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Review

Current and Future Options in the Treatment of Malignant Ascites in Ovarian Cancer

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Abstract. *Background: Malignant ascites is a frequent problem for ovarian carcinoma patients. Typical symptoms such as abdominal pain, nausea and dyspnea reduce quality of life. In this study, different treatment options for malignant ascites due to ovarian carcinoma were sought. Materials and Methods: Articles and reviews found in PubMed and reference books were evaluated and compared to each other. Results: Many treatment options exist. Current treatment options include paracentesis, intraperitoneal chemotherapy and therapy using intraperitoneal tumor necrosis factor alpha for example. Compared to other reviews, catumaxomab, a new antibody, was presented and the treatment options were focused on ovarian carcinoma patients. All these methods are palliative. Conclusion: The treatment of malignant ascites keeps a demanding difficulty and requires further study especially on progressive free survival and overall survival. Paracentesis and systemic therapy with a later effect are recommended at the moment. Catumaxomab is the only medication that could achieve an improvement.*

Ovarian cancer (OC) is a rare tumor type. One to two percent of women will be diagnosed with OC which makes it the seventh most common type of cancer in women (1-3). The incidence rate in Germany is approximately 8,000 per year (3), with mostly women between 70 and 80 years affected (1). Usually OC is not diagnosed in an early stage so that only 30-40% of the patients survive the first five years after their initial diagnosis (3).

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One of the typical symptoms and complications is the occurrence of malignant ascites. Its emergence reduces the patient's quality of life enormously and it is associated with a poor prognosis (4). Malignant ascites is a fluid within the peritoneal cavity consisting of different proteins and tumor cells, mesothelial cells, fibroblasts, macrophages, leucocytes and cell detritus (4), whereby no clear definition of the different parameters and their concentration appears to exist. Ascites results from an imbalance between the production and resorption of plasma exudate in the peritoneal cavity. There are different hypotheses for this imbalance (4): tumor cells, mesothelial cells and vascular endothelia growth factor (VEGF) produce fluid additional to the normal amount. The permeability of microvessels increases due to elevated neoangionesis so that more fluid passes into the peritoneal cavity. Moreover, the ability of the lymphatic circulation to absorb fluid can be disturbed by micrometastases and the lymphatic drain is reduced, *e.g.* when the draining of the ductus lymphaticus is occluded due to metastasis in the diaphragm. Ascites is one of the typical symptoms at the first diagnosis. In fact, whereas 77% of all patients who are initially diagnosed with ovarian cancer experience ascites, only 31% of the women with first relapse of OC suffer from ascites and nearly all patients will develop ascites during tumor progression (4). Malignant ascites occurs in FIGO stages Ic, IIc, and almost regularly in FIGO stages 3 and 4 (2). Typical symptoms of ascites are abdominal swelling, pain, nausea, dyspnea, early satiety, vomiting, constipation and edema (4). These symptoms are often more unbearable than the cancer itself which causes symptoms very late in life such as dysmenorrhea, diffuse pain in the lower abdomen, a reduction of general health and loss of efficiency (3).

Despite radical surgery, with the primary aim of maximal tumor reduction, and subsequent chemotherapy with paclitaxel and carboplatin, many patients will relapse and die from tumor progression. With the diagnosis of the recurrence of ovarian cancer, clinical management is mainly focused on

tumor and symptom control and on maintaining and improving the patient's quality of life. This is why further treatments are required which can directly affect the development of ascites.

In this work, we present the currently available treatment options and discuss new cancer strategies.

Materials and Methods

The present work is an attempt to give an overview of the current treatment options for the treatment of ascites in advanced OC. Therefore, various sources of information and databases were analyzed. General information on this topic was found in books about gynecology (2, 3) and about OC (1, 4). MEDLINE and Cochrane Library were searched for treatment options for malignant ascites due to OC. Furthermore, Google.com was searched for 'ascites therapy' on December the 11th 2008. On 18th of December 2008 PubMed was also searched for 'ascites therapy' and 'ovarian carcinoma'. This was limited to additional keywords of humans, female, meta-analysis, practice guideline, and clinical trials. The same was repeated in the Cochrane Library. After an initial overview of the articles and the systematic reviews found in PubMed, certain treatment options were further sought: On the 8th of February 2009, search items were 'malignant ascites and diuretics', 'malignant ascites and paracentesis', 'malignant ascites and interferon/vascular endothelial growth factor/OK 432/tumor necrosis factor/metalloproteinase inhibitors', and on the 10th of February 2009, 'malignant ascites and intraperitoneal chemotherapy' as well as 'malignant ascites and peritovenous shunts'. Among *in vitro* studies, cases involving only a low number of patients and studies that did not refer to OC were excluded from all investigations found. Reference lists were analyzed in order to find additional relevant studies. Information related to catumaxomab was found in the manufacturer's brochure which includes general information and reports studies available on this antibody for which abstracts could be found in www.asco.org.

Results

Use of Diuretics. Twenty-nine publications were identified in MEDLINE. All studies which did not refer to OC, or to humans or those articles not written in English or German were excluded. In the end, one was chosen. Additionally, one was identified *via* Google and one more was found *via* PubMed with the search items 'malignant ascites and ovarian carcinoma'. Sharma and Walsh (5) recommend diuretics as a first-line therapy. An aldosterone antagonist such as spironolactone with at initial dosage of 100-200 mg daily is suggested. Its combination with a loop diuretic, the most commonly used one being furosemide at an initial dosage of 40-80 mg per day was found to be useful. Patients without peripheral edema should lose 1 kg body weight per day (5). Common risks are hypovolemia, hypotension and renal failure (5, 6). This method is only temporarily effective (5). Increase of the dosage may help as well as a restricted intake of sodium (7). Contraindications are hyponatremia <125 mmol/l, hepato-renal related decrease of sodium excretion to <30 mmol/day, renal insufficiency with serum creatinine >1.5 mg/dl, acute encephalopathy and acute bacterial infection (7). No prospective randomized trials supporting the use of diuretics as first-line therapy for malignant ascites were found. Furthermore, use of diuretics can increase the hematocrit additionally and can potentially induce thromboembolic events.

Paracentesis. In MEDLINE, 95 studies were found. We used the same exclusion criteria as described above. After having applied these criteria, seven articles were chosen. We also utilized the article by Sehouli (4). Paracentesis is the first-line therapy for ascites related to OC (4). It provides symptomatic relief, whereby comfort, physical activity, symptoms of pain and dyspnea are all improved (8). One of the main problems is that the ascites reaccumulates so that most patients require regular paracentesis (8). One should be aware of the risk of hypoproteinemia, hypotension, secondary peritonitis, perforation and pulmonary embolism (6, 9). Becker *et al*. (9) reported that a drainage of 5 l does not affect the plasma volume nor renal function significantly. They evaluated a study where 5% dextrose was infused simultaneously without any episodes of hypotension. However, the amount of the maximum drainage varied among the studies available (6). Blood tests should be run regularly and, if necessary, albumin or electrolytes should be compensated for (4). If huge amounts of ascites are being drained, volume substitution is recommended (4). The catheter should be removed within 1 day after the drainage in order to prevent infection (6); however, this recommendation is not based on any prospective trials.

Permanent drainage for patients with a life expectancy of more than 2-3 months and for patients in need of regular paracentesis can be considered (6). To reduce the risk of peritonitis and sepsis, antibiotics are sometimes used during the first week of treatment (10). Other risks may include catheter occlusion, as was found to occur in 12% of the patients in a study by Courtney *et al*. (11), and hypotension. The use of the pleurx catheter – a common type of catheter – which was kept in a patient for 70 days seemed to reduce the risk of septic complications (12). Researchers testing the pleurx catheter in patients with OC demonstrated similar results (13). In other studies using different catheters, episodes of peritonitis, hypotension and catheter-related sepsis occurred (6). Brooks and Herzog (14) reported a case where a semi-permanent catheter drained 2 l per day for 18 months.

Peritovenous shunts. A total of 84 articles were obtained in PubMed, among many articles related to intestinal cancer which we excluded as well as *in vitro* mouse model studies and articles not written in English or German. Two articles were chosen in the end as well as 2 other relevant articles

found in PubMed with the search items 'malignant ascites and ovarian carcinoma'. A peritovenous shunt is a one-way tube connecting the peritoneum to the vena cava. At a specific pressure, a valve opens and leads the fluid into the vein. Three different forms of shunt exist: those of Hyde, Denver and Le Veen (6).

Faught *et al*. (15) conducted a study to evaluate the safety and effectiveness of these shunts in patients with gynecological cancer; 25 patients were enrolled in this study including 21 with OC. The ascites symptoms improved. The median survival time was 80 days. However, two of the patients died within 10 days after the procedure and the shunt of four patients occluded. Besides the risk of occlusion, other complications were found to occur such as transient fever, coagulopathy, infection and tumor embolization (6). Contraindications are loculated ascites, portal hypertension, coagulation disorders, elevated bilirubin levels, advanced cardiac or renal failure, hemorrhagic ascites or fluid protein >4.5 g/l (8, 9). The problem of disseminating tumor cells inside the body was not able to be proven as clinically significant in patients with heavily pretreated OC relapse (6). Compared to gastrointestinal cancer (10% to 15%), ovarian and breast cancer (≥50%) patients seem to respond better to this procedure (8). The shunt is only indicated for patients who cannot benefit from any other further treatment and whose life expectancy is long enough to profit from it as the insertion of the shunt can be related to fatal side-effects such as pulmonary edema or emboli (9). The median survival ranged in the different studies from 52 to 266 days, reflecting the high heterogeneity of patients (9).

Intraperitoneal chemotherapy. With the search items 'intraperitoneal chemotherapy and malignant ascites', using the same exclusion criteria as above, we found 196 articles. Alongside three articles out of this search, we used publications already cited above. Another palliative attempt to moderate the symptoms of ascites is the application of chemotherapeutics into the peritoneal cavity. The idea is to minimize the systemic adverse effects and to increase the local concentration *via* elevated bioavailability. However, many side-effects have been reported. Walker *et al*. (16) evaluated the catheter-related complications: In 34% of the patients with primary ovarian cancer, the intraperitoneal application of cisplatin and paclitaxel had to be stopped because of catheter-related complications such as infections, blockage or leaks, and abdominal pain. Other limiting factors were described by Markman *et al*. (17): because of loculated ascites the therapeutic agent(s) cannot spread within the whole peritoneal cavity, there are only single and short-term effects when infiltrating a maximum of 5 mm into a great tumor burden and side-effects such as adhesions, abdominal pain, ileus, peritonitis, abcess, necrosis and intestinal perforation can occur. A review evaluated 257 installations with mitoxantrone (30 mg) and assessed it as being effective and well-tolerated for patients with gynecological cancer (18). Nevertheless, intravenous mitoxantrone has not been evaluated in randomized trials and is generally not accepted as a treatment of choice for patients with first or second recurrence of OC.

Mitoxantrone (30 mg) and cisplatin (80-100 mg) are diluted in 500-1000 ml of a carrier solution (saline) and then installed inside the peritoneal cavity for 24-48 hours (4). In various phase I/II trials, other cytotoxic drugs such as topotecan or taxanes are currently being investigated. These approaches are still experimental and are not yet recommended for routine clinical use.

There are at present attempts to try and increase the cytotoxicity of cisplatin and paclitaxel for example by a hyperthermic medium (40.5-43˚C) (6). This procedure is called intraperitoneal hyperthermic chemotherapy (HIPEC). The primary objective here is an increase of progression-free survival and overall survival, not the control of ascites itself.

Intraperitoneal tumor necrosis factor (TNF). Altogether 37 studies, mainly small, explorative trials, were found in PubMed. Intraperitoneal human recombinant tumor necrosis factor (TNF) α was commonly used for the therapy of malignant ascites. TNF at 0.08-0.014 mg/m^2 diluted in 5% human albumin is installed inside the abdomen for 24-48 hours. This procedure is repeated on day 8. Patients often suffer from flu-like symptoms which can be reduced by taking indomethacin or paracetamol before the infusion (4). In a study of Kaufmann *et al*. (19), in 87% of the patients with OC the production of ascites was suppressed or reduced to a minimum for at least four weeks after three doses of TNF. Malignant ascites due to mucinous OC does not seem to be affected by TNF (19). This study emphasizes the effectiveness of this palliative method. Other studies arrived at the same conclusion (6).

Interferons. Twenty-nine articles were found in MEDLINE, all those not referring to OC and all *in vitro* or mouse model studies, as well as studies in languages other than English or German were excluded. Three articles were thus included in this review. Intraperitoneal interferon α (IFN) 2b was evaluated in a study by Sartori *et al*. (20): 12 out of 41 patients had OC. Six courses with an interval of 4 days with 6 or 9 million units (depending on the body weight) of IFNα 2b were inserted with a 9-French catheter. Complete response, ie no fluid recurrence within 30 days after the treatment, occurred in 29.3%, a partial response in 36.6% and no response in 34.1%. Ovarian cancer patients had the highest global response (65%). The fluid reaccumulated after 11.4±4.4 days before and 70.5±75.3 days after the treatment on average. It was well-tolerated and side-effects were flu-like symptoms and vomiting, 2

patients had an infection with staphylococcus. The study reviewed success rates ranging from 40 to 70% . This group recommends the use of IFNα 2b for patients with OC as palliation. If there is no response after the first 3 courses, the treatment should be stopped.

Intraperitoneal IFNβ showed a 40% response rate in a study with 23 patients. The side-effects were mild; 3 patients suffered from transient pain (21).

Intraperitoneal IFNγ was able to stabilize ascites and intra-abdominal tumors (22). However, not enough cases were described to evaluate this treatment.

Vascular endothelial growth factor. Sixty studies were found in MEDLINE. We used 3 of these articles alongside one already cited above. Vascular endothelial growth factor (VEGF) increases vascular permeability and therefore supports ascites production (6). It was proven in a mouse model that anti-VEGF-antibodies reduced the amount of ascites, suppressing its formation and re-accumulation (23, 24). Biweekly bevacizumab, an anti-VEGF antibody, with weekly taxane has been successfully applied in humans (25). Ascites and other cancer-related symptoms were minimized significantly.

Immunmodulators. We found 46 publications in PubMed. One article was finally chosen as well as a publication already cited above. The first immunmodulator was OK-432. It is a lyophilized powder of *Streptococcus pyogenes* (6). Katano and Morisaki (26) treated 400 patients, mainly with gastrointestinal-related cancer, with OK-432 with a response rate of 60% . They concluded that this treatment might become useful after further research. Studies restricted to OC could not be found in the present search.

Metalloprotease inhibitors. A total of 16 studies were found in MEDLINE, where we again used the same exclusion criteria described above. We cite only one for this short summary as this method is not relevant for OC. Batimastat and marimastat are zinc-dependent enzymes. They play a role in angiogenesis, tumor invasion and metastasis (6). There are not many cases reported and its use in the treatment of malignant ascites due to OC has not been evaluated sufficiently.

Catumaxomab. Twelve articles were chosen out of the manufacturer's brochure and www.asco.org. Catumaxomab is an intact trifunctional antibody with two different antigen-binding sites and an additional functional binding site in its specifically combined Fc region. One binding site consists of a rat Fab fragment which binds human CD3 of T-lymphocytes. The other Fab-binding site (from a mouse) targets the human epithelial cell adhesion molecule (Ep-CAM), which is overexpressed on most epithelial carcinomas such as OC. Ep-CAM is not expressed on cells of the peritoneum. Therefore the expression of Ep-CAM in patients with malignant ascites due to carcinomas is tumor specific within the peritoneal cavity and catumaxomab is infused intraperitoneally. The hybrid Fc region activates positive accessory cells such as macrophages, natural killer cells and dendritic cells *via* binding of the Fcgamma-receptor 1 and 3.

Freeman *et al*. (27) and Kubicka *et al*. (28) reported that all important cells needed for the antitumor activity are found within the peritoneal cavity. Zeidler *et al*. (29-31) demonstrated that by assembling and activating T-cells as well as accessory cells, catumaxomab leads to a secretion of cytokines interleukin (IL)-1β, IL-2, IL-6, IL-12 and dendritic cell specific cytokine 1 within 24 hours. Activation markers on dendritic cells and natural killer cells are up-regulated. The activation of Fcγ-R-1 results in a direct phagocytosis of tumor cells (30). Riesenberg *et al*. (32) noticed that Ep-CAM-positive tumor cells were lysed due to osmosis. Tumor cells became necrotic and died. It was proven that lymphocytes targeted tumor cells to kill them *via* perforin, a protein which forms a pore, with consequent lysis. According to Schmitt *et al*. (33), CD4/CD8 positive T-cells excrete granzyme B, in a manner dependent on the presence of Ep-CAM-positive tumor cells, and this results in the lysis of Ep-CAM-positive cells, and release of IFNγ. These molecular effects result in the following clinical outcome; the results are only focused on the intraperitoneal administration in the indications ovarian cancer, gastric cancer and malignant ascites. In a prospective randomized study by Parsons *et al*. (34), the median puncture-free survival was 46 days *versus* 11 days in the control group ($p<0.0001$) in patients with malignant ascites due to Ep-CAM-positive epithelial tumors including ovarian and non ovarian cancer. The median time for the first need of therapeutic ascites puncture was 77 days compared to 13 days (control) being significantly longer in the catumaxomab group ($p<0.0001$). The tumor cell load in the ascites fluid decreased as well as did the ascites signs such as shifting dullness, fluid thrill and abdominal distension dull to percussion. Typical symptoms such as nausea, abdominal pain, early satiety and others also lessened, findings which definitely all increased the patients' quality of life.

Additional study data of catumaxomab in different settings to identify optimal dosage of catumaxomab are available: *e.g.* the study of the German AGO by Belau *et al*. (35) evaluated the efficacy of a low dose constant (LD) (10-10-10-10 μg) *versus* a high dose escalating (HD) (10-20-50-100 μg) treatment in platinum refractory ovarian cancer patients. The HD arm was associated with higher antitumor activity without compromising the safety profile when compared to the LD treatment group, with 1 PR and 5 stable diseases in the HD

compared to 2 stable diseases in the LD arm. After a median follow-up of 4.96 months, the median overall survival time was 182 days for the HD and 114 days for the LD-arm. Ströhlein *et al*. (36) conducted a study to identify the maximum treatment dose (MTD) in patients with peritoneal carcinomatosis due to gastrointestinal tumors. Two patients experienced dose-limiting toxicity (DLTs) such as systemic inflammatory response syndrome of common toxity criteria (CTC) grade 3, dehydration, exfoliative dermatitis, pyrexia and tachycardia in the group where 100 μg were applied at the 3rd dose. All of these events resolved without sequelae. In this setting an intraperitoneal application of 10, 20, 50 and 200 μg with premedication of 1,000 mg paracetamol was established. Concerning side-effects, no difference was found between infusions over 6 hours compared to 3-hour infusions in this setting.

Currently, Sehouli and co-authors have completed the enrollment of a multicenter first-line study in patients with OC in which catumaxomab was given immediately after radical surgery with the first dose (10 μg) intraoperatively followed by four additional applications on days 5, 7, 10 and 11 in a cohort of 42 patients (Study number IP-CAT-OC-02). Final results of an US consolidation study with catumaxomab after first-line therapy in ovarian cancer patients are pending.

Based on the pivotal study data (36), 4 intraperitoneal infusions of catumaxomab with 10, 20, 50 and 150 μg is the first in Europe approved as treatment for malignant ascites due to Ep-CAM-positive epithelial tumors where standard therapy is not available or no longer feasible. Fresenius Biotech, the company which initiated the clinical research of this monoclonal antibody, warns of common side-effects such as fever, chills, nausea and vomiting, during and after the antibody infusion. Burges *et al*. (37) suspects that these adverse effects are attributed to a systemic treatment-associated cytokine release as a consequence of the complex immunoreactions against tumor cells caused by catumaxomab. To moderate these adverse effects, it is recommended that 1,000 mg paracetamol are taken before the infusion. Prior to treatment the patient should have a BMI >17, a Karnofsky Index >60 and should not be suffering from an acute infection. To assure stable circulatory and renal functions, there should be a minimum ascites drainage until relief of symptoms and if necessary a supportive replacement therapy including crystalloids and/or colloids.

An international prospective multicenter study for patients with malignant ascites due to advanced epithelial cancer is also currently ongoing to further optimize the treatment with catumaxomab. In this trial patients will be randomized to receive steroids or not to receive any within the premedication. Moreover, an infusion period of 3 hours is investigated with an optional ambulant setting for the 3rd and 4th infusion.

Discussion

The treatment of malignant ascites due to OC is a challenging problem in the clinical setting. Ovarian carcinoma patients who generally have a very limited life span often suffer from the symptoms of ascites and their quality of life is reduced enormously. Many different treatment options exist but one that reduces and inhibits the production of ascites completely has not yet been found. The first-line treatment, paracentesis, has only a temporary effect and has to be repeated regularly. Diuretics seem to help only a little and after a relatively short amount of time dosage cannot be increased restricting its further effectiveness. The insertion of a peritovenous shunt is carried out under a general anesthetic which might be too risky for OC patients although these patients benefitted more from it than did other carcinoma patients (9). The procedure can only be conducted when the patient is going to benefit and has a certain life span and all other non-invasive treatment options have failed. Another problem for OC patients is the appearance of loculated ascites due to multiple adhesions induced by radical surgery, which is a contraindication as described above. Systematic data concerning efficacy of intraperitoneal chemotherapy in patients with malignant ascites is very limited. Newer treatments such as VEGF antibodies seem promising but are still only experimental. The new trifunctional antibody catumaxomab, which is the first European approved drug for the treatment of malignant ascites due to epithelian cancer, could become one of the most successful ways to treat malignant ascites due to OC in the future. Another potential impact of this antibody is its activity against the tumor cells themselves. The potential effect on progression-free survival and overall survival with and without systemic chemotherapy using this drug should be investigated in further prospective studies.

Further trials of targeting the malignant ascites should focus much more stringently on quality of life issues, such as tolerability and ascites-related symptom relief. Additionally, cost analyses should be integrated into the risk-benefit analyses.

This review differs from others as it is based on treatments of malignant ascites including OC. We have attempted to find all possible treatment methods available. Other studies of this kind often did not review everything obtainable and were mostly based on cases of gastrointestinal cancer.

To conclude, malignant ascites remains a common problem for OC patients. If malignant ascites becomes the most relevant symptom, the primary aim in this palliative situation is the improvement of the patient's quality of life. At the moment, there is generally only acute paracentesis or systemic chemotherapy, which can have a later effect, that can be reasonably applied in OC patients. Catumaxomab is so far the only medication that could achieve an improvement

within the framework of a prospective study with European approval for malignant ascites due to epithelial cancer. Further prospective studies are absolutely necessary in order to investigate the influence on ascites-triggered intervention on both progression-free and overall survival.

References

1 Sehouli J: Epidemiologie. *In*: Multimodales Management des Ovarialkarzinoms. Sehouli J and Lichtenegger W (eds.). Bremen, UNI-MED, pp. 14-19, 2006.

2 Maaßen V and Pietschmann D: Ovarialtumoren. *In*: Gynäkologie und Geburtshilfe. Stauber M, Weyerstahl T (eds.). Stuttgart, Georg Thieme Verlag KG, pp. 279-309, 2006.

3 Haag P and Müller M: Ovarialkarzinom. *In*: Gynäkologie und Urologie. Haag P, Hanhart N and Müller M (eds.). Breisach, Medizinische Verlags- und Informationsdienste, pp. 79-81, 2006.

4 Sehouli J: Symptomorientierte Therapien: Aszites. *In*: Multimodales Management des Ovarialkarzinoms. Sehouli J and Lichtenegger W (eds.). Bremen: UNI-MED, pp. 129-134, 2006.

5 Sharma S and Walsh D: Management of symptomatic malignant ascites with diuretics: Two case reports and a review of the literature. J Pain Symptom Manage *10*: 237-242, 1995.

6 Chung M and Kozuch P: Treatment of malignant ascites. Curr Treat Options Oncol *9*: 215-233, 2008.

7 Wiest R and Schölmerich J: Diagnostik und Therapie des Aszites. Deutsches Ärzteblatt Heft *28-29*: A1972-1981, 2006.

8 Adam R and Adam Y: Malignant ascites: past, present and future. J Am Coll Sur *198(6)*: 999-1011, 2004.

9 Becker G, Galandi D and Blum H: Malignant ascites: Systematic review and guideline for treatment. Eur J Cancer *42*: 589-597, 2006.

10 Belfort MA, Stevens PJ, DeHaek K, Soeters R and Krige JE: A new approach to the management of malignant ascites; a permanently implanted abdominal drain. Eur J Surg Oncol *16(1)*: 47-53, 1990.

11 Courtney AL, Nemcek AA and Rosenberg SM: Efficacy and safety of the pleurx catheter when used to treat recurrent malignant ascites (abstract). J Vasc Interv Radiol *17(2)*: S25, 2006.

12 Richard HM 3rd, Coldwell DM, Boyd-Kranis RL, Murthy R and Van Echo DA: Pleurx tunneled catheter in the management of malignant ascites. J Vasc Interv Radiol *12(3)*: 373-375, 2001.

13 Iyengar TD and Herzog TJ: Management of symptomatic ascites in recurrent ovarian cancer patients using an intra-abdominal semi-permanent catheter. Am J Hosp Palliat Care *19(1)*: 35-8, 2002.

14 Brooks RA and Herzog TJ: Long-term semi-permanent catheter use for the palliation of malignant ascites. Gynecol Oncol *101(2)*: 360-362, 2006.

15 Faught W, Kirkpatrick JR, Krepart GV, Heywood MS and Lotocki RJ: Peritoneovenous shunt for palliation of gynecologic malignant ascites. J Am Coll Surg *180(4)*: 472-474, 1995.

16 Walker JL, Armstrong DK, Huang HQ, Fowler J, Webster K, Burger RA and Clarke-Pearson D: Intraperitoneal catheter outcomes in a phase 3 trial of intravenous *versus* intraperitoneal chemotherapy in an optimal stage 3 ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol *100*: 27-32, 2006.

17 Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, Wadler S and Sickel J: Phase 3 trial of standard-dose intravenous cisplatin plus paclitaxel *versus* moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage 3 ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol *19(4)*: 1001-1007, 2001.

18 Link KH, Roitman M, Holtappels M, Runnebaum I, Urbanzyk H, Leder G and Staib L: Intraperitoneal chemotherapy with mitoxantrone in malignant ascites. Surg Oncol Clin N Am *12(3)*: 865-872, 2003.

19 Kaufmann M, Schmid H, Raeth U, Grischke EM, Kempeni J, Schlick E and Bastert G: Therapy of ascites with tumor necrosis factor in ovarian cancer. Geburtshilfe Frauenheilkd *50(9)*: 678-682, 1990.

20 Sartori S, Nielsen I, Tassinari D, Trevisani L, Abbasciano V and Malacarne P: Evaluation of a standardized protocol of intracavitary recombinant interferon α-2b in the palliative treatment of malignant peritoneal effusions. A prospective pilot study. Oncology *61(3)*: 192-196, 2001.

21 Gebbia V, Russo A, Gebbia N, Valenza R, Testa A, Palmeri S and Rausa L: Intracavitary beta-interferon for the management of pleural and/or abdominal effusions in patients with advanced cancer refractory to chemotherapy. In Vivo *5(6)*: 579-581, 1991.

22 Freedman RS, Kudelka AP, Kavanagh JJ, Verschraegen C, Edwards CL, Nash M, Levy L, Atkinson EN, Zhang HZ, Melichar B, Patenia R, Templin S, Scott W and Platsoucas CD: Clinical and biological effects of intraperitoneal injections of recombinant interferon-gamma and recombinant interleukin 2 with or without tumor-infiltrating lymphocytes in patients with ovarian or peritoneal carcinoma. Clin Cancer Res *6(6)*: 2268-2278, 2000.

23 Yukita A, Asano M, Okamoto T, Mizutani S and Suzuki H: Suppression of ascites formation and re-accumulation associated with human ovarian cancer by an anti-VPF monoclonal antibody *in vivo*. Anticancer Res *20(1A)*: 155-160, 2000.

24 Xu L, Yoneda J, Herrera C, Wood J, Killion JJ and Fidler IJ: Inhibition of malignant ascites and growth of human ovarian carcinoma by oral administration of a potent inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. Int J Oncol *16(3)*: 445-454, 2000.

25 Cohn DE, Valmadre S, Resnick KE, Eaton LA, Copeland LJ and Fowler JM: Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer. Gynecol Oncol *102(2)*: 131-133, 2006.

26 Katano M and Morisaki T: The past, the present and future of the OK-432 therapy for patients with malignant effusions. Anticancer Res *18(5D)*: 3917-3925, 1998.

27 Freedman RS, Deavers M, Liu J and Wang E: Peritoneal inflammation – a microenvironment for epithelial ovarian cancer (EOC). J Transl Med *2*: 23-33, 2004.

28 Kubicka U, Olszeweski WL, Tarnowski W, Bielecki K, Ziolkowska A and Wierzbicki Z: Normal human immune peritoneal cells: subpopulations and functional characteristics. Scand J Immunol *44*: 157-163, 1996.

29 Zeidler R, Mayer A, Gires O, Schmitt B, Mack B, Lindhofer H, Wollenberg B and Walz A: TNF α contributes to the anti-tumor activity of a bispecific, trifunctional antibody. Anticancer Res *21(5)*: 3499-3503, 2001.

30 Zeidler R, Mysliwietz J, Csanady M, Walz A, Ziegler I, Schmitt B, Wollenberg B and Lindhofer H: The Fc-region of a new class of intact bi-specific antibody mediates activation of accessory cells and NK cells and induces direct phagocytosis of tumor cells. Br J Cancer *83(2)*: 261-266, 2000.

31 Zeidler R, Reisbach G, Wollenberg B, Lang S, Chaubal S, Schmitt B and Lindhofer H: Simultaneous activation of T-cells and accessory cells by a new class of intact bi-specific antibody results in efficient tumor cell killing. J Immunol *163(3)*: 1246-1252, 1999.

32 Riesenberg R, Buchner A, Pohla H and Lindhofer H: Lysis of prostate cells by trifunctional bi-specific antibodies (α EpCAM x α CD3). J Histochem Cytochem *49(7)*: 911-917, 2001.

33 Schmitt M, Schmitt A, Reinhardt P, Thess B, Manfras B, Lindhofer H, Riechelmann H, Wiesneth M and Gronau S: Opsonization with a trifunctional bispecific (αCD3 x αEpCAM) antibody results in efficient lysis *in vitro* and *in vivo* of EpCAM-positive tumor cells by cytotoxic T lymphocytes. Int J Oncol *25(4)*: 841-848, 2004.

34 Parsons S, Murawa PX, Koralewski P,Kutarska E, Kolesnik OO, Stroehlein MA, Lahr A, Jaeger M and Heiss MM: Intraperitoneal treatment of malignant ascites due to epithelial tumors with catumaxomab: A phase II/III study. J Clin Oncol 26 (May 20 suppl; abstr 3000), 2008.

35 Belau A, Pfisterer J, Wimberger P, Kurzeder C, Du Bois A, Sehouli J, Loibl S, Burchardi N, Vergote I and Wagner U: Randomized, multicenter, two-dose level, open-label, phase IIa study with the intraperitoneally infused trifunctional bispecific antibody catumaxomab (anti-EpCAM × anti-CD3) to select the better dose level in platinum refractory epithelial ovarian cancer patients. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 5556, 2007.

36 Stroehlein MA, Lordick F, Ruettinger D, Gruetzner U, Menzel H, Bartelheim K, Jaeger M, Lindhofer H, Jauch K, Peschel C and Heiss MM: Treatment of peritoneal carcinomatosis due to GI-tract cancer by intraperitoneal application of the trifunctional antibody catumaxomab (anti-EpcAM x anti-CD3): results of a phase I/II trial. J Clin Oncol, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement): 2529, 2005.

37 Burges A, Wimberger P, Kümper C, Gorbounova V, Sommer H, Schmalfeldt B, Pfisterer J, Lichinitser M, Makhson A, Moiseyenko V, Lahr A, Schulze E, Jäger M, Ströhlein MA, Heiss MM, Gottwald T, Lindhofer H and Kimming R: Effective relief of malignant ascites in patients with advanced ovarian cancer by a trifunctional anti-EpCAM x anti-CD3 antibody: A phase 1/2 study. Clin Cancer Res *13(13)*: 3899-3905, 2007.

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