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Original Article

S-1 combined with docetaxel (SD) versus S-1 combined with cisplatin (SP) in the treatment of advanced gastric cancer: randomized, controlled, multicenter and clinical study

Jianwei Lu[1*], Zhaofei Zhou[1*], Changping Wu[2], Xiaoping Qian[3], Xiaofei Chen[4], Ping Chen[5], Guoxin Mao[6], Lin Wang[7], Yitong Zheng[8], Jifeng Feng[1]

[1]Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China; [2]Department of Oncology, The First People's Hospital of Changzhou (The Third Affiliated Hospital of Soochow University), Changzhou, China; [3]Department of Oncology, Nanjing Drum Tower Hospital, Nanjing, China; [4]Department of Oncology, The First People's Hospital of Huaian, Huaian, China; [5]Department of Oncology, The First People's Hospital of Yancheng, Yancheng, China; [6]Department of Oncology, Affiliated Hospital of Nantong University, Nantong, China; [7]Department of Oncology, 81 Hospital of PLA, Nanjing, China; [8]Department of Oncology, The First People's Hospital of Lianyungang, Lianyungang 222002, China. [*]Equal contributors.

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Abstract: Purpose: This study was conducted to evaluate the differences in the efficacy and safety of S-1 combined with docetaxel versus S-1 combined with cisplatin as a treatment for advanced gastric cancer (GC) patients. Patients and Methods: Three-hundred advanced GC patients who had recurrence or metastasis were enrolled in this study. All of the patients were randomly assigned to receive S-1 combined with docetaxel (experimental group) or S-1 combined with cisplatin (control group). All patients were evaluated and given an ECOG score of 0-1 points with the expectation of a survival of greater than 3 months. We then provided continued chemotherapeutic drugs for 4-6 cycles or until the disease progressed. Tumors were evaluated every 8 weeks until the use of other antitumor drugs, disease progression, death, or the end of the study prohibited further evaluation. The primary endpoint was progression-free survival (PFS), and the secondary endpoint was overall survival (OS), overall remission rate (ORR), 1-year survival rate, and safety. Results: The remission rate in the subjects given drug combinations was 86.33%. After the end of the second, fourth, and sixth cycles, the remission rate and the clinical yield of the experimental group was higher than that of the control group. The median progression-free survival (mPFS) duration of the test group was 180 days, whereas the control group was 171 days. The median overall survival (mOS) rates of the experimental group and the control group were 405 days and 378 days, respectively. There were 77 people in the test group whose survival rate was more than 1 year, and the 1-year survival rate was 51.33%; there were 72 people in the control group whose survival rate was more than 1 year, and the 1-year survival rate was 48.00%. The total 1-year survival rate was 49.67%. Adverse effects were similar in the experimental group and the control group. The main adverse effects were gastrointestinal reactions and bone marrow toxicity, which could be tolerated and relieved without symptomatic treatment. Conclusion: There was no significant difference between the treatment efficacy of the experimental group and the control group. However, regarding safety and tolerance, the experimental group subjects fared better than the control group subjects. Adverse effects were mainly grade I-II, and grade III-IV adverse effects could be relieved by symptomatic treatment with no unexpected adverse effects. This study further verified that S-1 combined with docetaxel had better efficacy and safety in the treatment of advanced GC compared to the treatment method of S-1 combined with cisplatin.

Keywords: GC, S-1, cisplatin, OS, PFS

Introduction

The incidence and mortality of gastric cancer (GC) is the second highest in cases of malignant tumors, with a tendency to form malignancies earlier than most other cancers [1, 2]. Surgery is the primary treatment for gastric cancer, but palliative care is the primary concern for gastric cancer patients. Due to the frequency of subclinical metastases, these tumors

easily form metastasis and lead to relapse, which results in poor overall prognosis.

For nearly half a century, 5-fluorouracil (5-FU) and cisplatin have been the main drugs in the treatment of gastrointestinal cancer; the curative effect is exact, and the safety is easily accepted. Tegafur is an oral anticancer agent that is the derivative of fluorouracil, and it is effective in both single and combined treatment of GC. S-1 is a compound preparation composed of tegafur, gamester, and potassium ozonate. As an anticancer drug of the third oral fluorouracil derivative, S-1 is extensively used due to its credible curative effect, mild AEs, convenient administration, and good compliance. S-1 is a precursor of 5-FU, and it is transformed into 5-FU by the cytochrome P450 system in the liver after oral administration, at which point it can then efficiently target cancer cells. The prolonged action time of 5-FU in tumor tissues and blood serves to inhibit the activity of dihydropyridine dehydrogenase, an effect that can otherwise only be achieved with continuous intravenous infusion. Potassium ozonate selectively acts on rotate phosphoribosyl transferase in the gastrointestinal tract to block phosphorylation of 5-FU and weaken AEs of 5-FU in the gastrointestinal tract. S-1 in combination with other chemotherapy drugs, therefore, has a synergistic effect. Currently, S-1 combined with other drugs such as platinum's paclitaxel is recommended for advanced GC. S-1 can result in better therapeutic effects as both a single agent and in combination with other anticancer agents. The rate of treatment efficacy of monotherapy is 20%-30%, and combination therapy efficacy is 30%-60% [6].

Our nation has approved S-1 for both locally advanced and metastatic GC, and S-1 combined with cisplatin (SP regimen) in the treatment of advanced GC has been listed as a Chinese first recommendation. Docetaxel is a partially synthesized taxeme that inhibits the growth of tumor cells by enhancing the polymerization of tubulin. The rate at which treatment of docetaxel combined with S-1 has a positive effect in first-line treatment of advanced GC is 52.4%. The combination of chemotherapy with docetaxel may be the most important innovation in the treatment of GC in 20 years [3]. This study aims to evaluate and compare the efficacy and safety of S-1 combined with docetaxel and S-1 combined with cisplatin in the treatment of advanced GC.

Methods

Study design and patients

This study is a randomized, open, controlled, and multicenter clinical trial. The plan included 300 patients with advanced GC in eight hospitals of the Jiangsu Province. All participants were randomly assigned, with 150 subjects in the experimental group and 150 subjects in the control group. The primary endpoint was PFS, and the secondary endpoint was OS, ORR, 1-year survival rate, and safety.

Inclusion and exclusion/termination criteria

In this experiment, we adopt the method of centralized random grouping.

Inclusion criteria

Participants were selected for this study only if they had locally advanced, recurrent, or metastatic GC with the inability to operate. The following criteria also had to be met for participation: provided signed written informed consent; be ≥ 18 and ≤ 75 years old; have an Eastern Cooperative Oncology Group (ECOG) score of 0-1 points; have gastric or gastroesophageal junction adenocarcinoma in histology; and have locally advanced, recurrent, or metastatic GC with the inability to operate. In addition, patients needed at least one of the following criteria for measuring the lesion: spiral computed tomography (CT), magnetic resonance imaging results for the lesion in which the maximum diameter is ≥ 10 mm, traditional CT results in which the maximum diameter is ≥ 20 mm, subcutaneous lesions, or a lymph node with a diameter of ≥ 15 mm. An eligible patient could not have been undergoing active chemotherapy or have had disease progression after the end of the new adjuvant chemotherapy 6 months following chemotherapy. Adjuvant, neoadjuvant chemotherapy with S-1, and oral docetaxel patients needed to have finished treatment more than 1 year before initiation in the study. Participants could not have received radiotherapy or should have displayed no signs of target lesion for > 4 weeks after radiotherapy with baseline blood, liver, and kidney functions in accordance with the following criteria: ade-

Table 1. The initial dose of S-1 was according to the body surface area

The body surface area	The initial dose (equal to Tegafur)
< 1.25 m^2	40 mg × 2/d
≥ 1.25 m^2, < 1.5 m^2	50 mg × 2/d
≥ 1.5 m^2	60 mg × 2/d

quate organ function [white blood cell count ≥ 3.0 × 10^9 cells/L, with neutrophils ≥ 1.5 × 10^9 cells/L, platelets ≥ 100 × 10^9 cells/L, and hemoglobin ≥ 9 g/L (corresponding to 9 g/dL); serum bilirubin ≤ 1.5 × upper limit of normal [ULN]; alanine aminotransferase and aspartate amino transferase ≤ 2.5 × ULN or ≤ 5 × ULN in the presence of liver metastases; and serum creatinine ≤ 1.5 × ULN], an estimated life expectancy of greater than 3 months, and normal heart and lung function.

Exclusion criteria

The following criteria were grounds for exclusion from the study: an allergy to fluorouracil or docetaxel; dysphagia, complete or incomplete obstruction of the digestive tract, gastrointestinal bleeding, perforation, and other difficulties when taking S-1 orally; brain metastasis; severe liver disease, kidney disease, respiratory disease, or diabetes; hypertension and other chronic diseases that cannot be controlled; heart disease with special clinical symptoms like congestive heart failure, symptomatic coronary heart disease, arrhythmia, and hypertension, all of which are difficult to control with drugs; an episode of myocardial infarction or heart failure within 6 months of the study start date; severe infections that need to be treated; disorders of the peripheral nervous system and a history of mental disorders and central nervous system disorders; a history of organ transplantation including autologous bone marrow transplantation and peripheral stem cell transplantation; long-term systemic steroid therapy (short-term users who stopped steroid therapy > 2 weeks prior to the study start date were permissible); other malignant tumors within 5 years, in addition to non-melanoma skin cancer and carcinoma in situs of cervix; pregnancy, active breast-feeding, and having a sexually active partner who refuses to take effective contraceptive methods to prevent pregnancy during the study duration; a history of illegal behavior; and anything else that may otherwise compromise the medical or ethical integrity of the study.

Subject participation was terminated if any of the following circumstances occurred: adverse effects made continuation difficult, the withdrawal period lasted for more than 28 days, their study value according to the RECIST 1.1 standard to determine the patient's comprehensive curative effect was progressive disease, the patients asked to withdraw from the study, the implementation process was in violation of the research program, or the investigators decided to terminate the study for any other reason based on a case-by-case evaluation.

Procedures

For the experimental group, the initial dose of S-1 was determined based on body surface area and in accordance with the standards listed in **Table 1**, while the optimal dosage of docetaxel was determined to be 40 mg/m^2 via intravenous administration for 1 hour on day 1 and day 8 of the study. For the control group, the initial dose of S-1 was the same as in the experimental group, followed by CDDP at 60 mg/m^2 intravenous administration for 2 hours on day 8. Each cycle was 21 days long for both the experimental group and the control group with 14 days for giving medicine and 7 days for rest. This was repeated for each treatment cycle, and it was continued for 4-6 cycles or until the disease progressed. Tumor assessment was performed every 8 weeks up until the use of other antitumor drugs, disease progression, death, or the end of the study. The standards for discontinuation of the cycle and re-administration of the drug within the treatment period are listed in **Table 2**.

Statistical analysis

Statistical analysis of the population

Full analysis set (FAS): Analysis of the efficacy of all drug treatments via random grouping was done according to the principle of intention analysis (ITT). In the event of the failure to observe the whole treatment process of a case, the last observation data would be used as the final results of the test.

Consistent scheme set (PPS, per protocol set): All study subjects must conform to the test plan with good compliance, and each subject must take at least one cycle of drugs without taking banned drugs during the study. Each subject must complete the case report form without filling in missing data resulting in imputation.

Table 2. The standards for discontinuation and re-administration of the drug

	Discontinuation of the drug	Re-administration of the drug	Administration of the drug next cycle
Neutrophil	< 1.0 × 10^9/L	> 1.0 × 10^9/L	> 1.5 × 10^9/L
Platelet	< 50 × 10^9/L	> 50 × 10^9 /L	> 90 × 10^9/L
Serum reatinine	> Upper limit of normal	< Upper limit of normal	< Upper limit of normal
Infection	> 38°C infective fever	There is no infectious fever	There is no infectious fever
Diarrhea, dental ulcer	> II degree	≤ I degree	< I degree
Other	The researchers determine to discontinue to give medicine when the AEs of outside happened.	The researchers can determine to start again when AEs relieve or recovered.	When the next cycle be postponed by outside the scope of AEs, after AEs to reduce or recovered, the research can begin to the next cycle.

Security analysis dataset (safety set, SS): In all cases, the drugs must be used at least one time, and all patients who have taken the medication must have their safety records, all of which belong to the safety analysis set. This dataset is used for security analysis.

Statistical methods

Main analysis: A non-inferiority test was taken between test groups. Correlation analysis was done on the progression-free survival rate using the FAS as the study population. To compare between the two groups, the hypothesis test used the bilateral test (two-sided test), $\alpha = 0.05$. When $P < 0.05$, there was a significant difference, and all of the confidence intervals were taken at 95%.

Side analysis: The FAS was used as the study population to calculate the median time of OS. We used the objective effective rate to calculate the ORR and the disease control rate. One-year survival rate correlation analysis was used to calculate the percentage of OS lasting over 1 year. We also carried out analyses related to adverse events and adverse drug reactions using the patients who had taken the drugs as the study population, and we calculated the incidence at each level. We analyzed medication compliance, using FAS as the study population, to calculate the number of days taking drugs and dosage during each cycle within the testing period.

Results

Distribution, shedding, and rejection of subjects

We enrolled 300 advanced GC patients in this study. Among the 300 patients, 14 experimental cases were shed at a rate of 4.33%; 7 cases were lost in the test group, 2 patients withdrew informed consent, 3 patients were lost during follow-up, 1 patient refused treatment, and 1 patient experienced adverse events. In the control group, 6 cases were lost, 1 case withdraw informed consent, 2 patients were lost during follow-up, 1 patient refused treatment, 2 and patients experienced adverse events. One patient was excluded completely, resulting in a rejection rate of 0.3%. One case was removed from the experimental group because it did not conform to the study standards. FAS of the clinical trials was 300 cases, including 287 cases as PPF and 300 cases as SS.

Baseline and comparability analysis of the subjects

There were no significant differences in age, the course of the disease, gender, Carnovsky score, pathological grade, and previous treatment patterns between the two groups ($P > 0.05$). Additionally, there were no significant differences between the groups in height, weight, body surface area, and other vital signs between the two groups of subjects ($P > 0.05$). Moreover, there were no significant differences in the physical examination results between the test group and the control group ($P > 0.05$).

Compliance analysis

We define poor compliance as subjects asking for withdrawal from the trial, subjects being lost during follow-up, and subjects not following the prescribed dose and duration of treatment. The proportion of poor compliance was 2.67%.

Results and analysis of drugs combination

All subjects were treated in strict accordance with the experimental plan, and medication was combined during the clinical trial. Out of the 300 cases, 259 cases had combined medication during the trial period, resulting in a total rate of drug combination of 86.33%. Following

analysis of the two groups of patients with drug combination, we were able to conclude that there are many types of drugs that could be combined without inhibition. These combinations could help to prevent a variety of adverse events like high blood pressure, hand foot syndrome, liver damage, and kidney function damage. The combinations can provide supportive treatment by protecting the liver; protecting the stomach; lowering blood pressure; serving as a diuretic; preventing infection; rising platelet counts; and treating fever, cough, phlegm, and hemorrhaging.

Curative effect analysis

Main curative effect index analysis

PFS analysis: By analyzing FAS, we found that the mPFS in the control group was 171 days but 180 days in the S-1 experimental group, which was not significantly different ($P > 0.05$). By analyzing PPS, we found that the mPFS in the control group was 173 days, but was 181 days in the S-1 experimental group, which was also not statistically significant ($P > 0.05$).

The secondary curative effect index analysis

OS analysis: By analyzing FAS, we found that the mOS of the experimental group and the control group was 405 days and 378 days, re spectively, with no significant difference between the two groups ($P = 0.5127$). By analyzing PPS, we found that the mOS of the experimental group and the control group was 406 days and 381 days, respectively, with no significant difference between the two groups ($P = 0.5419$). The analytic results of PPS and FAS are consistent.

Objective remission rate and control rate of disease/clinical yield rate: Analyzing both FAS and PPS, at the end of the second, fourth, and sixth cycles, we found that the remission rate of the experimental group was higher than that of the control group, but the difference was not statistically significant. The clinical yield of the experimental group was higher than that of the control group, but this, too, was not statistically significant.

The 1-year survival rate: There were 77 people in the test group whose OS was more than 1 year, with a 1-year survival rate of 51.33%. There were 72 people in the control group whose OS was more than 1 year, and the 1-year survival rate was 48.00%. The total 1-year survival rate was 49.67%.

Description and analysis of adverse events

In this study, 300 subjects were enrolled in the SS analysis, and the results showed that the incidences of adverse events in the experimental group and control group were 90.67% and 91.33%, respectively, with incidences of moderate and severe adverse events at rates of 31.33% and 32.67%. There was no significant difference between the two groups. The AEs rates were 85.33% for the experimental group and 87.33% for the control group. The rates of moderate and severe AEs was 26.00% for the experimental group and 24.67% for the control group, and there was no significant difference between the two groups. The AEs that occurred in the experimental group and the control group were similar, with the main adverse effects being gastrointestinal reactions and bone marrow toxicity, both of which could be tolerated and relieved without symptomatic treatment.

Discussion

Northeast Asia has one of the highest incidence rates of GC in the world. GC is also prone to malignancy, resulting in one of the highest morbidity and mortality rates for tumor cases in China. At present, we have no effective screening model for GC. As a result, most patients are diagnosed at the stage of an advanced tumor, at which point chemotherapy becomes the main method of treatment [4]. However, the unified and effective therapeutic method of chemotherapy for advanced GC remains underdeveloped. In recent years, combination therapy widely applied in advanced GC has had a better therapeutic effect, with a remission rate of over 40% [5].

Many clinical trials have assessed the efficacy and safety of combination chemotherapy with S-1 on advanced GC. Cisplatin is classical cell cycle non-specific agent, and in the SPIRITS test [7], it was combined with S-I and established as a standard first-line chemotherapeutic regimen of advanced GC that was widely applied in Japan. In this test, 305 patients with advanced GC were randomly divided into an S-I combined with cisplatin group and an S-1 single agent group. The results showed that the overall response rate (RR) in the combination

chemotherapy group and in the single agent groups, respectively, was 54.0% and 31.1% (P = 0.001), that the mOS was 13 months and 11 months (P = 0.04), and the mPFS was 6 months and 4 months (P < 0.001). Additionally, the RR, mOS, and mPFS were all significantly prolonged in the combination chemotherapy group. The FLAGS test [8] results showed that, compared with 5-FU and cisplatin, S-1 combined with cisplatin did not prolong the OS of advanced gastric carcinoma and adenocarcinoma of the gastroesophageal junction. The SC-101 test [9] revealed that the median survival (PFS) of patients with GC in our country receiving S-1 single agent and S-1 combined with cisplatin was 8.9 months and 14.4 months, respectively. The DIGEST test [10] compared the mOS and safety of S-1 combined with cisplatin and 5-FU combined with cisplatin in the treatment of metastatic gastric carcinoma. The results showed that the efficacy and safety of S-1 combined with cisplatin are not inferior to 5-FU, implying that it might be used as a new treatment of advanced gastric carcinoma.

Docetaxel is a podocyte-specific drug that inhibits tumor cell differentiation by causing cell cycle arrest in the M phase and inducing cell apoptosis. *In vitro* experiments have also revealed that docetaxel has an antiangiogenesis effect and induces apoptosis in tumor cells. The development of docetaxel-based chemotherapy has been one of the most important innovations in the treatment of GC in the latest 20 years [11]. The combination of S-1 and docetaxel showed synergism [12] and was effective as a first-line treatment method of advanced GC. Using combination treatment, we were able to achieve a RR of 52.4%, a median time to progress (mTTP) of 6.5 months, and an OS rate of 15.1 months [3]. A phase I/II study by Zang DY also showed that the RR of S-1 combined with docetaxel in the treatment of advanced GC could reach 66.7%, with a TTP of 6.5 months and an OS rate of 13.7 months [13]. The STAR test [14] compared the OS and mPFS of groups treated with the S-1 single agent and with S-1 combined with docetaxel in the first-line treatment of advanced GC. The results showed that the OS of the groups was 10.8 months and 12.5 months and that the mPFS was 4.2 months and 5.3 months, respectively.

A phase II multicenter clinical trial by Mochiki [15] compared the curative effect of S-1 combined with docetaxel and S-1 combined with cisplatin in the treatment of advanced gastric carcinoma. The results showed that the combination docetaxel and combination cisplatin groups' respective RRs were 52.3% and 48.7%, mPFS was 9 months and 6 months, and mOS was 16 months and 17 months. There was no significant difference between the two groups in terms of efficacy, but the incidence rate of grade III and IV AEs of the docetaxel group was lower. Our results are similar to those of Mochiki et al., with ours revealing a mPFS of S-1 combined with docetaxel and S-1 combined with cisplatin in the first-line treatment of advanced GC of 171 days and 180 days, and a mOS of 405 days and 378 days in their respective groups. Furthermore, the main AEs were grade I-II, while adverse effects of grade III-IV were able to be alleviated through symptomatic treatment with better overall efficacy and safety. We saw shorter mPFS and mOS compared to the results of Mochiki's research, though this might be due to the fact that 125 patients with advanced gastric carcinoma enrolled in the study of Mochiki, compared to the 300 patients enrolled in our study. However, both studies suggest that the two treatment protocols have good effectiveness and safety in the first-line treatment of advanced GC.

Disclosure of conflict of interest

None.

Address correspondence to: Jifeng Feng, Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China. E-mail: Fengjifeng0227@163.com

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