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ORIGINAL ARTICLE

A survey of treatment approaches of malignant ascites in Germany and Austria

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Abstract
Background Malignant ascites (MA) is a common manifestation of advanced cancer. Currently, there are no evidence-based guidelines for the management of MA. We conducted a survey with physicians throughout Germany and Austria, to get an overview of current approaches and opinions in the treatment of MA.
Methods One hundred and twenty-eight medical oncologists (MO), gastroenterologists (GE), and gynecologists (GYN) completed an electronic questionnaire consisting of 33 questions.
Results Ninety percent of the physicians were from Germany and 10 % from Austria; 48 % of those were MO, 30 % were GYN, and 14 % were GE. Most physicians treated an average of 34 patients (pts)/year with MA. Twenty-six percent of these pts suffered from ovarian, 20 % from pancreatic, 17 % from gastric, and 14 % from colorectal cancer. The majority of the physicians associated MA with poor prognosis (92 %) and significant reduction in quality of life (87 %). One third felt that MA was a contraindication for full dosing of systemic chemotherapy. Paracentesis (PC) was performed in 70 % of pts with symptom relieve and quality of life being the main reasons. Almost half of the pts required 3–5 PC, 50 % even more than 5 PC during the course of their disease. Only 15 % of pts needed multiple PC per week; the majority (79 %) needed the procedure either once a week or every 14 days. In 61 % of pts, 3–5 L of ascites fluid was drained. Only in 8 %, 5 L and more were removed. Volume substitution with IV albumin was performed in 40 % of pts. Most pts (55 %) had to stay 1–3 h in a healthcare facility for the procedure. However, 21 % had to stay ≥1 day. While almost all physicians (89 %) performed a PC at some point in the treatment of MA, 75 % felt that a systemic chemotherapy and 55 % thought a concomitant diuretic therapy were a necessary adjunct. Seven percent of the pts received a targeted treatment with catumaxomab.
Conclusions Repeated PC is the main pillar of treatment of MA; its effect is only temporary and requires significant hospital resources. Further treatment strategies of MA have to be evaluated in prospective studies. Targeted therapies like catumaxomab and VEGF inhibitors should be integrated into these.

Keywords Malignant ascites · Advanced cancer · Paracentesis · Catumaxomab

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Introduction

Malignant ascites (MA) is defined as an accumulation of fluid within the peritoneal cavity, as a result of increased fluid production from tumor and mesothelial cells lining the peritoneal cavity, increased permeability of blood vessels through enhanced neoangiogenesis, and release of inflammatory cytokines. The excess fluid production is aggravated by impaired lymphatic drainage due to tumor micrometastases [1, 2].

Various tumors can cause MA. Retrospective studies show MA emerges most frequently in ovarian cancer (37 %), followed by pancreatobiliary cancers (21 %) and gastric cancer (18 %). MA is a common manifestation of advanced cancer. It confers upon patients (pts) a poor prognosis with a median overall survival of 10–24 months in

ovarian cancer and 1–6 months in non-ovarian cancer. In addition, the symptoms associated with MA such as abdominal swelling and pain, nausea and vomiting, fatigue and dyspnea decrease quality of life considerably [3, 4]. There are no clinical predictors that could help identify cancer patients prone to development of MA, and hence, there are no preventive measures for its development. Paracentesis (PC) usually provides fast, however, only temporary symptomatic relieve. Effective systemic chemotherapy can prevent fluid reaccumulation after this procedure. However, when systemic treatment is no longer effective, other treatment options for recurrent MA are needed. These include repeated PC, intraperitoneal chemotherapy, use of diuretics, peritoneal-venous shunting and catheter drainage, or combinations of these [5–7]. None of these approaches have been established as standard therapy due to limited efficacy and severe side effects. Currently, there are no evidence-based guidelines for the management of MA, and only one agent approved for its treatment (Table. 1). Catumaxomab is a trifunctional, bispecific monoclonal antibody targeting EpCAM-positive tumor cells and CD3 positive T cells. In addition, the hybrid Fc region binds and activates accessory cells like macrophages, NK cells, and dendritic cells [8–10]. It is thought that catumaxomab simultaneously binds to tumor cells, T lymphocytes, and accessory cells inducing T cell-mediated lysis, phagocytosis, and antibody-dependant cell-mediated cytotoxicity of the tumor cells [11, 12]. The clinical benefits of catumaxomab in patients with recurrent symptomatic MA due to EpCAM-positive tumors include a significant prolonged puncture-free survival, an increased time to next PC, and a delayed deterioration in quality of life (QoL), as compared to PC alone [13, 14]. Common adverse events included cytokine release-related symptoms (fever, nausea) and abdominal pain. We conducted this study with physicians throughout Germany and Austria to get on overview of currently employed approaches and opinions in the treatment of MA.

Methods

One hundred and twenty-eight physicians specialized in medical Oncology, Gastroenterology, and GYN from Germany and Austria were asked randomly to complete an electronic survey regarding their views and management of MA in advanced cancer pts. The participants of the survey were recruited during various oncology congresses in Germany and Austria between March 2011 and June 2013. The questionnaire was constructed by us and consisted of 33 questions. Each respondent was asked to provide demographic information regarding speciality,

Table 1 Treatment of malignant ascites: trials summary

Author	Study design	No. of sub.	Primary tumor	Methods	Duration of effect	Complications
Ross et al. [15] (1989)	Case series	43	Various	109 Paracentesis	4–45 days, mean 10.4 days 87 % symptom relief	2 % fatal hypotension
Gough et al. [19] (1993)	Open Trial	68	Various	Diuretics	Relief of ascites, 58 % <8 weeks 42 % >8 weeks	–
Straus et al. [25] (1979)	Case series	33	Various	Le Veen Shunt	Control of ascites 81 % Shunt patency: 10.6 weeks	Shunt block 4 %, 3 % infection, 3 % pul. emboli
Schumacher [26] et al. (1994)	Case series	89	Various	Denver Shunt	Control of ascites 65 % Shunt patency, 12 weeks	Shunt block 29 %, 6 % infection, 13 % pul. edema
Rosenberg [27] et al. (2006)	Retro-spective	38	GI-cancer	PleurX Catheter	Daily drainage 500 mL Functional 37 days	11 % infection
Parsons [14] et al. (2009)	Phase II/III	258	Ovarian Non-ovarian	Catumaxo-mab	Median puncture-free days 52 vs. 11 ($p<0.001$) Improvement QoL	Cytokine release: fever, vomiting, skin reaction, liver function decrease

care setting, location, and type of practice. The physicians surveyed were questioned about their employed management modalities of MA and asked to rank those modalities they felt most effective. Answers were evaluated with descriptive statistics.

Results

A total of 128 physicians completed the questionnaire. Their demographic data is shown in Table 2. Ninety-two percent (115) of the physicians were from Germany, whereas only 8 % (13 %) practiced medicine in Austria. Of the 128 physicians, 49 % were specialized in medical Oncology, whereas 35 % in GYN and 12 % in Gastroenterology. Eight percent of the physicians had other specialities, however, treated cancer patients with MA. Seventy-five of the study participants worked in a hospital setting, whereas only 25 % were in private practice. Of the 75 % working in a hospital setting, 86 % of the physicians worked in or were associated with a certified cancer centre. Most physicians (50 %) treated between 100 and 500 patients with cancer a year, with breast cancer (24 %), colorectal cancer (23 %), and ovarian cancer (19 %) being the most frequent treated cancer types. Sixty-eight percent of the participants treated a median of 30 (11–50) patients per year with MA. Of these, 26 % were diagnosed with advanced ovarian cancer, 20 % pancreatic cancer, 17 % stomach cancer, and 14 % with colorectal cancer. Only 7 % of patients treated for MA suffered from breast cancer. Most patients with MA (70 %) needed a PC for symptom relief, whereas 30 % of the patients with MA never received a PC. Over 90 % of the physicians associated MA with poor prognosis and significant reduction in quality of life. One third felt MA was a contraindication for full dosing of systemic chemotherapy (Fig. 1). Twenty-nine percent of patients presented with MA at primary diagnosis with a Karnofsky index (KI) of 80 %, whereas almost 50 % of patients presented with MA after second-line chemotherapy with a KI of 50 %. Patients with MA early on in the course of the disease were treated mainly by physicians specialized in GYN, whereas patients presenting with MA after second-line chemotherapy or later typically were treated by medical oncologists and gastroenterologists. This difference is certainly due to the different tumor types (ovarian cancer vs. GI tumors) and biology treated primarily by respective specialities. Seventy-one percent of patients with MA were treated initially with PC, paramount indication being symptom relieved and quality of life. Patients' request was only in 36 % of cases as the reason for PC. One third of the physicians specialized in GYN and Gastroenterology preferred catheter drainage over repeated PC; only very few medical oncologists chose the application of a catheter for their patients.

Table 2 Demographic data of the 128 surveyed physicians

Demographic	No.
Total Physicians	128
Country	
Germany	115
Austria	13
Speciality (%)	
Medical Oncology	62 (48)
GYN	38 (30)
Gastroenterology	18 (14)
Other (Primary physician, palliative care physician)	10 (8)
Practice location (%)	
Hospital	93 (72)
Outpatient clinic	10 (8)
Privat practice	25 (20)
Cooperation with certified cancer center	
Yes	110 (86)
No	18 (14)
Participation in interdisciplinary tumor board (%)	
Yes	112 (87)
No	16 (13)
Number of pts treated per year (%)	
<100	26 (20)
100–500	87 (68)
500–1000	11 (9)
>1000	4 (3)
Tumor types treated with MA (median) (%)	
Pancreatic cancer	14
Breast cancer	7
Ovarian cancer	39
Stomach cancer	14
Colorectal cancer	12
Cancer of unknown origin	11

MA malignant ascites

PC was equally often performed in a hospital setting and in an outpatient setting. Asked how many PC were generally necessary per patient with MA, physicians thought that 48 % of the patients required 3–5 PC and 42 % of patients even 5–10 PC during the course of their disease. Only 15 % of patients needed multiple PC a week, the majority (40 %) needed the procedure once a week or every 14 days. In 61 % of pts, 3–5 L of ascites fluid was drained. Only in 8 %, 5 L and more were removed (Fig. 2a). Volume substitution with

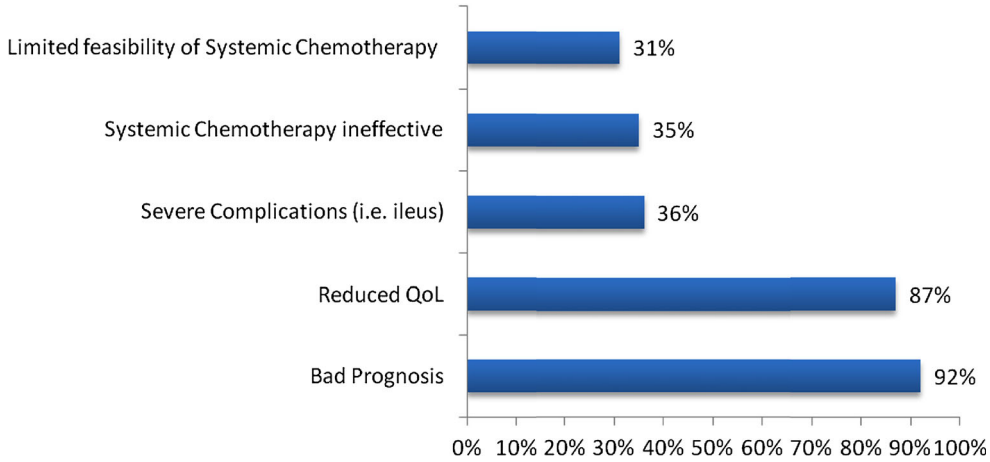

Fig. 1 Physician's associations with the diagnosis malignant ascites

i.v. albumin was performed in 40 % of patients, while 38 % of the patients received volume substitution with 0.9 % NaCl after PC (Fig. 2b). Most patients (55 %) had to stay 1–3 h in a healthcare facility to have PC performed. However, 21 % had to stay ≥1 day. While almost all physicians (88 %) performed a PC at some point in the treatment of MA, 61 % felt that a systemic chemotherapy and 48 % a concomitant diuretic therapy were a necessary adjunct. Ten percent of the medical

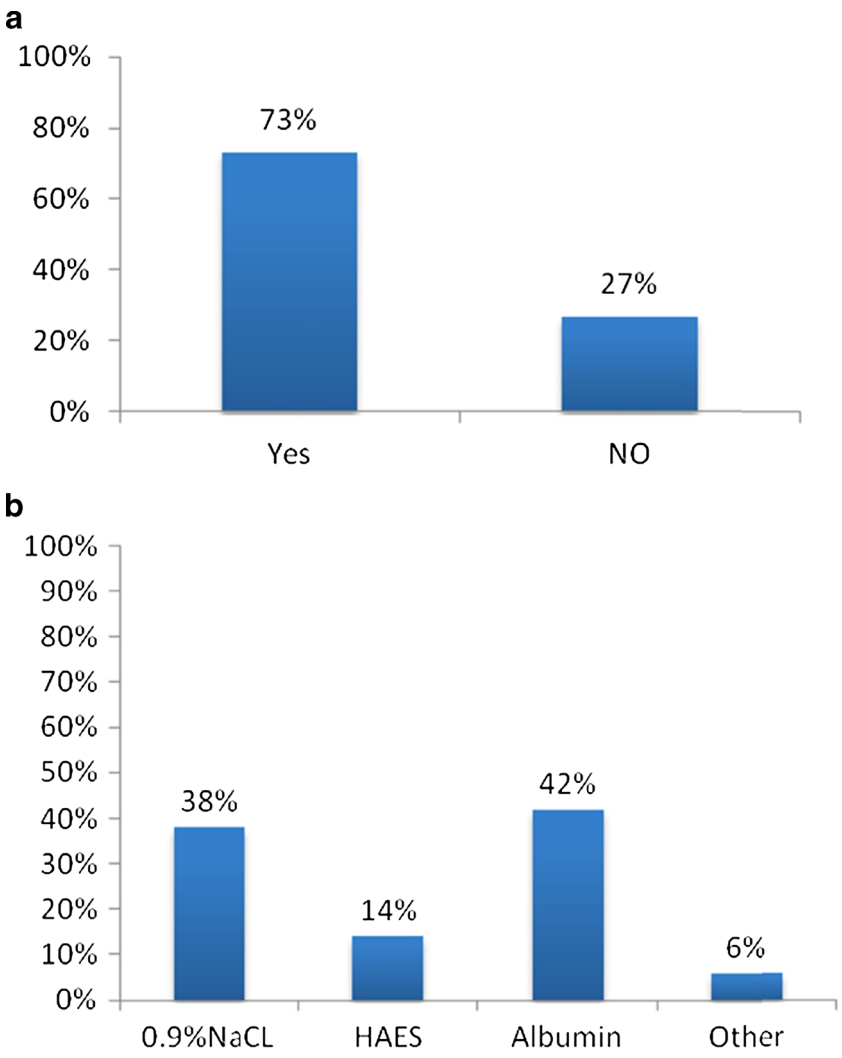

Fig. 2 **a** Volume substitution performed after PC 2. **b** Type of volume substitution preferred

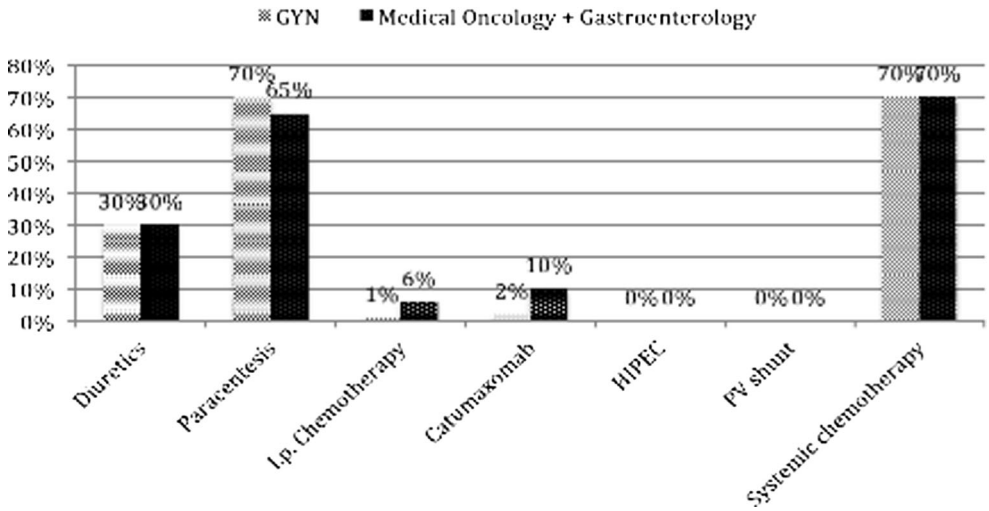

Fig. 3 Physician's preferred treatment modalities for malignant ascites

oncologists administered intraperitoneal catumaxomab in the treatment of MA, whereas only 2 % of the physicians specialized in GYN used this drug. None of the physicians incorporated the application of intraperitoneal cytotoxic chemotherapy, HIEPC, or peritoneal-venous shunting into their treatment algorithms (Fig. 3).

Discussion

Symptomatic malignant ascites is a significant problem in the palliative setting and is associated with reduced quality of life and poor prognosis. There are no generally accepted guidelines for the management of MA, although many physicians believe that with better diagnostic evaluation and multimodality therapy strategies the QoL and perhaps survival can be improved. Our intent was to assess physician's perceptions on preferred treatment modalities of MA.

The participants of the survey were randomly recruited during various oncology congresses in Germany and Austria; this inherent bias might explain the low response rate for gastroenterologists who treat MA. In addition, there was a low attendance by surgical specialist, since the focus of the meetings was medical oncology. The survey size lacked sufficient power to demonstrate any statistical differences in the practice of physicians of different specialties dealing with MA, but some useful observations can be made.

Two distinct groups of cancer patients with MA can be observed. The first group of patients presented early on in disease with MA and was mainly caused by ovarian cancer, where MA develops early in disease and has a better prognosis. The other groups of patients were treated in later stages of their disease for MA and were treated preferentially by medical oncologists and gastroenterologists. The underlying cancer types included stomach cancer, cancer of the GI, pancreas, or breast. The prevalence of MA for the different cancer types coincide with the literature [3, 4]. The immediate effect of PC on symptom relief and QoL made PC the most commonly used modality. This view is supported by body of studies demonstrating fast effects and safety [15, 16]. The initiation of a systemic chemotherapy was the second preferred treatment after therapeutic PC for physicians specialized in GYN and medical oncologists alike. This is different to the US/Canada, where, according to a similar survey, physicians preferred the use of diuretics, even though they were not convinced of its efficacy in MA [17]. There are no prospective studies evaluating the role of diuretics and no general consensus for the use of diuretics in the treatment of MA. The relative inefficacy of diuretics in MA is attributed the different pathophysiologic mechanisms contributing to fluid accumulation [1, 2]. In our survey, the use of diuretics in the treatment of MA still ranked third after PC and systemic chemotherapy. This attitude is perhaps a consequence of physician's frustration and lack of available alternatives. More physicians specialized in GYN and Gastroenterology preferred catheter drainage over repeated PC; this was in contrast to medical oncology. Interestingly, all of the surveyed physicians were reluctant to implement more invasive measures like peritoneovenous shunts. In a more surgical-oriented survey population, this might be different. This perceived discomfort in patients is contradicted by the literature, supporting their effectiveness (>50 % in breast and ovarian cancer) and low complication rate 6 % [18–20]. Shunt block occurs more often in patients with positive cytology, and the shunt tends to function longer in the patient with cytological negative fluid. The median shunt survival in patients with negative cytology was 140 days compared with 26 days in the positive group [21]. This leads

to the hypothesis that a prior intraperitoneal application of chemotherapy could increase the efficacy of such a shunt. However, in our survey, only 6 % of the physicians employed this treatment modality.

Most patients had to undergo 5–10 PC during the course of their disease. The majority of these required PC at least every 7–14 days. Three to five liters of ascites fluid was drained per PC. Almost half of the physicians felt a necessity to substitute i.v. albumin, even though there is no evidence for benefit with the use of albumin infusions for patients with MA as a means of maintaining intravascular volume after large volume PC or reducing relapse fluid accumulation [22], even though the infusion of 0.9 % NaCl after PC seems to comfort the physician more than its evident effectiveness.

Fifty-five percent of the patients had to stay 1–3 h in their healthcare facility due to PC, whereas almost a quarter of the patients stayed at least a day or more using considerable healthcare resources. This is consistent with other countries like the US or Great Britain [23, 24]. The considerable resources of repeated PC and its consequences should be invested in more permanent approaches. The trifunctional antibody catumaxomab has shown promising results in a subset of patients with MA, especially with ovarian cancer. However, the cumbersome application of this drug has left many physicians reluctant to introduce this treatment modality into their repertoire, as reflected in our survey. Novel drugs like, i.e., VEGF inhibitors might improve treatment results when incorporated into multimodal therapy strategies. Further multidisciplinary studies are needed to help palliate this misfortunate situation of these patients and lead to an improved quality of life.

Conflict of interest We declare that there are no conflicts of interest. We have full control of all the primary data. We agree to allow the journal to review the data if requested.

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