e., whether it is hemorrhagic or not, may be useful in diagnosing and predicting the refractoriness of ascites-related symptoms. Hanada *et al.* reported that in 13% of MA cases, the ascites was grossly hemorrhagic, and the study used a short paracentesis interval for these patients (40). The utility of potential biomarkers in the diagnosis of MA, such as mutations in tumor DNA and cytokines in ascites, should be studied in the future (38,41,42).

Assessment of symptoms due to ascites

About 60% of patients with MA experience distressing symptoms such as abdominal distention, abdominal pain, nausea and vomiting, anorexia, fatigue, dyspnea, early satiety, and heartburn (4). These symptoms worsen as the ascites volume increases with cancer progression, and are often difficult to manage when the disease becomes refractory to anticancer treatment (1,35,37).

One ascites-specific symptom rating scale is the Edmonton Symptom Assessment System Ascites Modification (ESAS:AM) (43-46). It consists of 11 items with the option of adding a 12th specific symptom, each rated on a numerical rating scale from 0 (symptom absent) to 10 (worst severity). The items include nine from the original ESAS, specifically pain, tiredness, drowsiness, nausea, appetite, shortness of breath, depression, anxiety, and well-being, as well as two additional items, namely abdominal distention and mobility. The reliability and validity of versions in languages other than English have been validated (45). Another symptom rating scale is the ascites impact measure (AIM), which is used to clarify a patient's motivation for requesting paracentesis (47). This is a six-point scale, ranging from 0 (none) to 5 (severe), that evaluates the severity of the following components over the past 24 hours: abdominal discomfort, abdominal bloating, abdominal pain, and ability to move normally.

Treatment

Diuretics

There is no clear evidence supporting the use of diuretics for the treatment of MA, because no randomized trial has been conducted. For liver cirrhosis, on the other hand, the use of diuretics is recommended by international guidelines (48,49). For patients whose ascites severity is moderate or greater, a single aldosterone antagonist is recommended as the initial treatment choice (e.g., spironolactone 100 mg/day as starting dose, increased to 400 mg/day), and a loop diuretic (e.g., furosemide) may be effective in combination for recurrent and refractory ascites. The efficacy and implementation of this approach has been reported in numerous randomized controlled trials (50-54).

Diuretics are traditionally used as the first-line treatment for ascites. Several previous studies, however, showed that they were ineffective for some patients with MA (36,55). One study by Lee *et al.* reported that diuretics were administered to 61% of patients with MA, but only 45% of them experienced positive effects (56). In another study reported by Mackey *et al.*, diuretics were only helpful for 22% of patients with liver metastasis (57).

Diuretics are most beneficial for patients with transudative ascites, which has a similar pathogenetic mechanism as ascites seen in liver cirrhosis and exhibits SAAG >1.1 g/dL; in contrast, these agents show minimal utility for exudative ascites, which forms in peritoneal carcinomatosis and has SAAG <1.1 g/dL (36,57,58). Diuretics tend to be effective in patients with high plasma renin-aldosterone levels (57). In the case of liver cirrhosis, renal sodium retention due to activation of the renin-angiotensin-aldosterone system contributes significantly to ascites production and patients have high plasma renin-aldosterone levels (59). These levels are elevated when there is a decrease in effective circulating blood volume secondary to portal hypertension. Therefore, SAAG may be useful for predicting the effectiveness of diuretics for MA by clarifying the cause of ascites. The variable efficacy of diuretics for MA may be due to the multifactorial etiology of the condition. Diuretics are expected to be effective for MA caused by portal hypertension secondary to hepatic tumors, tumor-induced hepatic vein obstruction, or portal obstruction.

Thus far there is no standard regimen for the use of diuretics to treat MA. Spironolactone, an aldosterone antagonist, is most often prescribed for MA in clinical

settings, and its efficacy is due to the optimization of renal reabsorption by decreasing plasma aldosterone levels. Sometimes loop diuretics such as furosemide (20–80 mg/day) are used in combination with spironolactone (14,60). One study by Pockros *et al.* reported that spironolactone at a dose of 100–400 mg/day improved ascites-related symptoms and reduced body weight by approximately 1 kg/day (58). Another study specified appropriate diuretic dosages for different regimens: the starting dose of oral furosemide alone was 20 mg/day, and its dose could be increased to 40 mg/day with the addition of spironolactone at 25 mg/day; in contrast, the initial dosages of furosemide and spironolactone in combination were 20 and 25 mg/day, respectively, and these could be increased to 40 and 50 mg/day, respectively (61). Another diuretic, tolvaptan, is a non-peptide arginine vasopressin V2 receptor antagonist that inhibits water reabsorption in the renal collecting ducts. Tolvaptan has been shown to be effective for decreasing fluid retention due to volume overload and congestion in heart failure (62), lowering the volume of ascites caused by portal hypertension with liver cirrhosis (63), and reducing renal volume and cysts volume by suppressing the vasopressin-induced increase in intracellular cAMP in autosomal dominant polycystic kidney disease (64). Thus, given the utility of tolvaptan for treating fluid retention, studies are being performed based on the expectation that the drug will be useful for MA. There is currently one phase 2 study on the efficacy of tolvaptan for MA, and because it did not show a clear benefit, tolvaptan cannot be recommended at present (10).

Diuretics have several side effects. High-dose spironolactone is most commonly associated with nausea and vomiting (59), and it can also cause hyperkalemia and hyponatremia, the latter especially when furosemide is used in combination. As mentioned above, there are suggestions that diuretic use in patients with peritoneal carcinomatosis may be at increased risk of hypotension due to the effective circulating blood volume or renal dysfunction, may be safer in hepatic tumors.

Abdominal paracentesis

Drainage by abdominal paracentesis is the most common treatment to alleviate symptoms caused by MA (65-67), although evidence supporting the efficacy and safety of this treatment is weak. Paracentesis provides rapid and temporary symptom relief for most patients, while it requires frequently repeated treatment to maintain symptom control because of the reaccumulation of ascites (65-67). In a recent multicentre prospective observational study by Becker and colleagues of patients admitted to a palliative care unit, 81% of patients with MA treated with paracentesis improved their NRS for abdominal distension by two or more after the procedure (66). And more than half of the patients received 2 or more paracentesis during their stay in PCU. An international prospective cohort study by Seah and colleagues showed that symptoms measured with Common Terminology Criteria for Adverse Events improved after a single procedure in 81% of patients, and 89% had some benefit within 28 days (67).

Paracentesis is generally safe, and recent prospective observational studies reported that severe adverse events were not common and survival of patients with MA treated with *vs.* without paracentesis was not significantly different (65,67-70). A large volume of drainage, however, may result in a higher incidence of hypotension and renal impairment (65,66,68,69). In addition, loss of electrolytes and proteins due to repeated procedures can be problematic (71). The incidence of severe bleeding complications is low, and a retrospective study in patients with liver cirrhosis by Pache *et al.* reported severe hemorrhage in <0.2% of the procedures (72). The use of ultrasonographic guidance reduces the risk of iatrogenic injury, especially in patients with bowel obstruction, organomegaly, intraabdominal adhesions, or a distended urinary bladder (69,73). Other adverse events include ascitic leak, fatigue, and abdominal pain (67).

The optimal procedure is often a balance between the potential for symptom improvement, the known risks of adverse events, and burden of repeated and prolonged hospitalization. While large volume paracentesis (LVP) with albumin infusion is the standard treatment for patients with diuretics resistant cirrotic ascites (20,22,74-76), there are limited data regarding the optimal amount and speed of ascites drainage in patients with MA. Although a guideline for the management of MA allows up to 5L of drainage (68), palliative care experts suggest that 1–3 L of paracentesis would be balanced for very frail patients with limited prognosis (77,78). This suggestion is supported by the following prospective observational studies. Intra-abdominal pressure and related symptoms significantly relieved after drainage of the first few liters (79). Moreover, paracentesis interval was not significantly different between 1.5–2.5 *vs.* >2.5 L of drainage, while abdominal distension was equally relieved after the procedure (66).

Drainage speeds vary considerably by region. Some procedures involve continuous drainage of the entire

volume of ascites fluid over a period of 10 hours to several days, while others use evacuated bottles or wall suction for drainage in about 30 min (67,80-82).

It is not well understood whether the patient would benefit from some type of infusion during ascites drainage. One guideline states that fluid infusion is not necessary (68), but a survey conducted in Germany and Austria found that 73% of physicians gave some type of fluid infusion, including albumin (83).

Indwelling peritoneal catheters

Indwelling peritoneal catheters may be useful for MA that is refractory to treatment with diuretics or single puncture and therefore necessitates frequent paracentesis. Indwelling pleural catheters were initially developed for pleural effusions associated with refractory malignant pleural mesothelioma (84). Because of its efficacy and safety, the indications for this treatment were expanded to include refractory pleural effusions due to congestive heart failure (85), and techniques for intraperitoneal implantation were developed and used to treat cirrhotic ascites (86).

Indwelling peritoneal catheters have been reported to be effective for the management of MA (87-89). One end of the catheter is placed in the peritoneal cavity and is connected to the outside of the body through a subcutaneous tunnel. A vacuum bottle is connected to the end outside the body, and the negative pressure of the bottle results in ascites drainage. At the time of catheter placement, the average amount of drained ascites was 8.5 L (90). Another study reported that the average amount of drained ascites after catheter placement was approximately 1.2–2 L every other day (88), probably due to the capacity of the vacuum bottle.

In addition to diuretics, paracentesis is commonly used for the early treatment of MA, and one of its benefits is that the volume of ascites drainage can be adjusted from a few liters to over 20 L/day (11). In some cases, paracentesis is performed in the patient's home by other professionals, such as trained nurses, or by homecare doctors, but in most cases, it is a procedure that can only be performed by physicians and therefore often requires an outpatient or hospitalization. Multiple invasive procedures may also be required, which increases the risk of complications such as bleeding and infection. In contrast, an indwelling peritoneal catheter can be placed in a single procedure and used continuously, and can be managed through home care. A previous study by Robson *et al.* found that ascites drainage was most common performed by home care nurses (40.0%), followed by patients themselves (33.3%) or by relatives (27.6%) (91). However, several catheter-associated complications have been reported. The most frequent of these is ascites leakage around the catheter insertion site, which was found to occur in approximately 20% of patients (88-90). The others notable complications were catheter occlusion, peritonitis, and cellulitis at the insertion site, but they were not severe and they only occurred in about 1–4% of patients, so were therefore considered tolerable (88,89,92).

Chan *et al.* performed a retrospective study showing that 96% of patients experienced relief from ascites-related symptoms such as abdominal pain, abdominal distension, and dyspnea (87). Another study found that patient QOL was improved 1 week after the procedure, as determined using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the McGill Quality of Life Questionnaire (MQoL) (91). Furthermore, prospective studies showed that 4 weeks after catheter placement, 85.7% of patients exhibited improvement in their general condition (91,93) and the median Karnofsky Performance Status score decreased from 60 to 50 (91). In terms of cost, indwelling peritoneal catheters have been reported to be less expensive than LVP (≥5 L) needed once every 10 days or more than nine times per a catheter placement (94).

Since previous studies have shown the efficacy and safety of indwelling peritoneal catheters, it is important to consider early catheter placement for refractory MA, which is difficult to control with diuretics and/or single paracentesis, so as to improve patient QOL and reduce costs.

Intraperitoneal drug administration

Intraperitoneal drug administration has been reported to be effective for MA. Previous studies reported the efficacy of several drugs, such as triamcinolone, catumaxomab, immunological agents, and several molecular target agents. In addition, HIPEC has demonstrated efficacy against MA through its effect on peritoneal dissemination.

Catumaxomab

Catumaxomab is a bispecific, trifunctional, non-humanized mouse/rat monoclonal antibody that targets both the epithelial cell-adhesion molecule (EpCAM) expressed by tumor cells derived from epithelial cells, and the CD3/T-cell receptor complex, which is expressed by T cells. Catumaxomab also binds to Fcγ receptor I-, IIa-, and III-positive immune cells. The drug contributes to the activation of some immune cells, such as natural killer cells,

dendritic cells, and macrophages, and therefore eliminates tumor cells by an immunological cytotoxic mechanism (95-98). Catumaxomab is generally administered via intraperitoneal catheter at four escalating doses (i.e., 10, 20, 50, and 150 mg) given at 3- or 4-day intervals over 2 weeks (97,99,100). In several studies published in European countries, intraperitoneal catumaxomab prolonged paracentesis intervals and relieved various symptoms (e.g., anorexia, dyspnea, abdominal pain, abdominal swelling, and early satiety). Puncture-free survival in patients with epithelial cancer and MA was reported by Heiss *et al.* to be 77 days in the catumaxomab group versus 13 days in the control group [hazard ratio (HR) =0.169; 95% confidence interval (CI): 0.114–0.251] in a phase 2/3 study (97). These studies also indicated that catumaxomab markedly decreased the number of EpCAM-positive tumor cells in MA. More than 85% of patients who received this treatment experienced at least one adverse event. The most prevalent adverse events associated with intraperitoneal catumaxomab were pyrexia, nausea, and vomiting, each of which is thought to be caused by cytokine release; their frequencies were 60.5%, 33.1%, and 27.4% for any grade, respectively, and 5.7%, 3.2%, and 2.5% for grade 3 or more, respectively (97). However, these symptoms were tolerable, reversible, and mild in intensity. Notable severe side effects include ileus, effusions, anastomotic leak, and gastrointestinal bleeding (95-97,99,100). Thus, catumaxomab was approved by the European Medicines Agency in 2009 because of its efficacy and safety, but unfortunately, sales were discontinued in 2014 and the approval was withdrawn in 2017, so it is not currently available in clinical practice.

Bevacizumab

Bevacizumab is a monoclonal antibody drug that targets VEGF and is used as a standard treatment for colorectal and other cancers. VEGF plays a significant role in tumor progression through angiogenesis, and in the formation of MA by increasing vascular permeability. Bevacizumab is expected to be effective for the pathophysiology of MA, and is being studied. The efficacy of intraperitoneal bevacizumab was investigated in two prospective phase 2 trials (101,102), the results reported by Jordan *et al.* showed a prolonged paracentesis interval; 14 days in the intraperitoneal bevacizumab group versus 10.5 days the control group (HR: 0.74, 95% CI: 0.40–1.37, P=0.16) (101). The recommended dosage of bevacizumab is 400 mg (71), and safety at this dose has been confirmed. Vomiting and nausea are the most common side effects, but both are tolerable and manageable.

Ziv-aflibercept

Ziv-aflibercept, a molecular targeted agent, is a recombinant fusion protein that acts as a soluble receptor binding to VEGF-A, VEGF-B, and placental growth factor (PlGF) (103). This drug was approved by the Food and Drug Administration (FDA) for metastatic colorectal cancer. Additionally, a phase 2 study in patients with advanced ovarian cancer reported that intravenous ziv-aflibercept reduced MA volume in all patients and more than doubled the paracentesis interval in 62.5% of patients (104). According to a retrospective study by Lu *et al.*, ziv-aflibercept is more effective against MA when administered intraperitoneally than intravenously (105). Their results showed that 73.3% of patients exhibited no early recurrence (within 4 weeks) and achieved symptomatic relief from ascites and reduced ascites volume. The efficacy of intraperitoneal ziv-aflibercept was also shown to be dose independent, as some patients who received 50 mg had a higher response rate than those received 100 mg (105).

HIPEC

HIPEC with cytoreductive surgery followed by intravenous chemotherapy has received attention as another intraperitoneal treatment for MA (106-108). HIPEC is performed as follows: first, ascites in the peritoneal cavity is completely drained and suctioned. Second, the peritoneal cavity is filled with saline that circulates continuously at a constant temperature of 40–42 ℃. Third, chemotherapy is perfused for 30–90 min depending on the regimen appropriate for the primary tumor. At the end of the procedure, the fluid remaining in the peritoneal cavity is drained as much as possible (107,108). The studies cited above showed that HIPEC was effective for prolonging recurrence-free survival and paracentesis intervals. However, HIPEC was not sufficiently effective in certain patient populations, such as those with perforated colon cancer (109). Additionally, health-related QOL was not significantly different after cytoreductive surgery with or without HIPEC (110). These results indicate that HIPEC is tolerable in terms of adverse events, but careful discussion is needed about which patients are best suited for HIPEC. Thus, there is still inadequate evidence regarding HIPEC, and future research is expected.

Triamcinolone

Triamcinolone is a slowly metabolized steroid that is commonly administered via intra-articular injection for the treatment of inflammatory arthritis. It is also thought to be effective for refractory ascites in hemodialysis patients with

end-stage renal failure when administered intraperitoneally after complete ascites drainage (111,112). Due to the drug's low water solubility and slow metabolism, the peritoneal membrane and peritoneal cavity are exposed to high triamcinolone concentrations for a relatively long period. Its usefulness has also been suggested for MA (113-116). Ito and colleagues have reported that intraperitoneal triamcinolone administration combined with paracentesis was successful in prolonging the paracentesis interval, with a response rate of approximately 80% (113). The volume of ascites drainage was 2–6 L, and the triamcinolone dosage was set to approximately 10 mg/kg. Some side effects were reported, including peritonitis, abdominal pain within an hour after paracentesis and drug administration, and most seriously, intestinal perforation.

PVS

PVS is considered when frequent paracentesis is required for refractory ascites. PVS involves using a subcutaneous catheter to drain ascites into the central venous system, usually the internal jugular or femoral veins (117). PVS was developed in the 1970s, originally as the Le Veen shunt and Denver shunt (65,117). These variations are very similar, but the one-way valve opens at a pressure of 3 cmH_2O in the former, and 1 cmH_2O in the latter. In addition, the Denver shunt is equipped with a reflux prevention valve (65). The main drawbacks of repeated paracentesis, namely hypovolemia and hypoalbuminemia, are unlikely with PVS (65). Although PVS was originally used for ascites associated with cirrhosis, it is now also used to manage malignancy-related ascites (55,56).

At present, there are no studies comparing PVS and paracentesis in patients with malignancies. In a study of patients with cirrhosis and refractory ascites, Ginès *et al.* reported their experiences with PVS compared to repeated LVP accompanied by intravenous albumin infusion (118). They found that PVS was more effective for long-term control of ascites, as indicated by the time to ascites-related readmission (2±2 *vs.* 8±17 months in the paracentesis and PVS groups, respectively). There was no significant difference in patient survival between the two groups.

According to a meta-analysis of 21 case series and one non-randomized open controlled trial of PVS in patients with malignancy, effective ascites control was achieved in 77.95% of patients, as determined by outcomes including relief of ascites-related symptoms, increased diuresis, decreased weight, decreased abdominal girth, and number of paracentesis procedures required (65). Sugawara *et al.* reported that PVS with a median duration of 26 days improved ascites-related symptoms, including abdominal distension, anorexia, and nausea, by 7 days or more in 82.7% of patients (119).

PVS is contraindicated in patients with loculated ascites, portal hypertension, poor cardiac or renal function, and gastrointestinal cancers (65,117). Complications related to PVS were reported in 25–50% of patients (120-122). Shunt occlusion was relatively common, occurring in 19.06% of cases (110,111), and for this reason, it is contraindicated for hemorrhagic ascites and ascites with a protein concentration of more than 4.5 g/L (55,123). Shunt occlusion is reportedly more common with Denver shunts than Le Veen Shunts, but this has not been definitively proven (124). Coagulation abnormalities such as disseminated intervascular coagulation (DIC) are also a concern with PVS (117). Sugawara *et al.* reported that subclinical and clinical DIC occurred in 27.8% and 5.3% of patients with malignancies, respectively (119). Fibrin split products and collagen in ascites are reportedly associated with coagulation abnormalities (125-127). Low platelet counts, prolongation of prothrombin time, and hyperbilirubinemia have also been found to be associated with the development of DIC (128). However, the reason coagulation abnormalities occur with PVS remains unclear. As ascitic fluid drains directly into the central venous system, it is necessary to monitor the fluid balance of patients for at least 24 hours after inserting a shunt (65). While cancer cells also drain into the systemic circulation, there is no evidence that this contributes to hematological metastasis (55,129).

Although PVS may contribute to the management of refractory ascites and can alleviate ascites symptoms for longer than paracentesis, clinicians should be aware of the risk of shunt occlusion and coagulation abnormalities. Furthermore, significant complication rates have led to the abandonment of PVS in patients with cirrhosis-related ascites (22). Of note, there is no established evidence for PVS in patients with cancer, as no RCTs have compared PVS with LVP in this population. For these reasons, PVS in patients with cancer-related ascites should only be considered when other treatment options have failed and when the patient's life expectancy is long enough for the procedure to be beneficial. In this context, Arai *et al.* reported the feasibility and safety of a modified method for placing a PVS catheter between the jugular vein and abdominal cavity via the hepatic vein in patients with MA, a procedure referred to as transjugular transhepatic

peritoneovenous venous shunting (130). Although PVS is generally inadvisable for patients with MA at present (65,71), its utility may be demonstrated by future studies comparing its efficacy and safety with those of paracentesis.

CART

CART is a treatment option for refractory ascites that is considered when repeated paracentesis is required. CART involves reinfusing the processed ascites after paracentesis (131). The mainstream therapy for refractory ascites is LVP (4,56,83), and while it can relieve ascites-related symptoms such as abdominal distension, it is associated with a risk of hypovolemia (66). The goals of CART include alleviating physical symptoms caused by ascites, and maintaining plasma osmotic pressure by reinfusing ascites proteins, thereby reducing the risk of hypovolemia after LVP. CART was first used in the 1970s to treat refractory ascites related to both malignancy and liver cirrhosis (131), and it has been covered by the Japanese health insurance system since 1981. Although CART has been used mainly for cirrhotic ascites since its development, it has also been performed for MA in recent years (132,133).

CART consists of the following three steps: (I) paracentesis, (II) filtration and concentration of ascites, and (III) intravenous reinfusion of processed ascites (131). In the second step, ascites is filtered to remove all cell components, including cancer cells or microbes. Then, to avoid volume overload in the third step, the ascites is concentrated to reduce its volume. Steroid agents are often administered to prevent fever in the reinfusion step (134). The most significant difference between CART and PVS is that the former includes removal of the cellular components of ascites.

In a prospective observational study conducted primarily in patients with cancer, CART was reported to alleviate a wide range of physical symptoms, including abdominal distension, nausea, fatigue, and shortness of breath (133). Considering that fatigue is a concerning side effect of LVP (117), the ability of CART to reduce its severity might be a strong point. Ito *et al.* reported that 62.9 g of protein in MA was recovered when 3,350 g of ascites was processed (134). Increased urine output after CART has also been reported in patients with malignancies (132,134), probably due to the presumed ability of CART to maintain plasma osmotic pressure. Hanada *et al.* reported that CART may extend the paracentesis interval in patients with cancer compared to LVP alone (40), likely the result of reinfusing ascites proteins.

Although reports have described the favorable effects of CART on symptom management, no RCTs have investigated its effects in comparison to LVP. At present, the superiority of CART over LVP remains uncertain.

In patients with MA, adverse events associated with the reinfusion step were observed in 21.6% of patients (134). The most common of these was elevated body temperature, followed by chills, spasms, and nausea. Importantly, none of these were clinically relevant. Reduced platelet counts after the reinfusion of processed ascites is another concern. Ito *et al.* reported that the platelet count in patients with cancer decreased by $2.2\times10^4/mm^3$, which does not indicate clinical DIC (134). However, the underlying mechanism is still unknown. Although hypovolemia may occur with LVP, an observational study conducted primarily in patients with cancer found no clinically significant changes in blood pressure during CART procedures (132).

Contraindications of CART include immunodeficiency, the detection of endotoxin in ascites, varices, poor liver function, jaundice, hepatic encephalopathy, gastrointestinal bleeding, bleeding tendency, and hemorrhagic ascites.

CART is currently performed mainly in Japan. Although it was shown to relieve symptoms and prolong paracentesis intervals in patients with cancer (40,133), at this point no RCTs have compared it with LVP. In addition, the cost-effectiveness of CART (113,600 JPY per procedure) must be considered. In determining the role of CART as a treatment option against refractory ascites, future studies considering multiple perspectives are required.

The alfapump system drains ascites from the peritoneum into the bladder

The alfapump system is a subcutaneously implanted device powered by an external rechargeable battery, and is used to continuously drain ascites at low speed from the peritoneum into the urinary bladder. It was originally used for refractory cirrhotic ascites, and its effectiveness in this setting has been confirmed (135). Fotopoulou *et al.* also reported its efficacy and safety in patients with MA, demonstrating that 303.6 mL of ascites was drained daily and only one of 12 patients with available data after implantation required LVP of 5 L or more (136). Seventy-one percent of the patients experienced improved QOL parameters, including abdominal fullness, tiredness, and shortness of breath. Adverse events were reported in 29.4% of patients, including renal failure, technical issues related to the pump or catheter such as infection and wound dehiscence.

Although further research is needed, the alfapump system may also be effective for MA, reducing the necessity of LVP and improving patients' QOL.

Thoracic epidural analgesia against abdominal fullness in patients with cancer and ascites

In a small case series, thoracic epidural analgesia used for pain control also relieved abdominal fullness in patients with cancer and ascites (137). In one patient with massive ascites, the numerical rating scale for abdominal fullness decreased from 4–7 to 1–2, depending on the ropivacaine dose. The authors suggest that this technique might reduce somatic nervous system activity associated with abdominal wall extension, but this remains unclear. Although it is also necessary to mention the effects against pain related to peritoneal dissemination or intraperitoneal mass, the effect of epidural analgesia against intractable abdominal fullness related to massive ascites may be suggested. Its efficacy and safety should be evaluated more precisely with a larger sample size.

Research agenda and challenges in conducting clinical trials for MA

No standard treatment has been established for MA thus far because few trials have been conducted in this area (35,36,38,65,117). Paracentesis is the most common treatment for MA worldwide (4,56,83). Thus, the efficacy and safety of other treatments, such as paracentesis with intraperitoneal agents, PVS, and CART, must be confirmed in comparative studies with paracentesis (85,130,138).

Regarding paracentesis, the lack of a standard methodology should be addressed in future research (35,36,38,65). The optimal volume and speed of ascites drainage in frail patients should also be clarified so that paracentesis can be performed effectively and safely. A recent prospective observational study by Ito *et al.* reported that in terminally ill patients with MA who were admitted to a palliative care unit, an ascites drainage volume of around 2 L seemed to be the best balance (66). The optimal procedure for outpatients undergoing chemotherapy or receiving care at home must also be clarified.

Furthermore, it is inconclusive whether any fluids should be infused during ascites drainage (65). While LVP plus intravenous albumin is the standard of care for hepatic ascites, it is commonly believed that hydration is unnecessary during drainage of MA (48,65). In practice, however, some physicians do perform hydration, including with intravenous albumin (83). Whether or not hydration is useful, and in what patients or procedures this might be true, are subjects for future research (65).

Some physicians and patients are concerned that repeated paracentesis may shorten survival due to protein loss (70). A prospective observational study in patients with MA who had been admitted to a palliative care unit found no significant difference in survival according to whether or not paracentesis was performed (70). Further studies are needed to determine whether repeated paracentesis shortens patient survival.

Indwelling catheters have been shown to be useful in patients requiring repeated paracentesis (88,94,139,140). They may reduce the numbers of punctures, hospital visits, and hospitalizations, and they may be cost effective. However, these benefits may vary depending on the healthcare system. In countries with low hurdles to hospital visits, the burden of living with an indwelling catheter may be greater than the burden of undergoing repeated paracentesis.

As for diuretics, it is not known what diuretics are effective in what patients, though it may be effective in about 40% of all patients with MA (65). Small observational studies have shown that diuretics may be more effective for ascites due to liver metastases than for that caused by peritoneal dissemination, but further studies are needed (57,58). In addition, there is growing interest in whether vasopressin V2 receptor antagonists are as effective for MA as they are for hepatic ascites (141,142).

Challenges in conducting clinical trials of treatments for MA include patient recruitment, treatment standardization, and defining outcomes. Recruitment is a challenge because only a few percent of cancer patients require ascites drainage (66). Also, as mentioned above, the different treatments are not necessarily standardized, and procedures may vary by region and institution (65). Furthermore, the outcomes of ascites treatment have not been established. The ascites puncture interval has been frequently used in previous studies (40,66,97,113,115,138,143), but this outcome is often unreliable, especially in unblinded trials, because it can be manipulated by clinicians (138). It may be preferable to use patient-reported outcomes measured over several weeks, for instance the ESAS:AM total score or daily abdominal distention assessed using a numerical rating scale. Objective measures such as body weight and abdominal circumference are also potential outcome measures (130), but they may not always accurately reflect treatment efficacy because they are affected by diet, constipation, edema, and other factors (138). Thus, establishing the outcomes of clinical trials on ascites

treatment is an important topic for future research.

Conclusions

As discussed above, studies have been conducted on MA but there is insufficient evidence to inform clear practice guidelines. There remains significant gaps in our understanding, and many patients with MA still suffer from its symptoms. There are many issues to be investigated, and future research and treatment development are expected.

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Footnote

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