Purpose

Malignant ascites represents a severe clinical problem for physicians and patients being confronted with this common symptom of advanced-stage gastrointestinal cancer. Unfortunately, there is no standardized and evidence-based treatment for malignant ascites and therapies which are commonly being used are only temporarily effective. Newer modes of therapy, such as the application of the tri-functional antibody catumaxomab, are associated with significant side effects and are limited to patients in stages of good overall performance. Therefore, there is still an urgent need for more effective, longer-lasting, and less toxic modes of treatment for peritoneal effusions caused by gastrointestinal cancers.

Preclinical data strongly suggest that bevacizumab might be a very effective agent for the treatment of malignant ascites, which is in large part caused by the hyperpermeability-promoting factor VEGF. Emerging clinical results from cancer patients with malignant ascites treated with bevacizumab add further support to this idea. Bevacizumab has been tested in a variety of large clinical trials, has a good toxicity profile, and is effective in a number of human cancers underlying malignant ascites.

In the present study, Bevacizumab will be administered as an intraperitoneal infusion at an absolute standardized dosage of 400 mg. This dosage was chosen because it is comparable to the approved standard dosage for intravenous administration which was also used in both studies reporting the successful and safe intraperitoneal administration of Bevacizumab to patients with malignant ascites. Finally, a standardized dosage seems more practical in the particular patient population treated in this study.
Further study details as provided by AIO-Studien-gGmbH:

Primary Outcome Measures:

- paracentesis-free survival (ParFS) [ Time Frame: one year ]  
  [ Designated as safety issue: No ]

  The first primary endpoint will consist of paracentesis-free survival (ParFS) which will be calculated as the time period between the initial puncture after randomization to the first subsequent paracentesis or other symptomatic treatments for ascites with the exception of diuretics or until death (whichever occurs first)

Secondary Outcome Measures:

- Best Response (BR) [ Time Frame: 12 weeks from 1st application ]  
  [ Designated as safety issue: No ]

  Best Response representing the longest period of time from one paracentesis until next paracentesis within the treatment period or, if longer, from the last paracentesis performed within the treatment period until first subsequent symptomatic treatment for ascites with the exception of diuretics (before end of the standard 4 week follow-up) or, if longer, from the last paracentesis performed within the treatment period until death (before end of the standard 4 week follow-up) or, if longer, from the last paracentesis performed within the treatment period until 4 week follow-up

- Volume of ascites [ Time Frame: 12 weeks ]  
  [ Designated as safety issue: No ]

  Volume of ascites drained by routine paracentesis (ascites volume minus lavage volumes, if applicable)

- Quality of life [ Time Frame: 12 weeks ]  
  [ Designated as safety issue: No ]

  Quality of life as assessed by standardized questionnaires

- Changes in ECOG performance status [ Time Frame: baseline and 12 weeks ]  
  [ Designated as safety issue: Yes ]

  Calculation: 12 weeks minus baseline

- Pharmacokinetics of Bevacizumab and VEGF concentrations [ Time Frame: 12 weeks ]  
  [ Designated as safety issue: No ]

- Proportions of patients with adverse events grades 3, 4, or 5. [ Time Frame: 12 weeks ]  
  [ Designated as safety issue: Yes ]

- Proportions of patients with adverse events of special interest [ Time Frame: 12 weeks ]  
  [ Designated as safety issue: Yes ]

  any grade of gastrointestinal perforation, gastrointestinal fistulas or
other internal fistulas, wound-healing disturbances, hemorrhagic events and arterial thrombo-embolic events.

- All adverse events [ Time Frame: 12 weeks ]
  [ Designated as safety issue: Yes ]
- Changes in laboratory values and vital signs. [ Time Frame: baseline, every two weeks up to week 12 ] [ Designated as safety issue: Yes ]

  Calculation: Value from later timepoints minus baseline value

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**Eligibility**

**Inclusion Criteria:**

1. Age >= 18 years
2. Written informed consent has been obtained prior to inclusion into the study
3. Patient is capable and willing to comply with the study
4. Histologically confirmed esophageal, gastric, pancreatic, cholangiocellular, hepatocellular, or colorectal carcinoma
5. Cytologically confirmed ascites OR diagnosis of an exudate (total protein in ascites > 30 g/l) clinically suggestive for malignant ascites OR morphological diagnosis of peritoneal carcinosis by CT, MRT or ultrasound
6. Ascites clinically judged as not responsive to conventional systemic therapies for primary malignancy
7. Ascites clinically judged as not responsive to diuretics

**Exclusion Criteria:**

-**Ages Eligible for Study:** 18 Years and older
-**Genders Eligible for Study:** Both
-**Accepts Healthy Volunteers:** No

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**Arms**

<table>
<thead>
<tr>
<th>Experimental: Arm A Bevacizumab</th>
<th>Assigned Interventions</th>
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<tbody>
<tr>
<td>48 patients randomized into arm A will receive repeated intra-peritoneal application of Bevacizumab</td>
<td>Drug: Bevacizumab Patients will receive paracentesis as needed for symptom control. In addition, patients will receive up to 4 intraperitoneal administrations of 400 mg Bevacizumab after paracentesis has been performed. During the 8-week treatment period, a minimum interval of 14 days will be kept between applications of the study medication. Other Name: Avastin</td>
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<tr>
<th>Placebo Comparator: Arm B Placebo</th>
<th>Assigned Interventions</th>
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<tbody>
<tr>
<td>26 patients randomized into arm B will receive repeated intra-peritoneal application of Placebo</td>
<td>Other: Placebo Patients will receive paracentesis as needed for symptom control. In addition, patients will receive up to 4 intraperitoneal administrations of Placebo after paracentesis has been performed. During the 8-week treatment period, a minimum interval of 14 days will be kept between applications of the study medication.</td>
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**Estimated Enrollment:** 72

**Study Start Date:** February 2010

**Estimated Primary Completion Date:** October 2013 (Final data collection date for primary outcome measure)
8. At the time of inclusion paracentesis required at least twice within past 4 weeks.
9. Before inclusion of the patient into the study, a 4-week screening period will allow for a stringent evaluation of the patient regarding fulfillment of inclusion and exclusion criteria. Importantly, no treatments for malignant ascites other than paracentesis and diuretics are allowed during the 4-week screening period.

10. ECOG performance score 0-3
11. Life expectancy > 12 weeks
12. Laboratory parameters:

   Hematology
   - Neutrophils > 1,500/µl
   - Platelets > 100,000/µl
   - Hemoglobin >= 9 g/dl or 5.59 mmol/l

   Hemastasiology
   - INR <= 1.5 x ULN and aPTT <= 1.5 x ULN within past 7 days

   Clinical chemistry
   - Creatinine clearance > 30 ml/min, serum creatinine < 2.5 x ULN
   - Serum bilirubin < 3.0 x ULN
   - Alkaline phosphatase and transaminases < 3.0 x ULN (in case of liver metastases < 7 x ULN)

   Urinalysis:
   - Patients with < 2+ proteinuria on dipstick urinalysis.
   - Patients with >= 2+ proteinuria on dipstick urinalysis, who demonstrate < 2.0 g of protein/24 h on 24-h urine collection

Exclusion Criteria:
1. Concomitant malignancies other than gastrointestinal cancers (Patients with curatively treated basal and squamous cell carcinoma of the skin and/or in-situ carcinoma of the cervix are eligible).
2. Bacterial peritonitis as indicated by laboratory results (neutrophil count > 250/µl ascites) or clinical suspicion
3. Hemorrhagic ascites (ascites hematocrit > 2%)
4. Transudative ascites (total protein in ascites < 30 g/l)
5. Parallel treatment with anti-tumor agents other than the study medication from inclusion into the study until safety follow-up. Chemotherapy may be continued if started before screening phase (~4 weeks before inclusion). Parallel Treatment with Bevacizumab i.v. is not allowed.
6. Therapy naïve patients
7. Parallel treatment of ascites with measures other than paracentesis, diuretics, and the study drugs from 4 weeks before inclusion into the study until safety follow-up.
8. Patients with extensive metastases of the liver making up > 70% of the total liver mass
9. Child C cirrhosis of the liver
10. Occlusion or thrombosis of the portal vein.
11. Evidence of current and symptomatic central nervous system (CNS) metastases or spinal cord compression.
12. Clinically significant cardiovascular diseases, e.g., uncontrolled hypertension, uncontrolled arrhythmia, hemoptoe, cardiovascular accident within the last 6 months before treatment start, unstable angina, congestive heart failure (CHF) NYHA grade III/IV, symptomatic coronary heart disease, peripheral arterial disease stage II.
13. History of fistula formation involving an internal organ (e.g. tracheo-oesophageal, bronchopleural, biliary, vagina and bladder)
14. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study.
15. Concomitant treatment with intravenous Bevacizumab for primary malignancy

http://clinicaltrials.gov/ct2/show/NCT01200121?term=AIO-SUP-0108&rank=1
from inclusion into study until safety follow-up. Prior treatment with Bevacizumab for primary malignancy is not exclusionary.

16. Serious non-healing wound, ulcer or bone fracture.
17. Radiotherapy for purposes other than local control of symptoms.
18. Evidence of bleeding diathesis or coagulopathy.
20. Known intra-abdominal inflammatory process or serious gastrointestinal ulceration.
21. History of chronic intestinal diseases associated with severe diarrhea.
22. Thrombo-embolic events or severe hemorrhage (<= 6 months before treatment start).
23. Known hypersensitivity to the test drug Bevacizumab.
24. Evidence of any other disease, metabolic dysfunction, physical examination finding, or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
25. With the only exception of full dose (INR > 1.5) oral coumarin-derived anticoagulants, the use of full dose anticoagulants is allowed as long as the INR or a PTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for at least two weeks at the time of randomisation.
26. Patients who participated within the last 30 days prior to enrolment in a clinical trial and received a non approved investigational drug (e.g. follow up within the trial is not exclusionary).
27. Patients who have participated in this study before.
28. Women, lactating, pregnant or of childbearing potential and fertile men not using a highly effective contraceptive method. [Women of childbearing potential must have a negative pregnancy test (serum ß HCG) within 7 days before the first dose of study drug].
29. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities (according to § 40 (1) 4 AMG).
30. Patients who are underage or patients who are incapable to understand the aim, importance and consequences of the study and to give legal informed consent (according to § 40 (4) and § 41 (2) and (3) AMG).
31. Patients with a history of a psychological illness or condition such as to interfere with the patient's ability to understand the requirements of the study.
32. Patients who possibly are dependent on the sponsor or investigator.

▶ Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01200121

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More Information
Additional Information:
Related Info
No publications provided
Bevacizumab as a Palliative Treatment for Patients With Symptomatic Malignant Ascites due to advanced-stage gastrointestinal cancers

Keywords provided by AIO-Studien-gGmbH:
Symptomatic malignant ascites due to advanced-stage gastrointestinal cancers

Additional relevant MeSH terms:
- Ascites
- Gastrointestinal Neoplasms
- Pathologic Processes
- Digestive System Neoplasms
- Neoplasms by Site
- Neoplasms
- Digestive System Diseases
- Gastrointestinal Diseases
- Bevacizumab
- Angiogenesis Inhibitors
- Angiogenesis Modulating Agents
- Growth Substances
- Physiological Effects of Drugs
- Pharmacologic Actions
- Growth Inhibitors
- Antineoplastic Agents
- Therapeutic Uses

ClinicalTrials.gov processed this record on July 19, 2012