Effect of S-1 combined with cisplatin intraperitoneal circulatory hyperthermia perfusion treatment on malignant molecule expression in gastric cancer patients with ascites as well as side effect assessment

Shuo Jian

Department of Medical Oncology, Suining Central Hospital of Sichuan Province, Suining City, Sichuan Province, 629000, China

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ABSTRACT

Objective: To study the effect of S-1 combined with cisplatin intraperitoneal circulatory hyperthermia perfusion on malignant molecule expression in gastric cancer patients with ascites as well as the related side effect. Methods: Gastric cancer patients with ascites who were treated in our hospital from February 2012 to July 2015 were selected as research subjects and randomly divided into perfusion chemotherapy group and routine chemotherapy group, and then overall chemotherapy conditions, ascites FGF molecule content, peripheral blood immune function indexes and the degree of side effect were compared between two groups. Results: Average treatment cycles of perfusion chemotherapy group were more than those of routine chemotherapy group, and ascites drainage volume within two cycles of chemotherapy was significantly less than that of routine chemotherapy group; after two cycles of chemotherapy, bFGF, FGF-2, FGF19 and FGFR4 content in ascites of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group, CD3+CD4+, CD3+CD56+ and CD3-CD56+ cell content in peripheral blood were higher than those of routine chemotherapy group, and CD3+CD8 cell content was lower than that of routine chemotherapy group; during chemotherapy, the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group. Conclusions: S-1 combined with cisplatin intraperitoneal circulatory hyperthermia perfusion chemotherapy can more effectively improve treatment compliance, suppress ascites, kill gastric cancer cells and improve immune function. It has fewer side effect and is the ideal way to treat gastric cancer with ascites.

1. Introduction

Malignant ascites is a more serious complication when malignant abdominal tumors develop into the end-stage, the survival time of patients with ascites is short, and the prognosis is poor. Gastric cancer is the malignant abdominal tumor with highest clinical incidence, the peritoneal implantation or microvascular peritoneal metastasis of cancer cells will cause ascites, and the main goals of clinical treatment of gastric cancer with ascites are to extend the survival time, reduce the symptoms of ascites and delay the development of ascites[1,2]. Intravenous chemotherapy is the principal means of clinical treatment of malignant tumors that can not be surgically removed, it has certain killing effect on the cancer cells, but the adverse reactions are relatively more, and patients’ treatment compliance is poor. In addition, intravenous chemotherapy cannot form enough drug concentration in peritoneal local metastatic lesions, and has poorer control of ascites[3].

Hyperthermia perfusion chemotherapy is a way to treat malignant ascites and pleural effusion developed in recent years, it can make chemotherapy drug directly act on the peritoneal or intraperitoneal metastatic lesions and kill free cancer cells in ascites or pleural effusion, and it is also able to kill the cancer cells by thermal
In addition, the thermal effect has regulating and promoting effect on the body's immune function, and is able to exert anti-tumor effect by enhancing immune function. In the following study, the effect of S-1 combined with cisplatin intraperitoneal circulatory hyperthermia perfusion treatment on malignant molecule expression in gastric cancer patients with ascites was analyzed and the side effect was assessed.

2. Materials and methods

2.1. Research subjects

A total of 58 gastric cancer patients with ascites who were treated in our hospital from February 2012 to July 2015 were selected as research subjects, all patients were diagnosed through biopsy and ascites cytologic test, Kamofsky score was 40-70 points, and the expected survival time was more than 3 months. After informed consent was obtained, the included patients were divided into perfusion chemotherapy group and routine chemotherapy group according to random number table, 29 cases in each group. Perfusion chemotherapy group included 19 male cases and 10 female cases, they were (62±8) years old, and KPS score was (59.4±7.4) points; routine chemotherapy group included 20 male cases and 9 female cases, they were (60±9) years old, and KPS score was (60.2±8.1) points. Comparison of general information between two groups showed no significant differences.

2.2. Chemotherapy methods

Both groups received intraperitoneal perfusion chemotherapy with cisplatin, and for routine chemotherapy group, 90 mg and 60 mg cisplatin were added in 100 mL saline respectively on the first day and on the eighth day, which was injected into the abdominal cavity via abdominal puncture tube; for perfusion chemotherapy group, in vitro circulatory hyperthermia perfusion chemotherapy machine was adopted for perfusion chemotherapy, temperature was set to 45 ℃, the temperature input in the body was 42-44 ℃ and the temperature drained out of the body was 41-43 ℃. After chemotherapy, both groups received oral administration of S-1 for continuous 14 days and then stopped it for 7 days, and 21 days was a treatment course.

2.3. Observation of overall chemotherapy conditions

The chemotherapy conditions of two groups were followed up, and the number of cycles of chemotherapy was counted; within the first two cycles of chemotherapy, the ascites drainage volume was counted.

2.4. Assessment of clinical indexes

After two cycles of chemotherapy, ascites samples were collected and centrifuged, the sediment was discarded and the supernatant was kept, and then ELISA kit was used to determine b fibroblast growth factor (bFGF), FGF-2, FGF19 and FGFR4 content; during the same period, 5 mL peripheral blood was collected, mononuclear cells were separated, CD3, CD4, CD8 and CD56 fluorescence antibody were incubated, and flow cytometer was used to determine the content of different cell subsets.

2.5. Assessment of side effect

During chemotherapy, the side effect of two groups was assessed, including the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea.

2.6. Statistical methods

SPSS20.0 software was used to input and analyze data, measurement data was analyzed by t test, count data was analyzed by chi-square test, and P<0.05 indicated statistical significant differences.

3. Results

3.1. Overall chemotherapy conditions

Average treatment course of perfusion chemotherapy group were (4.93±0.72) d, average treatment course of routine chemotherapy group were (2.77±0.45) d, average treatment course of perfusion chemotherapy group were significantly longer than those of routine chemotherapy group (t=8.125, P<0.05); within the first two cycles of chemotherapy, the total ascites drainage volume of perfusion chemotherapy group was (4471.2±752.7) mL, the total ascites drainage volume of routine chemotherapy group was (5725.9±914.3) mL, ascites drainage volume of perfusion chemotherapy group was significantly less than that of routine chemotherapy group (t=6.352, P<0.05).

3.2. Expression of FGF and receptors in ascites

After two courses of chemotherapy, bFGF content, FGF-2 content,
FGF-19 content and FGFR-4 content in ascites of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group ($P<0.05$).

### 3.3. Content of T cell and NK cell subsets in peripheral blood

CD3$^+$CD4$^+$ cell content, CD3$^+$CD56$^+$ cell content and CD3$^+$CD56$^+$ cell content in peripheral blood of perfusion chemotherapy group were higher than those of routine chemotherapy group, CD3$^+$CD8$^+$ cell content was lower than that of routine chemotherapy group ($P<0.05$).

### 3.4. Side effects of chemotherapy

During chemotherapy, the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea of perfusion chemotherapy group were 1, 2, 1 and 1 respectively, and the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea of routine chemotherapy group were 7, 10, 7 and 8 respectively. After chi-square test, the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group.

### 4. Discussion

Hyperthermia perfusion chemotherapy is a way to treat malignant ascites and pleural effusion rising in recent years, chemotherapy drugs directly act on the local lesions, the killing effect on cancer cells is stronger and systemic adverse reactions are less, and patients can stick to more cycles of chemotherapy and have more survival time[7]. Thermal effect can dilate local capillaries and lymphatic vessels and increase chemotherapy drug distribution concentration within tissue, and can also induce cancer cell ultrastructure change, destroy the cell metabolism and kill cancer cells[8,9]. In the research, hyperthermia perfusion chemotherapy and intravenous systemic chemotherapy were compared, the average treatment cycles of perfusion chemotherapy group were more than those of routine chemotherapy group and the ascites drainage volume within the first two cycles of chemotherapy was significantly less than that of routine chemotherapy group. On the one hand, it indicates that hyperthermia perfusion chemotherapy compliance is better, and patients can stick to more courses of treatment; on the other hand, it shows that hyperthermia perfusion chemotherapy can better control ascites, and ascites drainage volume is less during chemotherapy.

The most prominent value of hyperthermia perfusion chemotherapy is that chemotherapy drugs can act directly on the peritoneal and intraperitoneal metastatic cancer cells and exert killing effect, and at the same time, it can induce cancer cell apoptosis by thermal effect. The peritoneal implantation of cancer cells by direct dissemination and microcirculation metastasis is a key link in gastric cancer patients complicated with ascites, and the dissemination and metastasis of cancer cells are mediated by a variety of malignant molecules[10,11]. FGF is an important cytokine that mediates the formation of new blood vessels and lymphatic vessels as well as the cancer cell metastasis through blood and lymphatic pathway, among which bFGF, FGF-2 and FGF-19 as well as the corresponding receptor FGFR-4 is associated with the metastasis of gastric cancer[12-14]. In the research, analysis of the expression of the above cytokines and receptor in ascites confirmed that bFGF, FGF-2, FGF-19 and FGFR-4 content in ascites of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group. This means that hyperthermia perfusion chemotherapy can effectively kill the cancer cells in ascites and inhibit the expression of fibroblast growth factors.

Immune escape is the important mechanism of the pathogenesis of malignant tumors, the immune function of patients with advanced gastric cancer is inhibited to different extent, and the thermal effect produced by hyperthermia perfusion chemotherapy can stimulate
and activate the immune system[15]. NK cells are the important components of the innate immune system and can directly kill cancer cells[16,17], and NK-like T lymphocytes (CD3⁺CD56⁻) and NK cells (CD3⁺CD56⁺) content increase significantly in peripheral blood of patients after hyperthermia perfusion chemotherapy. Cellular immune response is the main mechanism of the body’s anti-tumor immunity, and T lymphocytes play a leading role. CD4⁺ cells are helper T cells that can help to complete the killing and scavenging effect of cellular immune response on cancer cells; CD8⁺ cells are suppressor T cells that can suppress cellular immune response [18]. After hyperthermia perfusion chemotherapy, CD3⁺CD4⁺ cell content in peripheral blood of perfusion chemotherapy group were higher than those of routine chemotherapy group while CD3⁺CD8⁺ cell content was lower than that of routine chemotherapy group. Thus it confirms that hyperthermia perfusion chemotherapy can enhance the immune function of gastric cancer patients with ascites.

Finally, the safety of hyperthermia perfusion chemotherapy was analyzed in the research, the degree of adverse reactions was mainly assessed, and the number of cases with decreased numeration of leukocyte, abnormal liver function, abnormal kidney function and diarrhea of perfusion chemotherapy group were significantly lower than those of routine chemotherapy group while CD3⁺CD8⁺ cell content was lower than that of routine chemotherapy group. Thus it confirms that hyperthermia perfusion chemotherapy can enhance the immune function of gastric cancer patients with ascites.

To sum up, S-1 combined with cisplatin intraperitoneal circulatory hyperthermia perfusion chemotherapy can more effectively improve treatment compliance, suppress ascites, kill gastric cancer cells and improve immune function, has less side effects and is the ideal way to treat gastric cancer with ascites.

References