Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/58/20241325

Analysis of gastric cancer medication by exploring fluorouracil drugs

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Abstract. Gastric cancer (GC), as one of the most important types of cancer with a very high incidence rate in China, is in urgent need of treatment. China has made certain progress, such as the widespread use of fluorouracil and other drugs in the treatment of gastric cancer, as well as the use of various treatment methods such as surgery and chemotherapy. This article aims to explore the efficacy of fluorouracil drugs in the treatment of gastric cancer and their combined application with other drugs. By analyzing the correlation between peripheral blood platelet levels and the efficacy of oxaliplatin combined with fluorouracil chemotherapy in gastric cancer patients, as well as the effects of two chemotherapy regimens, docetaxel combined with oxaliplatin, tigio and docetaxel combined with cisplatin and fluorouracil, on advanced gastric cancer, it was found that fluorouracil drugs, as cell cycle inhibitors, have an inhibitory effect on cell division and have a significant effect in the treatment of gastric cancer. Future research can further deepen the combined application of fluorouracil drugs with other drugs to reduce complications and improve treatment effectiveness. It is suggested that future research should focus on in-depth exploration of targeted drug delivery, combined with new biotechnology, to improve the efficiency and accuracy of gastric cancer treatment.

Keywords: gastric cancer, anti tumor drugs, fluorouracil class.

1. Introduction

GC has become one of the most important cancers with a high incidence rate in China. With the development of society and the advancement of medical technology, treating cancer has also become a crucial step in modern medicine. According to the 2020 National Cancer Report statistics, the global number of new cases of GC is about 1.089 million, and the number of deaths is about 768000. Among them, the number of new cases of GC in China is about 478000, and the number of deaths is about 373000, accounting for 43.9% and 48.6% of global new cases and deaths of GC, respectively

Regarding GC, China has gradually taken a big step in cancer treatment and medication. For example, 5-FU in fluorouracil drugs has been widely studied and applied, and many drugs with certain therapeutic effects on GC have been developed, such as Zhenqi Fuzheng Capsules and Huangqi Granules.

At the same time, the treatment methods for GC in China usually include surgical treatment, combined intraoperative chemotherapy, radiotherapy, and biologically targeted therapy. Early stage patients usually use surgical treatment, and patients can achieve curative treatment after surgery;

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Progressive patients need comprehensive treatment based on the pathological type and clinical stage of GC to achieve the goal of prolonging the treatment period.

At present, the current treatment methods for GC take laparoscopic GC surgery as an example. In response to the shortcomings of traditional open surgery, such as large trauma, slow wound healing, and postoperative complications, it achieves the characteristics of small incision, less pain, and fast healing after surgery, greatly reducing the pain of patients. In terms of chemotherapy, the research on 5-Fu is the most thorough, but the effect of single drug application is not satisfactory, with a total reaction rate of up to 21%. Combination chemotherapy began to appear in the 1970s, with FAM (fluorouracil, doxorubicin, and mitomycin C) regimen being widely used. However, randomized controlled studies have shown that there is no significant difference in response rate and survival among FAM, FA (5-Fu, doxorubicin), and monotherapy 5-Fu in the treatment of gastric cancer.[1]

Regarding GC, China is still searching for more suitable drugs and methods to treat it, such as improving cure rate and efficiency. Currently, there is a higher demand for research on more scarce treatment methods.

This study is based on the correlation between peripheral blood platelet levels and the chemotherapy efficacy of oxaliplatin combined with fluorouracil in GC patients, and the efficacy analysis of two chemotherapy regimens, docetaxel combined with oxaliplatin, tigio and docetaxel combined with cisplatin, and fluorouracil, for advanced GC. The study aims to investigate the therapeutic effect of fluorouracil drugs on GC and the special points and significance of GC.

2. Symptoms of GC and possible causes of its formation

2.1. Symptom

The typical symptoms of GC can be divided into four parts. The first part is premonitory, generally asymptomatic, but patients with precancerous lesions may present with symptoms of precancerous lesions, such as heartburn, indigestion, upper abdominal pain, etc; The second part is early symptoms. 80% of early GC patients have no symptoms, and some have bloating, indigestion, upper abdominal pain, etc [2]. They are usually considered as ordinary gastritis and miss the treatment opportunity; The third part is the mid-term symptoms, with the most common symptom being upper abdominal pain. Some patients are accompanied by anemia, anorexia, palpation of a lump in the upper abdomen, and the pain is irregular and not related to eating. It is often located in the left upper abdomen, and a small number are accompanied by gastric ulcers, manifested as eating pain. The fourth part is the late stage symptoms, mainly characterized by upper abdominal pain, but the degree and frequency of pain increase, accompanied by vomiting blood, black stools, cachexia, etc. Black stools are accompanied by bleeding. If the amount of bleeding is large, it manifests as vomiting blood and weight loss. In addition, there are usually accompanying symptoms. If the cancer cells are located at the entrance of the stomach, there may be swallowing difficulties; If located at the exit, there is nausea and vomiting; If transferred to the liver, it can cause swelling and pain in the upper right abdomen; If transferred to the peritoneum, ascites may appear.

2.2. Causes

2.2.1. Age growth

As the human body ages, the likelihood of cancer occurring is as follows: Firstly, long-term exposure to carcinogenic factors: As the body ages, the duration of exposure to carcinogenic factors in the environment increases. These carcinogenic factors may include poor dietary habits, smoking, drinking alcohol, environmental pollution, etc., which may increase the risk of developing GC in the long run; Secondly, the damage and repair ability of the gastric mucosa decrease: the gastric mucosa is an important protective layer of the stomach, but as age increases, the self repair ability of the gastric mucosa will gradually decline; Furthermore, aging often accompanies a decline in the body's immune system, which weakens the body's ability to clear cancer cells and increases the probability of developing

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GC; Finally, due to the influence of genetic factors, the role of genetic factors in the development of GC may gradually become apparent with age. People with a family history of GC may increase their risk of developing it as they age [3].

2.2.2. Poor lifestyle habits

Poor lifestyle habits can also greatly lead to cancer. Firstly, long-term consumption of high salt, high sugar, high fat, and low fiber foods, as well as excessive reliance on pickled and smoked foods, may increase the risk of GC. These foods may contain carcinogens such as nitroso compounds and polycyclic aromatic hydrocarbons, and insufficient intake of fresh vegetables and fruits can also increase the risk of stomach cancer. Secondly, frequent overeating or liking to eat dry, hard, or hot foods, as well as unhealthy eating habits such as eating too quickly, can cause damage to the gastric mucosa and increase the risk of GC in the long run; Furthermore, smoking has been proven to be one of the important risk factors for GC. The harmful substances in smoke can directly or indirectly cause damage to the gastric mucosa, increasing the risk of developing GC; Moreover, long-term excessive drinking, especially red wine and Baijiu, may increase the incidence of GC. Alcohol can directly stimulate the gastric mucosa, cause damage, and may promote the growth of cancer cells; Finally, long-term lack of exercise may lead to obesity and an increased risk of stomach cancer. The relationship between obesity and GC may involve multiple mechanisms, including insulin resistance, inflammatory response, etc.

3. Current research status of GC drugs

3.1. Case analysis of first-line medication

3.1.1. Fluorouracil and oxaliplatin

Oxaliplatin is a third-generation platinum based anticancer drug, and its pharmacological effects are not fundamentally different from other platinum based drugs. Both drugs target DNA and achieve inhibition of cancer cells through cross coupling, antagonism, replication, and transcription of platinum atoms with DNA. Generally speaking, oxaliplatin can be used alone in combination with fluorouracil to treat advanced GC, etc. Oxaliplatin is classified as other anticancer drugs with cytotoxic effects, with ATC number L01XA03, and is a novel platinum based anticancer drug. Among them, platinum atoms combine with 1,2-diaminocyclohexane and an oxalate group to form a single corresponding structure, namely cis oxalic acid (trans-1,1,2-DACH) platinum. The form of this drug is a white or almost white freeze-dried loose block, which can be used for adjuvant treatment of various primary tumors after complete resection or for the treatment of advanced primary tumor diseases. At present, the clinically proven pharmacological and toxicological effects of oxaliplatin have shown broad-spectrum in vitro cytotoxicity and in vivo anti-tumor activity in various tumor model systems, including gastric and colon cancer. In vivo and in vitro studies have confirmed that oxaliplatin is still effective even in cisplatin resistant tumor models. This study focuses on the short-term efficacy and prognostic effects of oxaliplatin combined with fluorouracil in the treatment of advanced GC. Sixty GC patients admitted to the Oncology Department of Nanping Second Hospital in Fujian Province from January 2017 to May 2018 were selected and randomly divided into oxaliplatin+fluorouracil group and cisplatin+fluorouracil group using a random number table method, with 30 cases in each group. There was 1 male and 13 female in the oxaliplatin+fluorouracil group, with inclusion criteria as follows:

1) Patients diagnosed with advanced GC were found to have metastatic cancerous lesions through endoscopic, X-ray barium meal, and PET-CT examinations; 2) Patients who only receive the treatment chosen in this study during the treatment period; 3) The patient's liver and kidney functions have not been damaged, the bone marrow hematopoietic function is normal, and there is no coagulation dysfunction; 4) Patients and their families can fully cooperate with medical staff, sign informed consent forms, and have high compliance; 5) The hospital ethics committee has approved this study after multiple considerations.

Exclusion criteria:

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1) Patients with early GC; 2) Patients who are allergic to the drugs used in this study, such as oxaliplatin and fluorouracil; 3) Patients who underwent total gastrectomy and radiation therapy at the same time; 4) Patients who lack sufficient understanding of modern medicine and have unrealistic fantasies about treatment outcomes; 5) Patients with poor compliance and inability to actively cooperate with our hospital's medical staff during treatment; 6) Patients with severe cardiovascular and cerebrovascular diseases, severe liver and kidney dysfunction, and coagulation dysfunction.

Patients received cisplatin+fluorouracil treatment.

1) Cisplatin for injection, with a general dose calculated based on body surface area as 20 mg/m2, is intravenously injected once a day for 5 consecutive days, considered as one course of treatment; Alternatively, intravenous injection at a dose of 30 mg/m2, once a day for 3 consecutive days, is considered as one course of treatment, and appropriate hydration diuretic treatment is required. High dose: intravenous infusion of 80-120 mg/m2, once every 3-4 weeks (twice is a course of treatment), with a maximum dose standard not exceeding 120 mg/m2. To reduce the toxic effects of cisplatin on the kidneys, sufficient hydration is required before use.

2) Fluorouracil Injection [produced by Shenyang Yaoda Pharmaceutical Co., Ltd., national drug approval number H21023380, specification: 10 ml: 40 mg (fluorouracil)] Usage and Dosage: intravenous infusion, initial dose of 80 mg per day, gradually increasing the dose thereafter, with a maximum daily injection dose not exceeding 160 mg. Before use, the corresponding dose of fluorouracil should be mixed with 500 ml of physiological saline, mixed evenly, and then intravenous drip should be administered [4].

The speed should be controlled at 50 drops/min, and the maximum speed should not exceed 60 drops/min, once a day. The total amount of fluorouracil used in one course of treatment should be controlled between 3-4 g; After one course of treatment, the patient needs to rest for 1-2 weeks before proceeding to the next course of treatment, with no changes in dosage or method. Oxaliplatin+fluorouracil group: Patients were treated with oxaliplatin combined with fluorouracil, with the same dosage and dosage of fluorouracil as the cisplatin+fluorouracil group. Oxaliplatin Injection (produced by Shenzhen Haiwang Pharmaceutical Co., Ltd., national drug approval number H20031048, specification: 20 ml: 40 mg) is calculated as 130 mg/m2 based on body surface area. The intravenous infusion time of 250-500 ml of 5% glucose injection is 2-6 hours. If the patient does not feel any discomfort or toxic effects, the medication should be administered once every 21 days, twice as a course of treatment, for a total of 2 courses of treatment.

The final result showed that the tumor control rate of the cisplatin+fluorouracil group reached 73.33%; The tumor control rate of the oxaliplatin+fluorouracil group reached 76.67%, and among advanced GC patients, the one-year survival rate of the cisplatin+fluorouracil group was 63.33%, while the one-year survival rate of the oxaliplatin+fluorouracil group was 66.67% [5].

3.1.2. Docetaxel and fluorouracil

Docetaxel is the main taxane anticancer drug used in clinical treatment of malignant tumors. It can prevent microtubule aggregation by inhibiting microtubule activity, and block cancer cell division and proliferation. Pathological types: 17 cases of mucinous adenocarcinoma, 14 cases of differentiated adenocarcinoma, and 9 cases of signet ring cell carcinoma. In the control group, there were 24 males and 16 females; Age range from 49 to 78 years old, with an average age of (58.97 ± 8.22) years; Pathological types: 16 cases of mucinous adenocarcinoma, 13 cases of differentiated adenocarcinoma, and 11 cases of signet ring cell carcinoma.

Before chemotherapy, the patients in both groups took dexamethasone 7.5 mg/time, twice a day, for 3 days to prevent water and sodium retention, and were given symptomatic treatment such as full hydration, anti allergy, and antiemetic. The chemotherapy regimen for the observation group patients is DSOX: intravenous infusion of 75mg/m2 docetaxel for 60 minutes on the first day of each course, and oxaliplatin at 130 mg/m2 for 180 minutes; On the 1st to 14th day, take oral Tegio 40mg/m2 twice a day. The chemotherapy regimen for the control group patients is DCF: intravenous infusion of docetaxel and cisplatin 75mg/m2 each for 60 minutes on the first day of each course; On the 1st to 5th day, intravenous

DOI: 10.54254/2753-8818/58/20241325

infusion of 500 mg/m^2 fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., National Medical Standard H31020593, specification: 10mL: 0.25g). 21 days is one course of treatment, and both groups of patients are treated for three courses. Observation indicator ①: Compare the clinical efficacy of two groups of patients. Evaluate the treatment effect of patients after 3 cycles of chemotherapy. Complete remission (CR): The lesion completely disappears, or at least disappears for 4 weeks; Partial remission (PR): The maximum diameter of the lesion decreases by ⩾ 30%; Stable condition (SD): reduced maximum diameter of lesion [6].

3.1.3. Platelet level combined with oxaliplatin and fluorouracil

All patients received chemotherapy with a combination of oxaliplatin and fluorouracil drugs. Oxaliplatin (Jiangsu Hengrui Pharmaceutical Co., Ltd., National Medical Approval No. H20000337): 130 mg/m2 was intravenously administered on the first day of chemotherapy. Fluorouracil drugs: 5-fluorouracil (Chongqing Yaoyou Pharmaceutical Co., Ltd., National Pharmaceutical Approval Letter H20010615) 500 mg · m-2, intravenous infusion on the first to fifth day of chemotherapy; Or take capecitabine tablets orally (Qilu Pharmaceutical Co., Ltd., National Pharmaceutical Approval Letter H20133361), 1000 mg · m-2, twice in the morning and evening, continuously for 14 days; Alternatively, oral administration of Tegio capsules (Jiangsu Hengrui Pharmaceutical Co., Ltd., National Pharmaceutical Approval Letter H20100135) is recommended. The initial dosage for patients is usually determined based on their body surface area, with a dosage of 2 times a day. For patients with a body surface area of less than 1.25 m2, the dosage is 40 mg per session, while for those with a body surface area of less than 1.5 m2, the dosage is 50 mg per session. For patients with a body surface area of more than 1.5 m2, the dosage is 60 mg per session. Continuous medication for 14 days. Three weeks is one course of treatment, and chemotherapy treatment is two courses.

Multivariate logistic regression analysis of the efficacy of oxaliplatin combined with fluorouracil chemotherapy, with oxaliplatin combined with fluorouracil chemotherapy efficacy as the dependent variable (Y), and single factor analysis selecting statistically significant factors as independent variables (X) for logistic regression analysis. The results showed that age>60 years old and peripheral blood platelet levels>280 × 109 L-1 were risk factors for the efficacy of oxaliplatin combined with fluorouracil chemotherapy in GC patients ($P<0.05$). Spearman correlation analysis showed that the peripheral blood platelet levels in GC patients were negatively correlated with the chemotherapy effect of oxaliplatin combined with fluorouracil ($r=-0.582$, $P<0.05$) [7].

3.2. Research on fluorouracil

Also known as 5-fluorouracil, with the chemical formula C4H3FN2O2, it is a pyrimidine analogue. Currently, common fluorouracil derivatives such as 2,4-ditrimethylsilane-5-fluorouracil and 2-phenylsulfonyl-4-trimethylsilane-5-fluorouracil are all non cyclic nucleoside derivatives. Deoxythymidine nucleotide is one of the four substrates in DNA replication, which is synthesized by deoxyuridine nucleotide and coenzyme 5,10-dimethyltetrahydrofolate under the catalysis of thymine synthase. The drugs that have been used in clinical practice and are currently in use include furfurouracil (II), difluorouracil (III), fluorouracil deoxyribonucleoside (IV), and carbamofur (V). Except for 5-fluorouracil deoxyribonucleoside, they have good lipophilicity and are conducive to penetrating tumor cells. They are hydrolyzed into 5-fluorouracil, which is then converted into 5-fluorouracil deoxyribonucleotide and 5-fluorouracil deoxyribonucleotide, and then inhibit thymidine synthase to exert therapeutic effects.

DOI: 10.54254/2753-8818/58/20241325

4. Introduction of the development theory of anti-GC drugs using a single drug as a primer

4.1. Fluorouracil drug needle for anti-GC drugs

4.1.1. The mechanism of action of cancer cells

Firstly, the production of cancer cells is often related to genetic and DNA mutations. These mutations may lead to the loss of normal growth regulation mechanisms in cells, leading to unrestricted proliferation. The proliferation mode of cancer cells is unrestricted mitosis, which means they can continuously undergo cell division, leading to the formation and expansion of tumors. Secondly, cancer cells have invasiveness and metastasis. They can invade blood vessels, lymphatic vessels, or body cavities through primary cells, and then transfer to other parts of the body through channels such as blood and lymph, where they continue to grow and reproduce. This ability to metastasize and spread makes cancer more difficult to treat and increases the risk of death for patients. In addition, cancer cells can also affect surrounding normal cells and tissues during their growth and spread. They may disrupt the structure and function of normal cells, leading to a decline in bodily functions. Meanwhile, cancer cells may also affect the body's immune system and metabolic processes by releasing some bioactive substances, further exacerbating the progression of the disease.

4.1.2. The mechanism of action of fluorouracil

Constructing a 5-Fu resistant cell model (AGS/5-Fu) by treating AGS cells with 5-Fu, detecting the effect of 5-Fu on AGS and AGS/5-Fu cell activity using CCK8 method, and detecting the expression of hsa-circ-002179 and miR-143-3p in cells using fluorescence quantitative PCR (qRT-PCR); Flow cytometry and Western blot were used to detect the levels of cell apoptosis and the expression of autophagy related proteins LC3, Beclin-1, and p62, respectively. Meanwhile, the binding site between hsa-circ-002179 and miR-143-3p was predicted through software, and its binding effect was verified through RIP and dual luciferase experiments. Compared with the control group, the cell activity (172.33 ± 9.53)% and autophagy level (106.00 ± 6.16)%, as well as the apoptosis rate (20.5% and 43.8%, $P<0.01$), and the expression of has-circ-002179 were increased in the resistant group [8].

5. Conclusion

This article found that fluorouracil drugs are cell cycle inhibitors that act on the cell cycle to inhibit cell division and eliminate cancer cells. They are also used as important chemotherapy drugs and are often used in combination with other anti-cancer drugs with significant effects. After analysis, it can be concluded that fluorouracil drugs have a relatively high-quality effect on the treatment of GC. At the same time, other research methods and theories for the treatment of GC drugs can be introduced based on fluorouracil drugs. In view of this study, I personally believe that the focus of research can be on the synergistic effects with other drugs and targeted drug delivery to reduce complications and losses. At the same time, early detection and judgment can be carried out in conjunction with clinical and other early detection methods. For this study, I hope to conduct more in-depth research in the direction of targeted drug delivery, while also combining it with other common complications and new era forward-looking technologies for research and treatment.

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