Phase I study of intraperitoneal bevacizumab for treating refractory malignant ascites

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Abstract

Objective: This prospective, dose-escalation phase I study evaluated the safety and efficacy of intraperitoneal bevacizumab in managing refractory malignant ascites and explored the recommended dose of bevacizumab for further study.

Methods: Patients with refractory malignant ascites were enrolled. Bevacizumab was intraperitoneal administered weekly at an initial dose of 2.5 mg/kg, with dose escalation to 5 and 7.5 mg/kg performed following the standard ‘3 + 3’ rule. The total duration of treatment was 2 or 3 weeks.

Results: Between December 2013 and September 2014, 13 patients (2.5 mg/kg, n = 4; 5 mg/kg, n = 3; 7.5 mg/kg, n = 6) with refractory malignant ascites were enrolled. Bevacizumab was well tolerated, and the most common treatment-related adverse events were abdominal pain (5/13), abdominal distension (2/13), and fatigue (2/13). The dose-limiting toxicity at 7.5 mg/kg was grade 3 bowel obstruction (1/13). The maximum tolerated dose (MTD) was not reached. The overall response and disease control rates were 7.7 and 61.5%, respectively.

Conclusions: Intraperitoneal bevacizumab safe and well tolerated for treating malignant ascites, and the MTD was not reached at doses of 2.5 to 7.5 mg/kg. Intraperitoneal bevacizumab at 7.5 mg/kg weekly is recommended for further study to verify its anti-tumor activity.

Trial registration: Clinical Trials NCT01852409.

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Introduction
Malignant ascites is a severe complication of various late-stage cancers, such as colorectal, gastric, pancreatic, ovarian, breast, and lung cancers, which can cause several symptoms affecting patient quality of life and survival. In addition, malignant ascites usually indicates tumor progression and treatment failure, and the mean survival time is approximately 20 weeks after diagnosis.

Unfortunately, the treatment of malignant ascites remains challenging and often frustrating. Currently, common established treatments include salt restriction, diuresis, and systemic chemotherapy. In addition, hyperthermic intraperitoneal chemotherapy (HIPEC), paracentesis, and intraperitoneal antineoplastic drugs have been applied in select patients. However, these methods have several limitations, such as intolerance to systemic chemotherapy because of poor performance status, electrolyte disorder and hypoalbuminemia caused by repeated paracentesis and ascites drainage, and the low efficacy and severe adverse events (AEs) of conventional intraperitoneal drugs. Catumaxomab, a bispecific (anti-human epithelial cell adhesion molecule and anti-CD3) monoclonal antibody, combined with paracentesis produced pronounced and prolonged reductions in ascites and delayed the deterioration of quality of life. However, overall survival (OS) was not evaluated in these studies, and catumaxomab is not widely used clinically.

Vascular endothelial growth factor (VEGF) can promote angiogenesis as well as increase the permeability of vessels, which is a key step in tumor growth and ascites formation. High VEGF levels have been found in malignant ascites, and the introduction of VEGF antisense oligonucleotides decreased VEGF levels and inhibited ascites formation. Bevacizumab is a humanized anti-human VEGF-A monoclonal antibody that specifically binds to VEGF, and it has been approved by the Food and Drug Administration for the treatment of several types of cancers, including colorectal, non-small-cell lung, renal, and ovarian cancers. Bevacizumab is intravenously injected using common doses of 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. In addition, intravenous bevacizumab has displayed safety and efficacy in some patients with malignant ascites.

Recently, investigators explored the possibility of intraperitoneal bevacizumab therapy. El-Shami et al. reported that intraperitoneal bevacizumab therapy at 5 mg/kg monthly relieved ascites in several patients with cancer in a small-scale prospective study. Hamilton et al. described a case of ovarian cancer involving refractory ascites that was successfully managed by intraperitoneal bevacizumab at 5 mg/kg. A phase II study revealed that intraperitoneal bevacizumab (300 mg) was effective and well tolerated in the management of malignant ascites compared with placebo.

In these previous studies, bevacizumab was intraperitoneally administered with different doses and frequencies. These studies did not explore the optimal dose of bevacizumab. To date, there is no standard recommended dose or frequency for intraperitoneal bevacizumab. Therefore, we
conducted this prospective, dose-escalation phase I study primarily to evaluate the safety and tolerability and confirm the maximum tolerated dose (MTD) of intraperitoneal bevacizumab in managing refractory malignant ascites. The study also evaluated anti-tumor efficacy and survival in an effort to clarify the recommended dose of bevacizumab.

**Materials and methods**

**Patient selection**

Patients with refractory malignant ascites admitted to Department of Gastrointestinal Oncology in Peking University Cancer Hospital were enrolled in this study. The eligibility criteria included histologically or cytologically confirmed non-squamous cell carcinoma that did not respond to standard systemic therapy. Malignant ascites was diagnosed via cytology and imaging (ultrasound or computed tomography). The eligibility criteria were as follows: age of 18 to 75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, and expected survival of more than 8 weeks. The requirements included normal hematologic function, as demonstrated by an absolute neutrophil count $\geq 1500$ cells/mL, hemoglobin $\geq 9$ g/dL (transfusion allowed), and platelet count $\geq 100,000$ mL, as well as normal renal (creatinine <1.5 mg/dL) and hepatic function (bilirubin <1.5 $\times$ the upper limit of normal).

Patients were excluded if they received chemotherapy, radiation therapy, immunotherapy, or targeted therapy (tyrosine kinase inhibitors or VEGF monoclonal antibodies) within the prior 4 weeks before study entry; underwent major surgery within 4 weeks without complete recovery; had concurrent gastrointestinal obstruction, peptic ulcer, Crohn’s disease, ulcerative colitis, and other gastrointestinal diseases that may cause gastrointestinal bleeding or perforation; had uncontrolled hypertension and active bleeding, hemoptysis, or bloody ascites; had thrombosis within 12 months or any psychiatric conditions; or had symptomatic brain metastasis. Patients who were pregnant or lactating were also excluded. Informed consent was obtained from all individual participants included in the study.

All procedures performed in studies involving human participants accorded with the ethical standards of Ethics Committee of Peking University Cancer Hospital and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was registered at the United States Clinical Trial registry (registration number: NCT01852409).

**Study design**

This study was a prospective, dose-escalation phase I study. A modified Fibonacci method was used to escalate the dose of bevacizumab (Avastin®, Roche, Basel, Switzerland), with an initial dose of 2.5 mg/kg (dose level 1) and subsequent doses were increased by 100 (5 mg/kg, dose level 2) and 50% (7.5 mg/kg, dose level 3). In addition, dose escalation followed the standard “3 + 3” rule. Briefly, each dose level consisted of at least three patients. In the absence of dose-limiting toxicity (DLT, defined as a grade 3 or greater AE), the subsequent dose level was initiated. If one patient experienced a DLT in this dose group, three additional patients were enrolled in this dose group. Enrollment at the subsequent dose level could only commence if none of the additional three patients experienced a DLT. If one or more DLTs occurred among the additional three patients, the trial was terminated. The dose used in the final group was regarded as the dose that produced a DLT, and the dose immediately below the DLT-associated dose was regarded as the
MTD. The protocol allowed investigator discretion in making upward dose adjustments in patients who were assessed as having progressive disease or withdrawal of consent.

**Treatment**

Peritoneocentesis was performed with the aid of ultrasound before the initiation of treatment. Ascites drainage and peritoneal lavage were applied until the abdominal drainage fluid was relatively clear. Bevacizumab (100 mg/4 mL per ampule) was delivered in 250 mL of normal saline that was warmed to body temperature and infused into the peritoneal cavity. After infusion, patients were asked to change positions at 15-minute intervals to facilitate adequate intra-abdominal distribution. Bevacizumab was administered weekly for 2 or 3 weeks.

**Evaluation of safety and efficacy**

AEs were classified into grades of 0 to 5 via direct questioning, physical examination, and laboratory tests and recorded according to the National Cancer Institute Common Toxicity Criteria Version 4.0. Ultrasound, which was used to determine the depth of ascites (unit: centimeter), was performed by the same doctor before each treatment and within 2 weeks after the last treatment. The efficacy of treatment was classified according to the 1998 WHO criteria as follows: complete response (CR), the complete resolution of ascites that was maintained for at least 4 weeks; partial response (PR), >50% decrease in the measured value of ascites versus baseline 1 month after intraperitoneal administration or no increase of the effusion and the response was maintained at least 4 weeks; no change (NC), >25% increase or <50% decrease in the measured value of ascites versus baseline 1 month after intraperitoneal administration that was maintained for at least 4 weeks; and progressive disease (PD), >25% increase in the measured value of ascites versus baseline. The overall response rate (ORR) was the percentage of patients with CR or PR among all patients. The disease control rate (DCR) was the percentage of patients with CR, PR, or NC among all patients. OS was calculated from the time of written informed consent to death from any cause or the last follow-up, at which time the data were censored.

**Statistical analysis**

Descriptive summary statistics were used to assess demographic characteristics, safety, and anti-tumor activity. The chi-squared test was used to compare proportions between groups. All P-values were two-sided, and P < 0.05 was considered statistically significant. The data cutoff date was December 1, 2018. SPSS (version 17.0, SPSS, Chicago, IL, USA) was applied for data analysis.

**Results**

**Patient characteristics**

Between December 2013 and September 2014, 13 patients (2.5 mg/kg, n = 4; 5 mg/kg, n = 3; 7.5 mg/kg, n = 6) with various solid tumors and refractory malignant ascites were enrolled. The primary tumors included gastric cancer (n = 6), colorectal cancer (n = 2), peritoneal mesothelioma (n = 2), gastric neuroendocrine tumor (n = 1), gallbladder cancer (n = 1), and occult primary adenocarcinoma (n = 1). This population was heavily pretreated, with all patients receiving systemic chemotherapy, four (30.8%) patients receiving surgery, and two (15.4%) patients receiving radiotherapy. In addition, eight (61.5%) patients received intraperitoneal treatments, including intraperitoneal anticancer drugs or HIPEC, before enrollment.
Patient characteristics are summarized in Table 1.

**DLT and MTD determination**

Three patients were initially entered at dose level 1. One patient experienced disease progression with clinical deterioration after the first treatment, making it difficult to ascertain the toxicity of bevacizumab in this individual. To verify the toxicity data at this dose level, a fourth patient was enrolled. No DLT was observed at dose level 1. At dose level 2, all three enrolled patients completed treatment without a DLT. At dose level 3, one DLT (grade 3 bowel obstruction) was observed in one of the first three patients. An additional three patients were accrued at dose level 3, and no additional DLTs were observed. Therefore, the MTD was not reached in our study.

**Safety and tolerability**

Of the 13 patients, seven (53.8%) patients experienced treatment-related AEs (TRAEs). The most frequently reported TRAEs were abdominal pain (5/13, 38.5%), abdominal distension (2/13, 15.4%), and fatigue (2/13, 15.4%). In total, 93.6% (15/16) of TRAEs were grade 1 or 2. Only one grade 3 TRAE (bowel obstruction) at dose level 3 was observed. This event occurred in a 38-year-old female patient with gastric cancer who received extensive prior therapy including surgery, multiple lines of chemotherapy, and HIPEC. She developed bowel obstruction during the first treatment, which was possibly related to treatment. However, an association with the underlying disease could not be completely eliminated. TRAEs of all grades per patient (TRAEs/patients) were 4/4, 4/3, and 8/6 at dose levels 1, 2, and 3, respectively. No treatment-related deaths were reported. Meanwhile, no common bevacizumab-related AEs (blood pressure changes, proteinuria, bleeding, embolism, or impairment of wound healing) were observed in any patients. Peritoneocentesis-related AEs, such as abdominal cavity infection or abdominal puncture site bleeding, also did not occur.

### Table 1. Patient characteristics.

| Characteristics                          | N = 13 (%) |
|-----------------------------------------|-----------|
| Age (years)                             |           |
| Median                                  | 51        |
| Range                                   | 38–77     |
| Sex                                     |           |
| Male                                    | 4 (30.8)  |
| Female                                  | 9 (69.2)  |
| Hypertension history                    | 1 (7.7)   |
| ECOG performance status                 |           |
| 0–1                                     | 12 (92.3) |
| 2                                       | 1 (7.7)   |
| Primary tumors                          |           |
| Gastric cancer                          | 6 (46.1)  |
| Colorectal cancer                       | 2 (15.4)  |
| Peritoneal mesothelioma                 | 2 (15.4)  |
| Gastric neuroendocrine tumor            | 1 (7.7)   |
| Gallbladder cancer                      | 1 (7.7)   |
| Occult primary adenocarcinoma           | 1 (7.7)   |
| Metastasis sites                        |           |
| Ascites only                            | 6 (46.2)  |
| Combined with other metastasis sites    |           |
| Liver                                   | 3 (23.1)  |
| Lung                                    | 2 (15.4)  |
| Ovary                                   | 2 (15.4)  |
| Lymph node                              | 7 (53.8)  |
| Prior treatments                        |           |
| Intraperitoneal treatment               | 8 (61.5)  |
| Systemic chemotherapy                   |           |
| First-line                              | 13 (100)  |
| Second-line                             | 4 (30.8)  |
| Third-line                              | 1 (7.7)   |
| Surgery                                 | 4 (30.8)  |
| Radiation                               | 2 (15.4)  |
| TACE                                     | 1 (7.7)   |

Intraperitoneal treatment included intraperitoneal anti-cancer drugs (cisplatin, albumin paclitaxel, paclitaxel, floxuridine, oxaliplatin, biological agents) and hyperthermia.

ECOG, Eastern Cooperative Oncology Group; TACE, transcatheter arterial chemoembolization.
The TRAEs at each dose level are presented in Table 2.

**Efficacy and survival**

Of all treated patients, the ORR and DCR were 7.7% (1/13) and 61.5% (8/13), respectively. At dose levels 1, 2, and 3, the ORRs were 0%, 33.3%, and 0% \( (P=0.164) \), respectively, whereas the DCRs were 50%, 100%, and 50% \( (P=0.296) \), respectively. The patient with a PR at dose level 2 had occult primary adenocarcinoma. NC was reported in seven patients (four, two, and one patient with gastric cancer, colorectal cancer, and gastric neuroendocrine tumor, respectively). Excluding the higher number of patients with gastric cancer, no other definable association between efficacy and clinical features could be identified because of the small number of patients. In addition, symptoms were palliated in patients with PR and NC. Details of efficacy are presented in Table 3.

The 13 patients received 29 infusions. The median number of infusions per patient was two (range, 1–3), with two patients receiving one infusion, six patients receiving two infusions, and five patients receiving three infusions. The preliminary survival information in this current study illustrated that the median OS was 103 days (range, 23–387), and two patients were still alive at the last follow-up (December 1, 2018). The patient with PR died after 62 days. The cause of death was tumor progression despite the initial observation of efficacy. This patient was a 77-year-old man who was heavily pretreated before enrolling in our study. After three infusions of intraperitoneal bevacizumab with a best ORR of PR, his symptoms were palliated. Subsequently, he was discharged home from the hospital, only receiving supportive care without any anti-tumor treatment until death. Details of the treatments at each dose level are summarized in Table 4.

**Discussion**

Differing from previous studies that did not explore the optimal dose of intraperitoneal bevacizumab, this prospective, dose-escalation phase I study used different doses of bevacizumab following the standard “3 + 3” rule for dose escalation in treating refractory malignant ascites for the first time.

| Table 2. Numbers of patients with treatment-related adverse events at each dose level. |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|
| Dose (mg/kg)                  | 2.5 (n = 4) | 5 (n = 3) | 7.5 (n = 6) | N = 13 (%) |
| Toxicity (grade)              | 1–2     | 3–4    | 1–2     | 3–4    | 1–2     | 3–4    |
| Hematological toxicity        |         |        |         |        |         |        |
| Leukopenia                     | 0       | 0      | 0       | 0      | 1       | 0      |
| Neutropenia                    | 0       | 0      | 0       | 0      | 1       | 0      |
| Non-hematological toxicity    |         |        |         |        |         |        |
| Abdominal pain                 | 1       | 0      | 1       | 0      | 3       | 0      |
| Abdominal distension           | 1       | 0      | 1       | 0      | 0       | 0      |
| Fatigue                        | 0       | 0      | 1       | 0      | 1       | 0      |
| Constipation                   | 1       | 0      | 0       | 0      | 0       | 0      |
| Diarrhea                       | 0       | 0      | 0       | 0      | 1       | 0      |
| Anorexia                       | 0       | 0      | 1       | 0      | 0       | 0      |
| Bilirubin increase             | 1       | 0      | 0       | 0      | 0       | 0      |
| Bowel obstruction              | 0       | 0      | 0       | 0      | 1       | 0      |

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As a phase I study, its main purpose was to evaluate the safety and tolerability. Our study revealed that intraperitoneal bevacizumab was safe and well tolerated, as indicated by a low incidence of grade 3 or 4 AEs and the MTD not being reached at doses ranging from 2.5 to 7.5 mg/kg. Meanwhile, intraperitoneal bevacizumab therapy also exhibited short-term efficacy and palliated symptoms in some patients. In our study, a low incidence (7.7% to 38.5%) of TRAEs was observed, and the most common events were abdominal pain (38.5%), abdominal distension (15.4%), and fatigue (15.4%), which accorded with previous studies and our expectations. One of the six patients treated at dose level 3 experienced grade 3 bowel obstruction (defined as a DLT). A similar result was reported in a study in which bevacizumab was intraperitoneally administered at 5 mg/kg monthly. In that study, one of the nine patients developed partial small bowel obstruction and received conservative treatment. Previous studies found that patients with peritoneal metastasis were prone to developing intestinal adhesion that was complicated by bowel obstruction. Laparotomy leads to changes of the abdominal cavity anatomy, which increases

### Table 3. Efficacy at each dose level.

| Dose (mg/kg) | CR | PR | NC | PD | ORR | DCR |
|--------------|----|----|----|----|-----|-----|
| 2.5 (n = 4)  | 0  | 0  | 2  | 2  | 0   | 2 (50%) |
| 5 (n = 3)    | 0  | 1  | 2  | 0  | 1 (33.3%) | 3 (100%) |
| 7.5 (n = 6)  | 0  | 0  | 3  | 3  | 0   | 3 (50%) |
| Total (N = 13)| 0  | 1  | 7  | 5  | 1 (7.7%) | 8 (61.5%) |

CR, complete remission; PR, partial remission; NC, no change; PD, progressive disease; ORR, overall response rate, (CR + PR); DCR, disease control rate, (CR + PR + NC).

### Table 4. Treatment with bevacizumab at each dose level.

| Dose (mg/kg) | Primary tumor                  | Number of infusions | Final status       | Efficacy | Survival time (days) |
|--------------|--------------------------------|---------------------|--------------------|----------|----------------------|
| 2.5          | Colorectal cancer              | 3                   | Completed treatment| NC       | 387                  |
| 2.5          | Gastric cancer                 | 3                   | Completed treatment| NC       | 201                  |
| 2.5          | Gastric cancer                 | 1                   | Disease progression| PD       | 23                   |
| 2.5          | Peritoneal mesothelioma        | 2                   | Withdrew ICF       | PD       | 52                   |
| 5            | Gastric cancer                 | 3                   | Completed treatment| NC       | 187                  |
| 5            | Colorectal cancer              | 2                   | Completed treatment| NC       | 132                  |
| 5            | Occult primary adenocarcinoma  | 3                   | Completed treatment| PR       | 62                   |
| 7.5          | Gastric cancer                 | 1                   | Bowel obstruction  | NC       | 100                  |
| 7.5          | Gastric cancer                 | 2                   | Disease progression| PD       | 36                   |
| 7.5          | Gastric neuroendocrine tumor   | 3                   | Completed treatment| NC       | 41†                  |
| 7.5          | Gallbladder cancer             | 2                   | Disease progression| PD       | 196†                 |
| 7.5          | Peritoneal mesothelioma        | 2                   | Completed treatment| PD       | 103                  |
| 7.5          | Gastric cancer                 | 2                   | Completed treatment| NC       | 34                   |

Notes: †Alive at the last follow-up.
ICF, informed consent form; PR, partial remission; NC, no change; PD, progressive disease.
the risk of bowel obstruction.\textsuperscript{20–22} The patient in our study who developed bowel obstruction had peritoneal metastasis and underwent surgery, which might have increased the risk of bowel obstruction. Considering that only one of the six patients treated at dose level 3 developed a DLT, the MTD was not reached, which indicated the relatively safety of this dose level.

Numerous studies found that the common AEs of intravenous bevacizumab were hypertension (34%, including a grade 3–4 AE rate of 7.9%), proteinuria (0.7% to 38%), hemorrhage (35.5%, with severe bleeding in 0.4% to 35.5% of patients), wound healing syndrome (10% to 20%), gastrointestinal perforation (0.3% to 2.4%), and venous thrombotic events (11.9%), whereas the most common toxicities were hypertension and proteinuria.\textsuperscript{24–26} These common AEs were not observed in our study. A meta-analysis aiming to quantify the risks of proteinuria and hypertension associated with bevacizumab revealed that the risk of AEs was dose-dependent.\textsuperscript{27} In our study, one patient at dose level 1 had a history of hypertension. Blood pressure was stable during bevacizumab treatment and follow-up in this patient. Hypertension and proteinuria were not observed in other patients. Based on the dose–risk relationship, we considered the low rate of AEs in our study was attributable to the relatively low doses of bevacizumab.

In a phase I study, assessing anti-tumor efficacy is not the key goal, although it was worth our attention in this study. In our study, intraperitoneal bevacizumab monotherapy ascites had short-term efficacy in managing malignant ascites, as indicated by an ORR of 7.7% (1/13), DCR of 61.5% (8/13), and median OS of 103 days (range, 23–387). The patient who experienced PR was at dose level 2 died after 62 days despite initial efficacy. However, the small number of patients precluded the determination of a meaningful association between dose and efficacy. Anti-tumor efficacy should be evaluated in the future.

In a phase I study bevacizumab in the treatment of advanced cancers, the results illustrated that higher doses of bevacizumab might increase the probability of stable disease.\textsuperscript{28} Meanwhile, another study found that higher dosages might be required to treat malignant effusion than needed to control the underlying cancers.\textsuperscript{18} Based on these studies, we speculated that higher doses of bevacizumab might generate better efficacy when treating malignant ascites.

Because bevacizumab was safe at doses ranging from 2.5 to 7.5 mg/kg, we recommended a higher dose of 7.5 mg/kg for dose extension to further verify the safety and efficacy of this drug for treating malignant ascites.

Intraperitoneal bevacizumab might represent a highly efficacious modality for palliating the symptoms of refractory malignant ascites. Previous studies demonstrated that VEGF expression decreased in ascites after bevacizumab therapy.\textsuperscript{1,16} Another study indicated that intraperitoneal bevacizumab could activate the immune system, including a temporary increase in effector CD8\textsuperscript{+} cell counts, which might be an underlying mechanism of the therapeutic effect of bevacizumab.\textsuperscript{29} It is worth confirming these immunological observations and clarifying the complex mechanisms in future studies.

Bevacizumab was used as monotherapy in our study; however, it is commonly used in combination with other drugs in clinical practice. A phase III clinical trial of intraperitoneal cisplatin plus bevacizumab for the management of malignant ascites enrolled 58 patients with ovarian epithelial cancer who were randomly assigned to receive intraperitoneal cisplatin only or cisplatin plus bevacizumab (300 mg, every 2 weeks). The result illustrated that the ORR in the combination group was
significantly higher than that in the monotherapy group (90.32% vs. 59.26%, \( P < 0.05 \)). The quality of life improvement rate was also higher in the combination group. All patients tolerated the treatments, and no serious adverse effect occurred.\(^{30}\) Another study found that intraperitoneal cisplatin plus bevacizumab (300 mg, every 2 weeks) compared with cisplatin alone improved the ORR and quality of life without increasing the rate of grade 3 or 4 toxicities in the management of malignant ascites.\(^{31}\) Therefore, subsequent research should evaluate the anti-tumor activity of bevacizumab at 7.5 mg/kg weekly combined with chemotherapy against refractory malignant ascites.

Our studies had several limitations. We did not explore the differences of the pharmacokinetic characteristics of bevacizumab between the two administration routes (intraperitoneal administration vs. intravenous injection). In addition, the small number of patients, heterogeneity of tumor types, and patient characteristics made it difficult to evaluate the relationships among tumor types, doses, and response.

Conclusion

Intraperitoneal bevacizumab appeared to be safe and well tolerated in this study, and the MTD was not reached at doses ranging from 2.5 to 7.5 mg/kg. This treatment also exhibited short-term anti-tumor efficacy and palliated symptoms. We recommend intraperitoneal bevacizumab at 7.5 mg/kg weekly for patients with malignant ascites to further verify its anti-tumor activity in subsequent research.

Declaration of conflicting interest

Shanghai Roche Pharmaceuticals Limited provided bevacizumab (Avastin\(^\text{R}\)) in this study, as well as revised the article. The authors declare no other conflicts of interest.

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