Clinical Research on Use of Oxaliplatin in Combination with HCPT, LV and 5FU in a Regimen for Advanced Gastric Cancer

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OBJECTIVE To observe the effects and adverse reactions of a OXA-HCPT LV / 5FU 3 regimen for patients with advanced gastric cancer.

METHODS OHLF 3 regimen: OXA 130 mg/m^2 iv d 1, HCPT 6 mg / m^2, iv d 1~5, LV 200 mg/ m^2 iv 2 h followed by a 5FU 400 mg/m^2 iv bolus and 5FU 600 mg/m^2 iv d 1~3, were given, every 21 days as 1 cycle. Assessment of the tumor was conducted after 3 cycles and the effective cases were confirmed after 4 weeks.

RESULTS Among 39 patients, 36 were actually evaluable. Overall response rates (CR + PR) were 50% ; the major adverse reactions were mild hematological toxicity, nausea and vomiting and peripheral nerve abnormalities.

CONCLUSION The OHLF 3 regimen using OXA and HCPT is effective and results in mild toxicity when used in combined chemotherapy for advanced gastric cancer.

KEYWORDS: oxaliplatin, HCPT, advanced gastric cancer, OHLF 3 regimen.

Combination chemotherapy plays an important role in the comprehensive treatment for advanced gastric cancer. [1] 5-Fluorouracil (5FU), mitomycin (MMC) and adriamycin (ADM) were traditionally administrated chemotherapy agents, but the efficacy of single drug is rather low, not exceeding 15%, and the efficacy of a combined FAM regimen is only 30% . So research on new chemotherapy drugs for advanced gastric cancer is needed. Oxaliplatin, the new third generation platinic drug, is considered to be one of the most promising drugs in treating advanced gastric cancer. It is also one of the agents of great interest in present chemotherapy study. In our study, a combination chemotherapy regimen of OXA plus HCPT, 5FU and LV was administrated in the treatment of 39 cases of advanced gastric cancer; good efficacy was achieved and is reported as follows.

MATERIALS AND METHODS

General data

The 39 cases of advanced gastric cancer were patients admitted and

treated in the 10 hospitals included in the National Multicenter Clinical Research from November 2001 to October 2002.

Inclusion criteria

1)With definitively confirmed pathological diagnosis. 2) Ages between 20 and 75 years, KPS scale ≥ 70 scores, with expected survival time > 3 months. 3) With at least one objectively measurable tumor focus, gastroscopy examination was compulsory before and after treatment for patients with primary gastric lesions, CT scan was the first option for metastatic foci. Tumor diameter was ≥ 2 cm, if < 2 cm, pathological or cytological examinations were needed to verify the diagnosis. 4) Patients receiving treatment for the first time were of prior choice. For retreated patients, latest chemotherapy was at least 1 month before and confirmed to be ineffective. For retreated patients, a combination of drugs which were the same as this regimen was not considered optimal and patients who were treated with HCPT and OXA with failed efficacy were excluded. 5) Without cardiac, hepatic, renal or hematological dysfunctions. Laboratory examinations: Hb > 90 g/L, WBC > 4.0×10^9/L, ANC > 2.0×10^9/L, TBIL ≤ double the upper limit of the normal range, Cr ≤ 1.5 times the upper limit of the normal range. 6) All patients gave written informed consent and a received follow-up visits.

Inclusion condition

Thirty-nine patients with biopsy-proven advanced gastric cancer were enrolled in our study, 30 were male, and 9 were female; ages between 28 and 73 years, median age 57 years. Previously untreated 22 cases and 17 retreated cases; 15 cases were poorly differentiated adenocarcinoma, 8 were moderately differentiated adenocarcinoma, 4 were tubular adenocarcinoma, 8 were adenocarcinoma, 2 were mucinous cell carcinoma, 1 was signet-ring cell carcinoma and 1 was gastric remnant carcinoma. Twenty cases had a solitary metastatic focus, while 17 had multiple metastatic foci (double foci in 14 cases, 3 foci in 2 cases and 5 foci in 1 case). The locations of the metastatic foci in the patients were 19 in the liver, 3 in the lungs, 15 in the lymph nodes and 8 in other sites (including bone, ovary, pancreas, etc.).

Exclusion condition

Among all 39 cases, 1 patient withdrew from the treatment after 1 complete cycle of chemotherapy, 1 patient who received no efficacy was evaluated after 2 complete cycles of treatment, and 1 patient who was previously treated with oxaliplatin were patients who did not meet the inclusion criteria and were excluded. Thirty-six cases were eligible for the study, while all 39 cases could be enrolled in ITT to evaluate life quality.

Chemothearpy regimen

OHLF 3 regimen: OXA 130 mg/m^2 iv d 1, HCPT 6 mg / m^2, iv d 1~5, LV 200 mg/ m^2 iv 2 h followed by 5FU 400 mg/m^2 iv bolus and 5FU 600 mg/m^2 iv 22 h continuously d 1~3, were given, every 21 days as 1 cycle. Tumor assessment was conducted after 3 cycles and the effective cases were confirmed after 4 weeks. Treatment efficacy was evaluated by WHO assessment criteria when 3 cycles were completed. For patients achieving a complete response (CR) or partial remission (PR), treatment efficacy was confirmed after 4 weeks. Oxaliplatin was manufactured by Nanjing Pharmaceutical Co. Ltd and HCPT manufactured by Huangshi Feiyun Pharmaceutical Co. Ltd.

Evaluation of responses

Short-term efficacy estimation was conducted by referring to the WHO solid tumor treatment efficacy evaluation criteria (1981): complete response (CR), partial respone (PR), mild response (MR), stable disease (SD), progressive disease (PD). CR+PR were considered response-positive and the effective cases were confirmed after 4 weeks.

Evaluation of adverse reactions

Toxic side effects were assessed according to common toxicity criteria proposed by the National Cancer Institue (NCI), USA. When evaluating sensory nerve toxicity, the NCI scale and Losadin□ specific criterion were adopted.

RESULTS

Short-term efficacy

Of all the 39 patients enrolled, 36 cases (92.3%) were eligible for the study. On average, 3.2 chemotherapy cycles were completed, the total response rates were 50%. Among the cases 2 showed CR, 16 PR, 2 MR, 9 SD and 7 PD. Treatment efficacy analysis for previously untreated patients (first-line) and retreated patients (second-line) revealed that for the 36 patients, outcomes for previously untreated were distinctly better than retreated cases, 2 patients had CR of which both were previously untreated (see Table 1). In addition, after administrating the OHLF3 regimen, good efficacy was observed for liver and lymph nodes metastatic lesions, the response rates were 52.6% and 60.0% respectively. In 2 cases the hepatic metastases disappeared and in 1 case the lymph node metastases disappeared (see Table 2).

Quality of life (QOL)

The Karnofsky (KPS) scale was employed to carry out Intension to Treat (ITT) analysis. We found 76.58± 12.95 scores before treatment and 81.58 ± 12.09 scores after the chemotherapy, QOL scale, 44.03 ± 7.76 scores before treatment and 47.55± 7.85 scores after the chemotherapy. The data were analyzed by the *t*-test, finding that *t* values were 0.001 and 0.014 respectively, thus showing a statistical difference and an indication of improvement in the quality of life after chemotherapy.

Adverse reactions

The major adverse reactions of the OHLF 3 regimen were hematological toxicity; leucopenia was the most common effect. In 1 case grade Ⅳ leucopenia and neutropenia were observed (see Table 3). Sensory nerve toxicity and nausea/vomiting were the second most common adverse effects, reaching mainly grade Ⅱ to grade Ⅲ. Diarrhea, stomatitis and alopecia were not occurred, but were mild (see Table 4).

DISCUSSION

Since curing advanced gastric cancer is difficult, the treatment is mainly palliative chemotherapy. In the middle of the 1980s, the regimen most commonly used of FAM (5FU, ADM, MMC) which showed a poor response rate, only about 30% . Some researchers reported the chemotherapy regimen of EAP (VP-16, ADM, DDP), achieved a efficacy of 64% for advanced gastric cancer. Howerve that treatment resulted in a grade Ⅲ to grade Ⅳ bone marrow suppression rate as high as 60%, which most patients could not tolerate. So to treat advanced gastric cancer, it is critical to explore new combined chemotherapy regimens with reliable efficacy and low toxicity.

Oxaliplatin is a new third generation platinic drug. In tumor cells its target sites are identical to cisplatin, while in its chemical structure, the amidogen of cisplatin is replaced by a diamino- hexamethylene radical. Its combining rate is over 10 times higher than

Table 1. Short-term treatment responses of OHLF regimen cases (%)

Classifications	Case	CR	PR	MR	SD	PD	CR+PR
Total	36	2(5.5)	16(44.4)	2(5.5)	9(25.0)	7(19.4)	(50.0)
First treatment	21	2(9.5)	10(47.6)	2(9.5)	4(19)	3(14.3)	(57.1)
Retreatment	15	0(0)	6(40)	0(0)	5(33.3)	4(26.7)	(40.0)

Table 2. Short-term responses for liver and lymph nodes metastatic foci cases (%)

Metastatic foci	Case	CR	PR	MR	SD	PD	CR+PR
Liver	19	2(10.5)	8(42.1)	2(10.5)	4(21.0)	3(15.8)	10(52.6)
Lymph nodes	15	1(6.7)	8(53.3)	0(0)	4(6.7)	2(13.3)	10(60.0)

Table 3. Hematological adverse reactions of OHLF 3 regimen in treating advanced gastric cancer cases (%)

Adverse reactions	Grade0	Grade I	Grade II	GradeIII	GradeIV	Grade I ~IV
Hb decrease	17(47.2)	9(25.0)	7(19.4)	3(8.3)	0(0)	19(52.8)
WBC decrease	12(33.3)	9(25.0)	11(30.6)	3(8.30	1(2.8)	24(66.7)
Neutropenia	16(44.4)	5(13.9)	10(27.8)	4(11.1)	1(2.8)	20(55.6)
Pt decrease	26(72.2)	6(16.7)	4(11.1)	0(0)	0(0)	10(27.8)
Bleeding	36(100)	0(0)	0(0)	0(0)	0(0)	0(0)

Table 4. Non-hematological adverse reactions of OHLF 3 regimen in treating advanced gastric cancer cases (%)

Adverse reactions	Grade0	Grade I	Grade II	GradeIII	GradeIV	Grade I ~IV
Nausea	7(19.4)	17(47.2)	10(27.8)	2(5.6)	0(0)	29(80.6)
Vomiting	18(50.0)	9(25.0)	7(19.4)	2(5.6)	0(0)	18(50.0)
Diarrhea	20(55.6)	6(16.7)	10(27.8)	2(5.6)	0(0)	16(44.4)
Stomatitis	20(55.6)	12(33.3)	3(8.3)	1(2.8)	0(0)	16(44.4)
Pyrexia	36(100)	0(0)	0(0)	0(0)	0(0)	0(0)
Alopecia	21(58.3)	9(25.0)	5(13.9)	5(13.9)	0(0)	15(41.7)
Skin	34(94.4)	2(5.6)	0(0)	0(0)	0(0)	2(5.6)
Sensory nerve	12(33.3)	16(44.4)	7(19.4)	7(19.4)	1(2.8)	24(66.7)
Motor nerve	29(80.5)	4(11.1)	2(5.6)	0(0)	1(2.8)	7(19.4)
Hepatic dysfunction	35(97.2)	1(2.8)	0(0)	0(0)	0(0)	1(2.8)
Renal dysfunction	36(100)	0(0)	0(0)	0(0)	0(0)	0(0)
Miscellaneous	36(100)	0(0)	0(0)	0(0)	0(0)	0(0)

cisplatin, its binding to target sites firmer, and cytotoxicity stronger. In addition it shows enhanced or a synergic effect with 5FU and many other chemotherapy drugs. In December 2002, Louvet et al. reported on a phase II clinical study in which the FOLFOX regimen consisting of OXA in combination with 5FU and LV for advanced gastric cancer was effective, the total response rate being 42.5%.[2] The total response rates of this regimen reported by researchers abroad were between 46% and 63%.[3-6] Furthermore Jin et al. reported a response rate of 42.5% for a FOLFOX regimen in treating advanced gastric cancer.[7]

HCPT is a drug that can act selectively on topoisomerase I to interfere with replication of DNA. The action site is specific and it has less drug resistence, as topoisomerase I is abundant in adenocarcinoma cells. In China, numerous studies are being conducted on the efficacy of the HCPT treatment regimen for gastrointestinal tumors. When it was solely used for gastric cancers, the response rate was reported to be 20%, but if used in combination with 5FU and ADM, the response rate was reported to be 30% to 50%.[8,9] In using the OHLF 3 regimen, oxaliplatin can bind to DNA to form a complex, yet topoisomerase I can undo this combination to free the DNA by excision repair. HCPT can suppress activity of topoisomerase I, so if given in combination, the effect of oxaliplatin can be enhanced resulting in a synergic effect. In China, Yang et al. reported on clinical research using oxaliplatinin in combination with the HCPT regimen for 24 advanced gastric cancer patients. The response rate was as high as 58.4%,[10] a result which drew extensive attention. The efficacy of chemotherapy regimens mainly comprised of oxaliplatin or HCPT is not less than a traditionally used regimen of DDP, ADM, 5FU combination, and the total response rate of the ECF-L regimen (comprised of epirubicin, calcium leucovorin, fluorouracil and cisplatin) reported by Chen was

33.3% for advanced gastric cancer.[11] The OHLF 3 regimen designed in our study was an application of the HCPT based on the FOLFOX regimen; the total efficacy was 50%, which was higher than the FOLFOX regimen. Besides, in this study, good efficacy of the OHLF3 regimen was observed for metastatic foci in liver and lymph nodes, the evaluated total response rates were 52.6% and 60.0% respectively. Among our patients, after treatment secondary tumors sites were eliminated in 2 cases with hepatic metastatic foci, and in 1 case with lymph nodes metastatic foci (these patients achieved CR). The elimination of the hepatic metastatic foci should receive further consideration. But the number of cases enrolled in this study were not sufficient to draw conclusions; so on this issue more research with a larger number of cases needs to be conducted.

The noteworthy adverse reactions of the OHLF 3 regimen were mild. These were mainly hematological toxicity, nausea and vomiting, mostly at grade Ⅰ to grade Ⅱ, suggesting that all patients showed favorable tolerance. One case developed abnormal liver function; no renal or cardiac toxicity was observed. Compared with the traditionally used FAM regimen, this regimen is more optimal for advanced cancer patients when drugs with an anthracene base are contraindicated, and treatment efficacy improved dramatically. Peripheral nerve toxicity was relatively common(66.7%), which is considered to be associated with oxaliplatin treatment. This was exacerbated in a condition of cold exposure mainly at a level of grade Ⅰ to grade Ⅱ, but alleviated spontaneously and caused no interruption in the treatment. In addition, diarrhea (44.4%), stomatitis (44.4%) and alopecia (41.7%) were also common adverse reactions, mostly at grade Ⅰ to grade Ⅱ. In conclusion, all patients showed good tolerance and were able to complete all treatments successfully. With regard to the improvement of the quality of life, KPS and QOL scores showed elevation after treatment.

In general, efficacy of the OHLF 3 regimen justifies its use in treatment for advanced gastric cancer, because it is relatively effective and the specific nerve toxicity, and other adverse reactions are rather mild. So its use is warranted in a combined chemotherapy regimen for advanced gastric cancer, a treatment that deserves further clinical research and more utilization. With the clinical application of new chemotherapeutic drugs such as Taxol, Taxotere and Xeloda, and a renewed understanding of radiotherapy for the treatment of gastric cancer protocols, advanced gastric cancer therapy is developing rapidly. Howerver, since the ultimate rational and effective strategy is still needed, further exploration for treating this cancer is required.

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