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Treatment of Advanced Gastric Carcinoma Patients with Calcium Folinate, a 5-Fluorouracil Bolus and Continous Infusion with 5-Fluorouracil Combined with Oxaliplatin

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OBJECTIVE To examine the therapeutic effects and toxicity of high-dose-folinic acid plus a 5-fluorouracil (5-FU) bolus and continuous infusion with 5-FU combined with locally produced oxaliplatin (L-HOP)in treating advanced gastric carcinoma patients.
METHODS Sixty-five patients with advanced gastric carcinoma were treated with high-dose-folinic acid plus a 5-FU bolus and a 48-h continuous infusion of 5-FU combined with oxaliplatin. The effects of treatment and toxicity were observed.
RESULTS There were 4 complete responses, 26 partial responses, 30 with no change and 5 with progressive disease. The overall effective response rate was 46.2% (30/65). The median duration was 7 months, with the main side effects including nausea and vomiting, peripheral phlebitis, alopecia, leukopenia, dental ulcers, peripheral neuritis and diarrhea. All the side effects were tolerated and minimal.
CONCLUSION The results showed that high-dose folinic acid plus a 5-FU bolus and continuous infusion of 5-FU combined with oxaliplatin appears to be a safe and effective therapy for patients with advanced gastric carcinoma. This therapeutic regimen is of value for these patients.

KEY WORDS: advanced gastric carinoma, calcium folinate, 5-fluorouracil, oxaliplatin, chemotherapy.

Introduction

In recent years[1,2], a regimen of calcium folinate, a 5-fluorouracil (5-FU) bolus and continous infusion of 5-FU combined with oxaliplatin has been extensively applied in therapy for advanced colorectal cancer. However the use of this treatment plan for gastric cancer is still rare. From September 2003 to August 2007, 65 patients with advanced gastric carcinoma were treated employing calcium folinate, 5-FU and oxaliplatin. The effects of treatment and toxicity were observed, and the value of the regimen was evaluated as described in this report.

Materials and Methods

Clinical materials

Sixty-five patients with advanced gastric carcinoma, who had received a pathological diagnosis of differentiated adenocarcinoma by surgery or gastroscopy, were employed in this study. These patients included 26 with poorly differentiated adenocarcinoma, 21 with mod-

erately differentiated adenocarcinoma and 18 with well-differentiated adenocarcinoma. Among these patients 37 were Stage III and 28 were Stage IV, 39 were male and 26 were female. The range of age was 21 to 63 years with a median age of 40. Other criteria for eligibility were a Karnofsky score > 60, a life expectancy > 3 months, normal cardiac and renal function, normal blood cell count and no allergies. All the patients received no other anti-tumor treatment for nearly 1 month.

Treatment plan

L-HOP (oxaliplatin, made in the Herui Pharmaceutical Co. Ltd in Jiangshu, brand name: Aihe, 50 mg/bot) 130 mg/m^2 i.v.gtt. (2 h), d 1, CF (calcium folinate) 200 mg/m^2 + 5% dextrose 500 ml, i.v.gtt. (2 h), 5-FU 0.5 g iv (10 min) (after finishing CF iv drip) and L-HOP with 5-FU 3 g/m^2 continuous infusion for 48 h. Treatment was repeated every 21 days (one cycle). Each patient was treated with 2 cycles or greater than 2 cycles. There were 195 cycles in all, including 20 patients who were treated with 2 cycles, 25 patients with 3 cycles and 20 patients with 4 cycles.

Evaluation standards of effects and toxicity

Complete response (CR): the lesion completely disappeared after treatment and for more than 4 weeks, no new lesion appeared; partial response (PR): the lesion was reduced more than 50% prior to treatment and remained as such more than 4 weeks with no new lesions appearing; no change (NC): the lesion showed no significant change, including lesions which were reduced less than 50% or increased less than 25%; progressive disease (PD): the lesion increased more than 25% or a new lesion appeared. CR and PR were considered to be effective in the regimen; paracme: the time from judged CR or PR to tumor's recidivation and progression. Toxicities were scored as 0~IV grade according to the common toxicity criteria of the WHO.

Method of observation

A comprehensive medical examination and a detailed record of changes in the lesion during treatment were recorded as follows: routine blood, sedimentation and urine tests, hepatic and renal function, electrocardiogram, abdominal B-type ultrasonography or CT, chest X-ray or CT were conducted prior to each treatment cycle. The blood cell count was examinated once during treatment. Hepatic and renal function, electrocardiogram, abdominal B-type ultrasonography or CT, chest X-ray or CT were rechecked after every cycle of chemotherapy, and the toxicity which developed in each cycle was recorded. Decisions regarding the nature of the treatment were based on the results of the patient imaging.

Result

Efficacy

Sixty-five patients with gastric carcinoma were treated with 195 cycles in all (average treatment was 3 cycles). The overall effective response rate for the 65 patients evaluated was 46.2% (30/65), including 4 complete responses (CR), 26 partial responses (PR), 30 no change (NC) and 5 progressive diseases (Table 1). The average of paracmasis was 7 months.

Table 1. Efficacy of treatment.

Case	CR	PR	NC	PD	CR+ PR
65	4	26	30	30	30(46.2%)

Toxicity

Table 2 shows the toxic effects of the regimen, which were mainly Grade I~II, including nausea, vomiting, peripheral phlebitis, alopecia, leukopenia, dental ulcer, peripheral neuritis and diarrhea. The rates of these effects were as follows: nausea/vomiting, 93.9%; peripheral

Table 2. Toxicity of treatment (cycles of chemotherapy: 195)

Toxicity	0	I	II	III	IV
Nausea/vomiting	13 (6.2)	118 (60.5)	38 (19.5)	27 (13.9)	0 (0.0)
Peripheral neuritis	99 (50.8)	51 (26.2)	30 (15.4)	15 (7.7)	0 (0.0)
WBC-descent	58 (29.7)	59 (30.3)	54 (27.7)	22 (11.3)	2 (1.0)
Dental ulcer	89 (45.6)	62 (31.8)	28 (14.4)	16 (8.2)	0 (0.0)
Diarrhea	113 (58.0)	59 (30.3)	23 (11.8)	0 (0.0)	0 (0.0)
Peripheral phlebitis	18 (9.2)	59 (30.3)	50 (25.6)	46 (23.6)	22 (11.3)
AlopeciA	43 (22.1)	64 (32.8)	57 (29.2)	31 (15.9)	0 (0.0)
PLT-descent	140 (71.8)	32 (16.4)	16 (8.2)	7 (3.6)	0 (0.0)
Electrocardiogram	153 (78.5)	29 (14.9)	13 (6.7)	0 (0.0)	0 (0.0)
Hepatic function damage	178 (81.3)	10 (5.1)	7 (3.6)	0 (0.0)	0 (0.0)
Renal function damage	184 (94.4)	9(4.6)	2 (1.0)	0 (0.0)	0 (0.0)

phlebitis, 90.8%; alopecia, 78.0%; leukopenia, 70.3%, including Grade I~II; 58.0%, Grade III; only 11.3% and Grade IV; only 1.0%. The rate of dental ulcers was 54.4%, peripheral neuritis was 49.2% and diarrhea was 42.0%.

Discussion

Gastric carcinoma is one of the most common malignancies, and China has one of the world's highest rates, with about 35% of the worldwide cases. There are more than 260,000 cases in China per year, and about 20% of these patients die from this disease. Deaths from gastric carcinoma accounts for the most cancer deaths in China's rural areas, and the second cause of deaths in cities.

Chemotherapy is the main therapeutic means for advanced gastric carcinoma, which is relatively sensitive to treatment, but at present there is no ideal standard combination chemotherapy for this cancer. An ideal chemotherapeutic regimen for gastric carcinoma has been a goal for oncologists[3].

5-FU is a common chemotherapeutic agent for intestinal malignancies, but its effect is only about 20%. It is known that CF can increase the antitumor efficacy of 5-FU. CF has no antitumor efficacy itself, but it can provide exogenous methylenetetrahydrofolate which can enhance the enzymatic inhibition and interfere with DNA synthesis resulting in greater antitumor efficacy of 5-FU. CF plus 5-FU has been extensively used to treat gastrointestinal malignancies. In recent years, the study of continuous infusion of 5-FU to treat tumors has been of major concern. In 1984 the GERCOD contribution group, which was leaded by de Gramont[4] from France, conducted a clinical study of the therapy of colorectal cancer. They found that high-dose folinic acid plus continuous infusion of 5-FU for 48 h could enormously enhance the activity of 5-FU and reduce toxicity. The study indicated that continuous infusion of 5-FU had several advantages over a single administration as follows: *i*) 5-FU is a cell-cycle specific agent, with a short (10~20 min) life, so its action is time-dependent. Continuous infusion subjects more tumor cells in the S phase to 5-FU which is the phase sensitive to 5-FU. *ii*) It reduces the days of using 5-FU in every cycle, thus avoiding the accumulation of drug toxicity and reducing 5-FU toxicity. *iii*) It can enhance the dose intensity of 5-FU[5,6]. In comparing continuous infusion of 5-FU with a bolus administration, one meta analysis confirmed that continuous 5-FU enhanced the tumor remission rate and improved the overall survival of the patients[7].

Oxaliplatin (L-OHP) is a new anti-cancer third-generation platinum derivative, which at present is useful in clinical applications. Compared with cisplatin, the toxicities of L-OHP are minimal. With routine-doses of L-OHP, there is no need to hydrate the patients and there have been no cases of heart injury or severe hearing impairment[8,9]. However, single-agent activity was reported to result in lower response rates in gastroenteric tumor patients. A regimen of 5-FU combined with oxaliplatin enhanced the effective response[10,11]. In recent years, a regimen of L-OHP combined with a high-dose folinic acid plus 5-FU for the treatment of gastric cancer has been thoroughly tested confirming its efficacy[12,13]. In our study, the overall effective response rate for the 65 patients with advanced gastric carcinoma was 46.2% (30/65), similar to reports from abroad[14-18].

The main toxicities that developed with our regimen were nausea, vomiting, peripheral phlebitis, alopecia, leukopenia, dental ulcers, peripheral neuritis and diarrhea. Although the rate of nausea/vomiting was 93.9%, most of patients were relieved after receiving a 5-HT3 receptor antagonist, which did not affect the mode of treatment. The rate of peripheral phlebitis was 90.8%, but most of the patients improved after application of hydropathic compresses with Yunan white powder plus alcohol. The rate of alopecia was 78.0%, but without development of IV alopecia. Leukopenia developed as follows: overall, 70.3%, Grade I~II 58.0%, Grade III only 11.3% and Grade IV only 1.0%. With G-CSF or GM-CSF treatment, the white blood cells increased to values in the normal range. Temporary peripheral neuropathy developed with the main symptoms of acroparesthesia and Grade I-II sensitivity to a cold stimulus. There was no neurotoxicity and these symptoms abated quickly with reducing dosage of the regimen. There were no deaths related to the chemotherapy in the study.

Our results showed that a regimen of high-dose folinic acid plus a 5-FU bolus with continuous infusion of 5-FU combined with locally produced oxaliplatin appears to be a safe, effective, first-line treatment with minimal toxicity for advanced gastric carcinoma patients.

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