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ORIGINAL ARTICLE

Efficacy of paclitaxel and S-1 combined with apatinib in the conversion therapy for unresectable advanced gastric cancer

Zhongping Wu[1], Haixing Fang[2]

[1]Department of Oncological Surgery, The First People's Hospital of Fuyang, Hangzhou, China. [2]Department of Hepatobiliary Surgery, The First People's Hospital of Fuyang, Hangzhou, China.

Summary

Purpose: *To explore the safety and effectiveness of paclitaxel and tegafur, gimeracil and oteracil potassium (S-1) combined with apatinib in the conversion therapy for unresectable advanced gastric cancer.*

Methods: *A total of 66 patients with advanced gastric cancer received treatment with paclitaxel + S-1 + apatinib. Patients evaluated as resectable advanced gastric cancer by the multiple disciplinary team (MDT) underwent the surgery. The clinical efficacy and adverse reactions of the patients receiving conversion therapy and the related indicators of those undergoing operation were recorded. Later, the survival of the patients was compared between successful conversion therapy (surgery) group and unsuccessful conversion therapy (non-surgery) group.*

Results: *All the 66 patients completed 3-7 cycles of chemotherapy, with a median of 5 cycles, and the objective response rate (ORR) after conversion therapy was 71.2% (47/66). Among them, 48 patients received operation for (225.2±37.3) min on average, with the intraoperative blood loss of (168.2±40.9) mL and (50.9±12.3) intraoperative dissected lymph nodes, including 34 (70.8%) cases of R0 resection. According to the postoperative pathological tumor regression grading (TRG), there were 2 (4.2%) TRG 0 cases, 10 (20.8%) TRG 1 cases, 28 (58.3%) TRG 2 cases and 8 (16.7%) TRG 3 cases. The follow-up results revealed that the one-year overall survival (OS) of the patients was 93.8% (45/48) in successful conversion therapy (surgery) group and 61.1% (11/18) in unsuccessful conversion therapy (non-surgery) group.*

Conclusion: *Paclitaxel and S-1 combined with apatinib can achieve a higher R0 resection rate, and improve the survival rate of patients with successful conversion therapy, showing high safety and efficacy.*

Key words: *apatinib, paclitaxel, S-1, gastric cancer, advanced, conversion therapy*

Introduction

Gastric cancer, one of the most frequently seen malignant tumors in China, ranks 2nd and 3rd in terms of morbidity and mortality rates among all malignant tumors. In gastric cancer cases, locally advanced gastric cancer cases take up about 70-80% [1]. As new targeted drugs emerge and the results of a number of clinical trials of perioperative chemotherapy are published in recent years, patients with advanced gastric cancer that was previously unresectable can acquire an opportunity of R0 surgical resection by preoperative radiotherapy and chemotherapy, which can prolong their survival [2,3]. Hence, more and more attention has been paid to the conversion therapy of stage IV gastric cancer.

Apatinib, a small molecule drug resisting angiogenesis, achieves positive results in advanced gastric cancer that fails to be treated by second-line therapy, indicating that applying apatinib in advance in the treatment of advanced gastric cancer may be more beneficial for these patients [4-6].

In this study, patients with advanced gastric cancer received conversion therapy of paclitaxel

Corresponding author: Zhongping Wu, BM. Department of Oncological Surgery, The First People's Hospital of Fuyang, 429 Beihuan Rd, Fuchun Street, Hangzhou 311400, China.
Tel: +86013868181904; Email: 13868181904@139.com
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and S-1 combined with apatinib, and the efficacy, surgical resection and survival of the patients were observed to investigate the safety and effectiveness of the conversion therapy in treating unresectable advanced gastric cancer.

Methods

General data

The clinical data of 66 patients with unresectable advanced gastric cancer treated with conversion therapy were analyzed retrospectively. Inclusion criteria were as follows: patients diagnosed with gastric adenocarcinoma by gastroscopy and biopsy before operation, those with stage IV gastric cancer that was unresectable due to at least one of the following factors: liver metastasis (n=14), peritoneal metastasis (n=15), ovarian metastasis (n=5), extensive fusion of cN3 (n=17), lymph node metastasis in the 16th group (n=13) and pancreatic invasion (n=2), those with at least one measurable lesion, and those whose survival period was estimated to be over 3 months. Exclusion criteria were as follows: patients with Her-2 positive gastric cancer, those who could not tolerate chemotherapy because of serious basic diseases, such as gastrointestinal bleeding or hypertension, those who were unable to eat orally, or those with other serious basic diseases or malignant tumors. The baseline data including age, gender, tumor location, tumor pathological type and Lauren classification of all patients are displayed in Table 1. In compliance with the *Declaration of Helsinki*, all the patients were informed of the study, and they signed the informed consent form. This study was approved by the ethics committee of The First People's Hospital of Fuyang.

Treatment methods

Conversion therapy referred to apatinib (500 mg, qd) + paclitaxel (50 mg/m^2 iv, 20 mg/m^2 ip, d1, d8, q3w) + S1 (60 mg, bid, d1-d14) chemotherapy. The application of apatinib was terminated at 1 cycle before operation.

The evaluation of multiple disciplinary team (MDT) confirmed that all the patients were resectable cases, who underwent one more cycles of chemotherapy with no apatinib and received surgical treatment after at least two cycles of the last chemotherapy. Operation method: After laparoscopic exploration confirmed no peritoneal metastasis to the naked eye, radical gastrectomy was conducted.

Observational indicators

Evaluation criteria of clinical efficacy of conversion therapy involved partial response (PR), stable disease (SD), progressive disease (PD) and objective response rate (ORR) [7]. Adverse reactions of the patients were observed during chemotherapy, and they were evaluated, recorded and quantified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE v4.0). It appeared that the severity of adverse reactions could be classified into grade I-IV. Besides, the R0 resection rate, tumor regression grading (TRG) [8], operation time, intraoperative blood loss, the number of lymph node dissection and postoperative complications (Clavien Dindo standard [9]) of patients after successful conversion therapy were recorded. Moreover, the 1-year overall survival (OS) of patients was compared between successful conversion therapy (surgery) group and unsuccessful conversion therapy (non-surgery) group.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s) and compared between two groups using t-test. Meanwhile, count data were presented as percentage (%) and compared using x^2 test between two groups. In addition, survival curves were plotted using the Kaplan-Meier method, and the log-rank test was employed to confirm the statistical

Table 1. Baseline demographic characteristics and chemotherapy clinical efficacy of the studied patients

Parameters	*n=66* *n (%)*
Age (years)	
≤50	26 (39.4)
>50	40 (60.6)
Gender	
Male	39 (59.1)
Female	27 (40.9)
Tumor location	
Gastric antrum	32 (48.5)
Gastric body	20 (30.3)
Total stomach	14 (21.2)
Pathological type	
Moderately differentiated adenocarcinoma	9 (13.6)
Poorly differentiated adenocarcinoma	27 (40.9)
Mucinous adenocarcinoma	11 (16.7)
Signet-ring cell carcinoma	19 (28.8)
Lauren classification	
Diffuse gastric type	51 (77.3)
Intestinal type	11 (16.7)
Mixed type	4 (6.1)
Tumor unresectable causes	
No.16 lymph node +	13 (19.7)
Hepatic metastasis	14 (21.2)
Peritoneal metastasis	15 (22.7)
Ovarian metastasis	5 (7.6)
cN3 fusion	17 (25.8)
Pancreatic metastasis	2 (3.0)
Chemotherapy clinical efficacy	
Partial response	31 (47.0)
Stable disease	16 (24.2)
Progressive disease	19 (28.8)
Objective response rates	47 (71.2)

significance of the difference in the survival rate between two groups. P<0.05 showed that the difference was statistically significant.

Results

Short-term efficacy of conversion therapy

All the 66 patients accomplished 3-7 cycles of chemotherapy, with a median of 5 cycles, and the efficacy in these patients could be evaluated. Following conversion therapy for 66 patients, there were 31 PR cases, 16 SD cases, and 19 PD cases, and the objective response rate (ORR) was 71.2% (47/66) (Table 1).

Adverse reactions of conversion therapy

All the 66 patients suffered from adverse reactions to varying degrees during chemotherapy, mainly including hematological adverse reactions, gastrointestinal reactions, liver and kidney dysfunction, neurotoxicity, hand-foot syndrome, hypertension and oral mucositis, among which there were 52 (78.8%) cases of leukopenia (a hematological adverse reaction), exhibiting the highest incidence rate, 47 cases of granulocytopenia (71.2%), 31 cases of anemia (47.0%), 10 cases of thrombocytopenia (15.2%), 43 cases of fatigue (65.2%), 19 cases of liver dysfunction (28.8%), 8 cases of proteinuria (12.1%), 24 cases of oral mucositis (36.4%), 23 cases of hypertension (34.8%), 17 cases of neurotoxicity (25.8%) and 20 cases of hand-foot syndrome (30.3%). A majority of the patients had grade I-II gastric cancer, and the incidence rate of adverse reactions in patients with grade ≥III gastric cancer was 51.5%. These adverse reactions were improved after timely symptomatic treatment by appropriately reducing chemotherapeutic drugs and increasing leucocytes, with no effects on the subsequent chemotherapy.

Table 2. Comparison of surgery parameters and surgery related complications after conversion therapy of the studied patients

Parameters	*n=48* *n (%)*
Surgical methods	
LADG +Billroth II reconstruction	24 (50.0)
LAPG + Gastroesophageal anastomosis	10 (20.8)
Total gastrectomy +Rous-en Y reconstruction	14 (29.2)
Operation time (min)	225.2±37.3
Blood loss (ml)	168.2±40.9
Number of lymph node dissection	50.9±12.3
Tumor resection degree	
R0	34 (70.8)
R1	14 (29.2)
Tumor regression grading	
0	2 (4.2)
1	10 (20.8)
2	28 (58.3)
3	8 (16.7)
Surgery related complications	
Hypoproteinemia	8 (16.7)
Incision infection	1 (2.1)
Esophagojejunostomy fistula	1 (2.1)
Duodenal stump fistula	1 (2.1)
Residual gastric emptying disorder	2 (4.2)
Postoperative intestinal obstruction	3 (6.3)
Fever (≥38.5°C, ≥5 days)	9 (18.8)

LADG: laparoscopic assisted distal gastrectomy; LAPG: laparoscopic assisted proximal gastrectomy

Surgical resection of tumors

After conversion therapy, 48 (72.7%) patients were treated by operation, including 24 (50.0%) patients undergoing distal gastrectomy + Billroth II reconstruction, 10 (20.8%) patients undergoing proximal gastrectomy + gastroesophageal anastomosis, and 14 patients undergoing total gastrectomy + Roux-en-Y reconstruction based on the evaluation of MDT and the willingness of the patients. The 48 patients were operated for 225.2±37.3 min on average, with intraoperative blood loss of 168.2±40.9 mL and 50.9±12.3 intraoperative dissected lymph nodes, including 34 (70.8%) cases of R0 resection and 14 (29.2%) cases of R1 resection. According to TRG, among these patients, there were 2 (4.2%) TRG 0 cases, 10 (20.8%) TRG 1 cases, 28 (58.3%) TRG 2 cases and 8 (16.7%) TRG 3 cases.

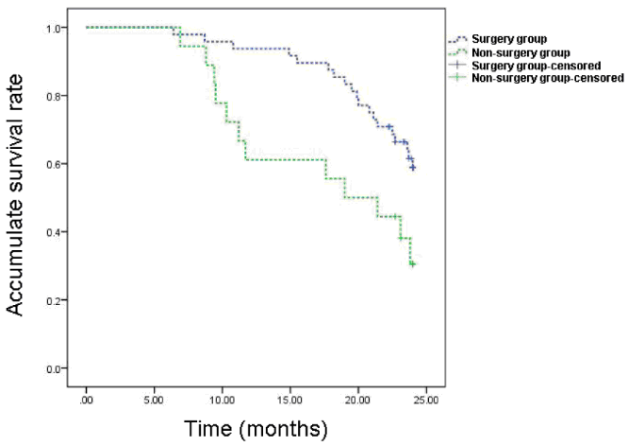

Figure 1. Kaplan-Meier survival curves of patients in Surgery group and Non-surgery group. The 1-year overall survival rate of patients in Surgery group was significantly higher than that of Non-surgery group (p=0.014).

As shown in Table 2, with regard to main related postoperative complications, hypoproteinemia occurred in 8 (16.7%) cases, incision infection in 1 (2.1%) case, fistula from esophagojejunostomy (probably caused by postoperative hypoproteinemia) in 1 (2.1%) case, duodenal stump fistula in 1 (2.1%) case, residual gastric emptying disorder in 2 (4.2%) cases, postoperative intestinal obstruction in 2 (4.2%) cases, and postoperative fever (≥38.5°C for over five days) in 9 (18.8%) cases. Besides, no case suffered from serious surgical complications or died.

Follow-up results of the patient survival

Patients were followed up for 6-24 months with a follow-up rate of 100%. During the follow-up, the one-year OS of patients was 93.8% (45/48) in successful conversion therapy (surgery) group and 61.1% (11/18) in unsuccessful conversion therapy (non-surgery) group. The survival curve of the patients was plotted using the Kaplan-Meier method (Figure 1), and the log-rank test demonstrated that the one-year OS exhibited a statistically significant difference between the two groups (p=0.014).

Discussion

Conversion therapy, a concept deriving from the treatment of liver metastasis in rectal cancer cases, refers to the operation during which the lesions of patients are turned to be resectable through effective chemotherapy, contributing to surgical resection and benefiting patients [10,11]. In recent years, experts and researchers began to focus on the conversion therapy for gastric cancer. Through conversion therapy, the initially unresectable part of gastric cancer in patients with the potential opportunity of surgical resection can be partially or completely relieved after systemic chemotherapy, which is conducive to completing R0 resection and prolonging postoperative survival and/or recurrence-free survival of patients [12,13].

Early single-center studies with a small sample size in Japan and South Korea have proven the safety and effectiveness of conversion therapy for gastric cancer [14,15]. Since then, there have been increasingly more trials on the feasibility of conversion therapy for gastric cancer [16,17]. A multi-center study in Japan included 100 cases of unresectable gastric cancer undergoing docetaxel + cisplatin + S-1 (DCS) conversion chemotherapy. After conversion therapy, 33 cases could be operated sequentially without perioperative complications, including 28 (28/33, 84.8%) cases undergoing R0 resection and 26 (26/33, 78.8%) cases sensitive to chemotherapy confirmed by pathology. The patients undergoing conversion therapy had a median survival of as high as 47.8 months (95% CI: 28.0-88.5), and the survival of 10% of patients undergoing conversion therapy with metastatic loci exceeded 5 years [18]. The research team of Gifu University in Japan carried out conversion chemotherapy for 259 patients with initially unresectable advanced gastric cancer. Tumors in 84 patients were surgically resected after chemotherapy, and the perioperative complication rate and mortality rate of patients undergoing conversion therapy were similar to those in previous clinical trials. In addition, the median survival of patients undergoing R0 resection and R1/R2 resection after conversion therapy was 41.3 months and 21.2 months, respectively, which indicated that the long-term survival of patients with initially unresectable gastric cancer can be remarkably prolonged by conversion therapy [19]. In 2017, research by Fukuchi et al [20] and Einama et al [21] also revealed that conversion therapy could prolong the survival of patients with initially unresectable gastric cancer.

A majority of the latest clinical studies on conversion therapy for gastric cancer have manifested that paclitaxel-based chemotherapy involving three drugs realizes a higher remission rate and gives the opportunity of R0 resection to patients with initially unresectable gastric cancer, so as to prolong their survival. Apatinib, a small molecule target drug resisting angiogenesis, achieves positive results in the third-line treatment of advanced gastric cancer. In China, Cheng and Mao reported the application of apatinib in the conversion therapy of advanced gastric cancer. They conducted conversion therapy with paclitaxel + S-1 + apatinib for 28 cases, with R0 resection rate of 63.4% [22]. In the present study, 66 patients received combined chemotherapy with paclitaxel + S-1 + apatinib, with the ORR of 71.2% and the R0 resection rate of 70.8%. The number of dissected lymph nodes, operation time and intraoperative blood loss were comparable to those of our center in the same period, and no secondary operation or operation-related death appeared. Meanwhile, TRG 0-1 cases took up 25.0%. Both safety and effectiveness of this therapy are consistent with previous research results, reflecting that paclitaxel and S-1 combined with apatinib is a safe and reliable conversion therapy that can be tolerated by patients and has a high rate of tumor regression in the treatment of advanced gastric cancer.

Conclusions about the timing of operation, namely, the duration of preoperative chemotherapy, still vary. Three cycles of preoperative chemotherapy were set in JCOG0405 study, and at least 4

cycles were set in FLOT3 study [23]. In this study, patients received 3-7 cycles of chemotherapy, with a median of 5 cycles. The conversion therapy period should be properly prolonged for patients with heavy tumors or complicated with peritoneal metastasis or ovarian metastasis, because the more cycles of chemotherapy, the poorer tolerance of patients to operation, and the higher the incidence rate of chemotherapy-related adverse reactions, which will increase the risk of operation. Hence, theoretically, the operation should be conducted when the response rate of chemotherapy begins to decline, that is, when the chemotherapeutic efficacy approaches the limit and the threshold of drug resistance.

Furthermore, the follow-up results of this study revealed that the 1-year OS in successful conversion therapy (surgery) group (93.8%) was evidently higher than that in unsuccessful conversion therapy (non-surgery) group (61.1%), and the results of Phoenix-GC Phase II study showed that the 1-year OS in surgery group was 77% [24], indicating that combined chemotherapy with paclitaxel + S-1 + apatinib is likely to further increase the effective rate of conversion therapy.

However, there were still many limitations in this study, such as a small sample size, short follow-up period and incomplete follow-up content. Therefore, multi-center randomized controlled studies with a large sample size are needed to verify the conclusions of this study in the future.

Conclusions

Paclitaxel and S-1 combined with apatinib can achieve a higher R0 resection rate, and improve the survival rate of patients with successful conversion therapy, exhibiting high safety and efficacy.

Conflict of interests

The authors declare no conflict of interests.

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