

CURATIVE EFFECT EVALUATION OF INTRAPERITONEAL HYPERTHERMIC PERFUSION CHEMOTHERAPY COMBINED WITH APATINIB FOR MALIGNANT ASCITES

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Abstract

This study aims to retrospectively evaluate the curative effect of intraperitoneal hyperthermic perfusion chemotherapy (IHPC) combined with apatinib for malignant ascites of advanced tumours. Twenty peritoneal tumour metastasis patients with ascites were treated with IHPC combined with apatinib. Apatinib was administered at 850 mg daily for four weeks as one cycle. IHPC was applied once a week, for four weeks as a course of treatment. After the initial treatment course of four weeks, indicators of its short-term effect, that is, changes in serum tumour markers CEA, CA125 and CA19-9, as well as ascites volume and scores of Karnofsky performance status (KPS) before and after the treatment, were evaluated.

Rezumat

Acest studiu și-a propus evaluarea efectului chimioterapiei hipertermice intraperitoneale (IHPC) combinată cu apatinib pentru ascita malignă a tumorilor avansate. Au fost incluși în studiu 20 de pacienți cu metastază tumorală peritoneală cu ascită. Apatinib a fost administrat în doză de 850 mg pe zi, timp de patru săptămâni/ciclu. IHPC a fost aplicat o dată pe săptămână, timp de patru săptămâni. După patru săptămâni de tratament, s-au modificat markerii tumorali serici CEA, CA125 și CA19-9, precum și volumul ascitei și scorurile statusului de performanță Karnofsky (KPS).

Keywords: apatinib, hyperthermic, intraperitoneal chemotherapy

Introduction

Malignant ascites is caused by a variety of malignant tumours, which often indicates tumour invasion and metastasis, and is the most common clinical manifestation of peritoneal metastasis in advanced cancers [1]. Malignant ascites caused by ovarian cancer is the most common, while others may be caused by gastro-intestinal cancer, pancreatic cancer, liver cancer, cervical cancer and other malignant tumours [2]. The occurrence of malignant ascites indicates short survival time and poor prognosis. For example, the peritoneal metastasis of gastric cancer forms peritoneal carcinomatosis (PC), in which the main manifestations include intractable pain, refractory ascites and rapidly progressive intestinal obstruction [3] and its prognosis is poor, with a median survival time of less than six months.

Recent studies suggest that the formation of malignant ascites is related to angiogenesis. The main causes for the formation of malignant ascites are the formation of new blood vessels and the increase of microvascular permeability caused by vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), adhesion molecules and other substances secreted by local tumours. VEGF is a highly conserved glycoprotein of 34 - 42 kDa, which can be produced by a variety of

solid tumours [4]. VEGF promotes tumour angiogenesis, and tumour growth requires new blood vessels to provide nutrients. In addition to promoting angiogenesis, VEGF can also increase microvascular permeability; thus, its overexpression leads to the occurrence of malignant ascites tumour [5]. Many studies revealed that the concentrations of VEGF in malignant ascites from a variety of solid tumours (e.g. ovarian cancer, gastric cancer, colorectal cancer, pancreatic cancer and breast cancer) significantly increased, but VEGF in non-malignant ascites were much lower [6]. A recent study analysed 21 different cytokine concentrations in malignant and non-malignant ascites and found that the overexpression of VEGF is associated with malignant ascites [7]. Malignant pleural ascites contains VEGF with high biological activity; thus, blocking VEGF may be beneficial for the treatment of patients with advanced malignant ascites [8]. In addition, VEGF concentrations in effusion are significantly higher than in serum. More importantly, VEGF concentrations in malignant ascites associate with sensitivity to chemotherapy and are independent predictors of progression-free survival time and overall survival rate of tumour patients [9, 10]. This suggests that anti-VEGF therapy should be able to directly influence the development of malignant ascites and has a direct anti-tumour effect [11].

As an anti-VEGFR-2 targeted drug, apatinib can inhibit tumour angiogenesis and reduce the occurrence of ascites. Normal tissues can withstand a higher temperature than tumour tissues. At a certain temperature range, the thermal effect can promote the apoptosis of tumour cells, enhancing the efficacy of chemotherapeutic drugs and inhibiting tumour angiogenesis, while stimulating the activity of the immune system of the body; thus, this effect is enhanced with increasing temperature [12]. Among the treatments of malignant ascites, peritoneal perfusion chemotherapy assembles the effects of local chemotherapy, heat therapy and the mechanical peritoneal lavage effect of large volume chemotherapy fluid, has the advantages of both pharmacokinetics and fluid dynamics, makes full use of the synergies of chemotherapy and heat therapy, can remove intraperitoneal free cancer cells and small tumour foci, and reduces the occurrence of malignant ascites; thus, it becomes another treatment of malignant ascites. This study was designed to assess the clinical manifestations of patients with malignant ascites who received intraperitoneal hyperthermic perfusion chemotherapy combined with apatinib and to evaluate the clinical efficacy.

Materials and Methods

Study design

Twenty patients diagnosed with peritoneal metastasis with ascites at Baotou Tumour Hospital between January 2014 and June 2015 were enrolled into this study. Among them, eight patients were male and 12 patients were female, with an age range of 25 - 75 years and a median age of 58 years. Nine patients had as primary disease ovarian cancer, three patients had stomach cancer, five cases had colorectal cancer, and three cases had pancreatic cancer. All ascites were examined by computed tomography (CT) and cytologically proved to be malignant. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the hospital

Clinical design

For all patients, after ultrasound localization catheters, 20 - 22 mm diameter trocars were placed in the left and right lower abdomen or unilateral for the purpose of draining the ascites and connecting to the TRL2000

perfusion chemotherapy machine. After full drainage of peritoneal fluid, 1,000 - 2,000 mL of sodium chloride 0.9% parenteral solution was infused at 43°C, single cycled three times, refilled with 500 mL of 0.9% sodium chloride solution at 43°C, and intraperitoneally retained, while docetaxel 75 mg/m² + cisplatin 40 mg/m² + dexamethasone 5 mg were intraperitoneally infused [13-15]. This clinical technique was conducted once a week, for four weeks. The following day after the intervention, patients received apatinib, 850 mg, once a day, for four weeks.

Clinical effects

Ascites volume, changes in tumour markers: carcinoembryogenic antigen (CEA), cancer antigen 125 (CA125) and serum cancer antigen 19-9 (CA19-9), as well as scores of KPS before and after the treatment were determined. All blood samples were collected *à jeun* before and after the treatment. Curative effect was assessed according to the WHO criteria: i) complete remission (CR): ascites disappears, symptoms alleviate and the clinical status maintains for more than four weeks; ii) partial remission (PR): ascites significantly decrease (> 50%), symptoms alleviate and the clinical status maintains for more than three weeks; iii) stable (SD): ascites' decrease was less than 50%; iv) progress (PD): ascites fully recovers within four weeks or even increase [16].

Statistical analyses

We used the software program SPSS 17.0 (IBM, Chicago, USA). The continuous variables of normal distribution were expressed as mean \pm standard deviation, the categorical variables were expressed as frequency (percentage [%]). For two comparisons, each value was compared by t-test for the normal distribution, while for the non-normally distributed continuous non-parametric tests were used. The counting data were tested by chi-square test. A value of $p < 0.05$ was considered statistically significant.

Results and Discussion

Tumour markers

Before and after the treatment of intraperitoneal hyperthermic perfusion chemotherapy combined with apatinib, the levels of serum tumour markers CEA, CA125 and CA19-9 significantly decreased after treatment ($p < 0.05$, Table I).

Table I

Comparison of serum indicators in metastasis patients with ascites before and after the treatment of intraperitoneal hyperthermic perfusion chemotherapy combined with apatinib (mean \pm standard deviation)

Detection time	Number of cases	CEA (U/mL)	CA125 (U/mL)	CA19-9 (U/mL)
Before treatment	20	42.19 \pm 20.29	116.98 \pm 21.96	147.91 \pm 21.23
After treatment	20	28.65 \pm 15.29	101.21 \pm 11.67	137.49 \pm 13.23
t-test		8.073	3.987	2.642
p		< 0.05	< 0.05	< 0.05

Ascites volume and KPS before and after the treatment

In all 20 peritoneal metastasis patients with ascites, before and after the treatment of intraperitoneal

hyperthermic perfusion chemotherapy combined with apatinib, the difference in ascites volume and KPS scores were statistically significant ($p < 0.05$, Table II).

Table II

Ascites volume and Karnofsky performance status (KPS) before and after treatment (mean \pm standard deviation)

Detection time	Number of cases	Ascites volume (mL)	KPS score
Before treatment	20	3609 \pm 826.12	56.03 \pm 15.14
After treatment	20	2578 \pm 463.03	65.32 \pm 9.73
t-test		4.868	-2.308
p		< 0.05	< 0.05

Due to large amounts of ascites in the abdominal cavity, patients may feel bloated, have difficulty breathing, feel short of breath, and have limited movement. In addition, a large amount of ascites limits the elasticity of the lung, resulting in poor appetite, reduced food intake, nausea and vomiting. What's worse, ascites patients often suffer from shortness of breath, hypoalbuminemia, oedema and other clinical manifestations; leading to a significant decline in quality of life [17].

There are many treatments for malignant ascites such as diuretics, abdominal paracentesis and peritoneal venous shunt; however, the overall effect is limited. Currently, the most common treatment for malignant ascites is repeated paracentesis, while a broad side effects like reduced effective circulating blood volume, hyponatremia, renal dysfunction, hypoalbuminemia [18]. Recently, intraperitoneal hyperthermic perfusion chemotherapy became an effective treatment for malignant ascites. Hyperthermic perfusion treatment could destroy tumour cells without damaging normal tissues. It can effectively wipe out free cancer cells and remnants of tiny cancer metastases in the body cavity, and has a positive effect on improving the overall efficacy of cancer treatment and preventing cancer recurrence [19]. The clinical evaluation revealed that intraperitoneal hyperthermic perfusion chemotherapy can significantly improve the status of 80% patients with ascites. [20]. Intraperitoneal hyperthermic perfusion has many advantages such as simple operating equipment, constant temperature, non-invasive infusion of medication, small difference between outer and inner body temperature, easy to control, no risk of burns and mild side effects. Its short-term effect is acceptable, and it can significantly prolong survival time and reduce the sufferings of patients; thus, these have promising prospects for clinical application [21-23].

The formation mechanism of malignant ascites was considered before as follows: i) lymphatic vessels were obstructed by tumour cells and lymphatic flow disorders, resulting in reducing the absorption of water and protein, which were detained in the abdominal cavity; ii) damaging of the peritoneum, intestinal wall and vascular endothelial cells leads to increased

vascular permeability, which promotes tumour invasion; iii) The plasma colloid osmotic pressure in cancer patients with hypoproteinaemia is decreased, while effective circulating blood volume is reduced, stimulating the renin-angiotensin-aldosterone system, thus, causing sodium retention. Recent studies have revealed that the main causes for the formation of malignant ascites are the formation of new blood vessels and increase of microvascular permeability caused by VEGF and MMPs, adhesion molecules and other cytokines secreted by local tumours. Furthermore, the most common cause is the overexpression of VEGF. Apatinib is a small molecule, a vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor. It may highly and selectively compete for the intracellular ATP-binding site of VEGFR-2, blocking downstream signalling and inhibiting the production of tyrosine kinases, thereby inhibiting the generation of new blood vessels in tumour tissues [24]. In this study, 20 patients were enrolled, diagnosed with malignant ascites combined with peritoneal metastasis in the hospital, and received intraperitoneal hyperthermic perfusion chemotherapy combined with apatinib treatment. It has been clinically proven that this therapy is safe, dependable and worthy of promotion [13, 14].

Study limitations

There were several limitations in this study. Firstly, this trial was not a randomized controlled trial. Secondly, this study was only single-centre trial and the sample size was limited. Thirdly, the clinical follow-up was short and it was necessary to observe the clinical long-term prognosis.

Conclusions

The treatment of intraperitoneal hyperthermic perfusion chemotherapy combined with apatinib has achieved a certain effect on malignant ascites which provided some reference for clinical treatments of patients with advanced peritoneal metastasis combined with malignant ascites.

Conflict of interest

The authors declare no conflict of interest.

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