

The efficacy and feasibility of adopting intravenous chemotherapy and oral S-1 as a sequential therapy for postoperative gastric cancer patients

Long Yan, MD, Hongbin Liu, MD*, Hongtao Li, MD, Xiaopeng Han, MS, Tingbao Cao, MS, Chaoyang Wang, MS, Gaitian Li, MS

Abstract

Some postoperative gastric cancer patients have to terminate systemic intravenous chemotherapy early due to adverse drug reactions. We performed a retrospective study to explore the efficacy and feasibility of sequential therapy.

We retrospectively analyzed 55 postoperative gastric cancer patients (Group A) who received sequential therapy (intravenous chemotherapy and S-1) and 53 patients (Group B) who received intravenous chemotherapy from January 2012 to December 2013 in our hospital. The therapeutic effect (including 1-year, 5-year tumor recurrence and survival rate) and the incidence of adverse reactions were analyzed.

When death and survival for more than 5 years was regarded as the end point of follow-up, the mean follow-up period was 40.6 months (34.7–46.4) in Group A and 39.2 months (33.0–45.3) in Group B. The 1-year tumor recurrence after the operation was 23.6% (13/55, Group A) and 28.3% (15/53, Group B). The 5-year tumor recurrence was 45.5% (25/55, Group A) and 49.1% (26/53, Group B). There was no significant difference in the 1- and 5-year tumor recurrence rates between these two groups ($P > .05$). The 1-year survival rates of Group A and Group B were 81.8% (45/55) and 79.2% (42/53), respectively, and the 5-year survival rates of Group A and Group B were 47.3% (26/55) and 45.3% (24/53), respectively. No significant difference was observed between these two treatments at either the 1- or 5-year survival benefit ($P > .05$). However, the patients in Group A had a lower incidence of gastrointestinal reactions (such as nausea and vomiting), leukopenia and liver function damage ($P < .05$). We also found that patients who underwent sequential therapy might show lower levels of adverse reactions.

Our retrospective study provided some evidence to suggest that sequential treatment is effective and safe for postoperative gastric cancer patients who are intolerant to intravenous chemotherapy.

Abbreviations: HR = hazard ratios, MDT = multidisciplinary team, S-1 = Tegafur, gimeracil and oteracil potassium, SD = standard deviation.

Keywords: chemotherapy, gastric cancer, gimeracil and oteracil potassium, tegafur

1. Introduction

Gastric cancer is an aggressive malignancy with a poor prognosis. Surgical resection remains the mainstay of potentially curative

therapy,^[1] but multimodality therapy, including neoadjuvant and adjuvant therapies, such as chemotherapy, has been demonstrated to have a survival advantage.^[2,3] At present, there are a variety of chemotherapy regimens for postoperative chemotherapy, but the adverse reactions to chemotherapy drugs are still the most common causes of the early termination of chemotherapy in patients.^[4]

As an oral chemotherapy drug, S-1 comprises tegafur and two kinds of targeted regulators, gimeracil and oteracil.^[5] S-1 has been proven effective for gastrointestinal cancer in North America and Asia, especially for advanced gastric cancer.^[6–8] Additionally, some researchers have found that S-1 may lead to a lower incidence and grade of adverse reactions.^[9] Therefore, oral S-1 as a monotherapy seems to be a reasonable choice for some gastric patients who are intolerant to intravenous chemotherapy. In our study, sequential therapy was performed since postoperative patients who could not tolerate intravenous chemotherapy may accept S-1 as a follow-up treatment, and we have adopted this chemotherapy regimen for some patients in the past few years. We compared the curative effect, survival benefit and adverse reactions of sequential therapy and systemic intravenous chemotherapy for postoperative gastric cancer patients.

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Department of General Surgery, 940th Hospital of Joint Logistics Support Force, Lanzhou, Gansu, China.

* Correspondence: Hongbin Liu, Department of General Surgery, 940th Hospital of Joint Logistics Support Force, Lanzhou 730050, Gansu Province, China (e-mail: lzy940@163.com).

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2. Materials and methods

2.1. Patients

We retrospectively analyzed the data for some patients who accepted postoperative chemotherapy in our hospital during the period from January 2012 to December 2013, and all of the selected patients had previously undergone laparoscopic radical gastrectomy. The plan for this study was submitted to and approved by the Ethics Committee of the General Hospital of Lanzhou Military Region.

Patients who initially underwent systemic intravenous chemotherapy and then had to accept S-1 because of adverse drug reactions were regarded as the sequential therapy group (Group A). The selected patients who only underwent systemic intravenous chemotherapy were considered Group B. The common inclusion criteria for Group A and Group B were as follows:

1. Patients had undergone D2-type laparoscopic radical gastrectomy, and gastric cancer was confirmed by preoperative and postoperative pathological findings.
2. None of the patients had serious postoperative complications, such as duodenal fistula, anastomotic fistula or massive abdominal bleeding, and no patient was converted to laparotomy.
3. The TNM stage of gastric cancer was \geq IIB, \leq IIIC.^[10]
4. The ages of the patients were \geq 18 years and $<$ 0 years.
5. The total number of postoperative chemotherapy for each patient should be \geq 5.
6. The chemotherapy regimens and changes in the treatment plan were based on the judgments of a multidisciplinary team (MDT) at our hospital, which consisted of a general surgeon, an oncologist, a gastroenterologist, a clinical pharmacist, and a dietician.

Additionally, Group A should meet the following criteria:

1. Patients had received intravenous chemotherapy at our hospital at least once, and the chemotherapy regimen was fluoropyrimidine (tegafur) plus platinum (oxaliplatin).
2. Patients had received S-1 as a monotherapy more than 3 times.

The MDT determined whether to change the chemotherapy regimens to the sequential therapy mainly based on the serious reactions of the patient to chemotherapy drugs, such as severe nausea and vomiting, diarrhea, severe liver function damage, or poor compliance with long-term intravenous infusion.

The exclusion criteria for these two groups were as follows:

1. Distant metastasis was identified preoperatively and intraoperatively (M1), or palliative gastrectomy was performed because the complete resection of the tumor was difficult;
2. The histological results were not adenocarcinoma;
3. Patients could not receive chemotherapy because of serious health conditions or other changes in the chemotherapy plan; or
4. Patients had other malignant tumor diseases or severe chronic disease, such as serious heart problems and serious respiratory diseases.

2.2. Treatment

The patients in both groups received the same intravenous chemotherapy regimen: oxaliplatin 130 mg/m² Day 1, Leucovorin 100 mg/m² Days 1 to 5, and tegafur 600 mg/m² Days 1 to 5. The patients in the sequential therapy group (Group A) accepted

S-1 at a daily dose of 80 mg/m² for 4 weeks, followed by 2 weeks of rest, i.e., 1 round of chemotherapy. All patients were advised to receive 6 rounds of chemotherapy.

2.3. Outcome measures

We retrospectively examined the medical records to obtain the characteristics of the patients. The postoperative survival of the patients was followed up by phone. Patients who died or survived beyond 5 years were regarded as the end point of follow-up. We compared tumor recurrence and survival data at 1 year and 5 years to evaluate the treatment effect. The HR value of the survival data for these two groups was also calculated. Patients with postoperative tumor recurrence were defined as patients with tumor recurrence anywhere and/or lymphatic metastasis, which was detected by gastrointestinal endoscopy, CT or MRI. The incidence of adverse reactions was analyzed to assess the safety of sequential therapy. The classification of adverse reactions conformed to the WHO criteria for the toxicity assessment of chemotherapeutic drugs. Because the patients in the sequential therapy group (Group A) experienced both intravenous chemotherapy and oral S-1, when we analyzed and compared the total adverse reactions of these two groups, we could not explain the difference between these two chemotherapy regimens. Considering that the selected patients in Group A received S-1 as a monotherapy at least 3 times, we only compared the adverse reactions of the last 3 times of chemotherapy in these two groups.

2.4. Statistical analysis

SPSS software, version 21 was employed for the statistical analyses. All data were presented as a median or the mean \pm standard deviation (SD). The independent two-sample test was used to compare the numerical data. Pearson's chi-square test and Fisher's exact test were performed for qualitative data. The HR and 95% confidence intervals (CI) were estimated using the univariate Cox regression analysis. The Kaplan–Meier analysis was used for the survival analysis. A *P* value below .05 was regarded as statistically significant.

3. Results

3.1. The characteristics of patients

A total of 68 patients met the inclusion criteria for the sequential therapy group (Group A), and 55 patients completed the follow-up schemes (the 5-year follow-up rate was 80.9%). These patients included 36 males and 19 females. In addition, 68 patients were randomly selected from the patients who met the inclusion criteria for Group B as the control group, and 53 patients accomplished the follow-up schemes (5-year follow-up rate was 77.9%). These patients included 32 males and 21 females. In our department, total gastrectomy and distal gastrectomy are performed regardless of the location of the tumor in the stomach. Thus, there were only two kinds of surgery in our comparison. There were no significant differences in the general condition of these two groups, including gender, age, surgical procedures, tumor differentiation degree, and TNM stage (Table 1).

3.2. Treatment effect

The mean follow-up period in Group A was 40.6 months (34.7–46.4), while that in Group B was 39.2 months (33.0–45.3). Five

Table 1
The general clinical data of Group A and B patients.

	Group A	Group B	$\chi^2/F/t$	P
Patients	55	53	-	-
Gender				
Male	36 (65.5%)	35 (66%)	0.004	.555
Female	19 (34.5%)	18 (34%)		
Age (years)	53.7 ± 6.8	54.4 ± 7.4	0.214	.644
Surgical procedures				
Total gastrectomy	23 (41.8%)	19 (35.8%)	0.405	.331
Distal gastrectomy	32 (58.2%)	34 (64.2%)		
Adenocarcinoma differentiation				
poorly differentiated	15 (29.3%)	14 (25.9%)	1.231	.540
moderately differentiated	24 (46.3%)	28 (51.7%)		
well differentiated	16 (24.4%)	11 (22.4%)		
TNM				
IIB	10 (18.2%)	10 (18.9%)	0.270	.966
IIIA	18 (32.7%)	15 (28.3%)		
IIIB	13 (23.6%)	13 (24.5%)		
IIIC	14 (25.5%)	15 (28.3%)		

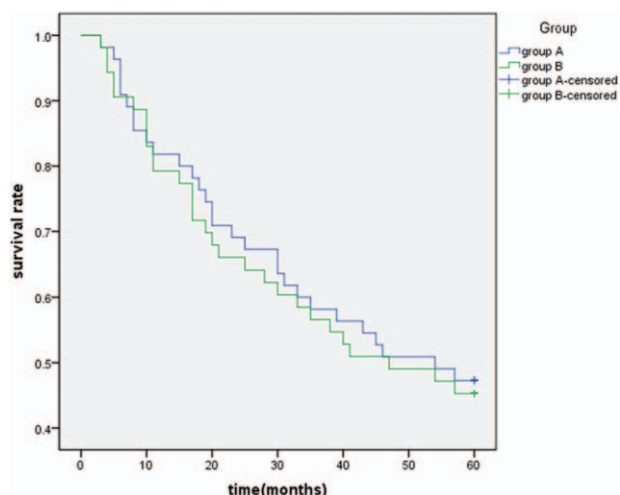


Figure 1. Kaplan–Meier cumulative survival curves of the two groups of patients for survival.

patients in Group A prematurely terminated chemotherapy because of poor compliance (3 patients) and uncomfortable reactions (2 patients). Nine patients in Group B prematurely terminated chemotherapy because of poor compliance (4 patients) and uncomfortable reactions (5 patients).

After systematic chemotherapy, similar therapeutic effects were obtained in both groups. Thirteen patients in Group A and 15 patients in Group B suffered tumor recurrence at 1 year after the operation. That is, the 1-year tumor recurrence rates of Group A and Group B were 23.6% and 28.3%, respectively. The 5-year tumor recurrence rates of Group A and Group B were 45.5% (25/55) and 49.1% (26/53), respectively. There was no significant difference in the 1-year and 5-year tumor recurrence rates between these two groups of patients ($\chi^2=0.306$, $P=.369$ and $\chi^2=0.141$, $P=.428$).

The 1-year survival rate was 81.8% (45/55) for the 55 patients in Group A and 79.2% (42/53) for Group B. Although there appeared to be some differences, we found no significant difference in the 1-year survival rate between the two groups of patients ($\chi^2=0.114$, $P=.462$). Similarly, no significant difference was found when compared with the 5-year survival rate ($\chi^2=0.043$, $P=.494$, Fig. 1), and the 5-year survival rates of these two groups were 47.3% (26/55) and 45.3% (24/53). The HR (Group A vs Group B) for 5-year overall death was 0.932 (95% CI, 0.557–1.560, $P=.789$). The overall survival curves obtained with the Kaplan–Meier method are shown in Figure 1.

3.3. The incidence of adverse reactions

In this study, although patients received two different therapeutic schedules, the types of adverse reactions were almost the same, including bone marrow suppression (such as leukopenia and thrombocytopenia), gastrointestinal reaction (such as nausea, vomiting, and diarrhea), and liver function damage. To find the difference in the adverse event rates between these two treatments more precisely, we compared the adverse reactions of these two groups after the last 3 rounds of chemotherapy (Table 2).

There were 2 patients in Group A and 5 patients in Group B that prematurely terminated the chemotherapy regimen because of adverse reactions. The patients in Group A had a lower incidence of some adverse reactions, such as leukopenia and liver function damage ($P<.05$), especially gastrointestinal reactions. More than half of the patients in Group B presented different levels of gastrointestinal reactions (nausea and vomiting), and the incidence was significantly higher than that in Group A ($P=.002$). Although there was no significant difference in thrombocytopenia between these two groups ($P=.368$), we observed 1 patient with refractory thrombocytopenia after receiving oral S-1 for 3 times. This effect directly led to the premature termination of chemotherapy. We also found that patients receiving sequential therapy might develop lower levels of adverse reactions (grade I and grade II), especially leukopenia, liver function damage and gastrointestinal reactions. However, the difference was not statistically significant.

Table 2
The incidence of adverse reactions in the last 3 times chemotherapy.

Adverse reactions	Group A (55)				Group B (53)				χ^2	P
	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV		
Anemia	2	1	2	0	1	3	2	0	0.147	.474
Leukopenia	4	9	5	2	6	9	13	3	5.302	.017
Thrombocytopenia	4	4	1	1	6	4	2	0	0.331	.368
Liver function damage	5	7	2	0	7	10	5	1	3.858	.039
Gastrointestinal reaction	5	8	2	0	11	13	6	0	9.554	.002
Diarrhea	3	2	2	0	4	3	1	0	0.126	.469

4. Discussion

In this study, we reviewed the clinical features and treatment outcomes of 55 postoperative gastric cancer patients who terminated intravenous chemotherapy due to serious adverse reactions and subsequently changed to S-1 as a follow-up chemotherapy regimen. We compared these patients with 53 postoperative gastric cancer patients who adopted intravenous chemotherapy at the same time in the hospital. The sequential chemotherapy, which included intravenous and oral chemotherapy, could achieve a similar therapeutic effect to complete intravenous chemotherapy for postoperative gastric cancer patients. Moreover, patients adopting sequential chemotherapy may develop fewer adverse reactions, especially some common reactions, such as leukopenia, nausea and vomiting, which usually disturbs routine chemotherapy for gastric patients.

The therapeutic principle and method for gastric cancer is comprehensive therapy, and neoadjuvant chemotherapy followed by surgery is considered to be an effective treatment for advanced gastric cancer patients.^[11] However, the recurrence and metastasis rates of postoperative patients are still high. Some studies have found that almost half of postoperative gastric cancer patients would have tumor recurrence and metastasis within 5 years after the operation.^[12] Therefore, much attention has been paid to postoperative chemotherapy, and naturally, the treatment has brought remarkable benefit to tumor patients.^[13,14] Due to the poor health condition and low tolerance for the adverse reactions to chemotherapy drugs, some gastric cancer patients could not receive postoperative chemotherapy successfully. Faced with this situation, the clinicians have to reduce the drug dose or even terminate chemotherapy.^[15] The effects eventually induce some patients to give up chemotherapy actively or passively. Therefore, we must provide more reasonable and personalized chemotherapy regimens for gastric cancer patients. The regimens must be equally effective and simultaneously reduce the incidence of adverse reactions. At present, for the chemotherapy of gastrointestinal tumors, fluorouracil or its derivatives are the essential medicines, and these drugs cannot be substituted. For example, fluorouracil plus a platinum-based chemotherapy regimen is a classic scheme for the treatment of patients with gastrointestinal malignant tumors because of its good effects.^[16] However, fluorouracil can lead to different degrees of adverse reactions, such as bone marrow suppression, gastrointestinal reaction, liver and kidney function damage, which can reduce the quality of life and survival of patients and even lead to the premature termination of chemotherapy.^[17] To improve the clinical curative effect of fluorouracil and reduce the incidence of adverse reactions, researchers have developed a variety of derivatives, such as tegafur.

S-1 is an oral preparation of fluorouracil derivatives. When this drug enters the body, tegafur transforms into fluorouracil and plays a role in antitumor activity. Although its effect is similar to that of fluorouracil, animal studies have shown that S-1 toxicity is 1/4 to 1/7 that of fluorouracil, and this drug has better bioavailability in the human body.^[18] Gimeracil could inhibit dihydropyrimidine dehydrogenase, the activity of which determines the decomposition of fluorouracil.^[19] Oteracil can block the phosphorylation of fluorouracil, thereby reducing the adverse reaction of fluorouracil.^[19] S-1 is employed for the treatment of gastric cancer in Japan. Since its application was approved in 1999, S-1 has brought great benefits to gastric cancer patients.

Studies have reported that the remission rate (RR) in patients with advanced gastric cancer treated with S-1 is 44.6%.^[20] In our study, there was no significant difference between intravenous systemic chemotherapy and sequential therapy in 1-year and 5-year tumor recurrence and survival after surgery. This finding indicates that if patients who could not accept their intravenous chemotherapy successfully because of poor tolerance, then they could obtain a therapeutic effect similar to intravenous chemotherapy by taking S-1. As S-1 is an oral drug, treatment compliance is much better. Although S-1 would also cause some adverse reactions, most of these reactions are low level (grade I or grade II), and the majority of patients could endure these reactions with some treatments.

Admittedly, our study has some important limitations. Although neoadjuvant chemotherapy has been regarded as the standard treatment for gastric cancer patients with stage IIb and above, this treatment did not receive enough attention in our center during the period from 2012 to 2013. Therefore, none of the selected patients in this study received neoadjuvant chemotherapy before the operation. This factor would have an unpredictable impact on the evaluation of the treatment effect in these gastric cancer patients. Second, we selected patients who had to receive S-1 because of the adverse drug reactions of systemic intravenous chemotherapy, and these patients were obviously few in number. Due to the small sample size, the evidence we provided is limited. Because of the small sample size, the subgroup analysis would have less significance, so we did not employ a subgroup analysis in our study. Hence, the validity of sequential therapy after operation remains unclear and should be examined in another study.

5. Conclusion

In conclusion, we believe that sequential therapy is a safe and effective chemotherapy regimen for postoperative gastric patients who are intolerant to conventional intravenous chemotherapy. The validity of this result should be examined in a retrospective or prospective study with a larger sample of patients or even in randomized trials.

Author contributions

Conceptualization: long yan, Hongbin Liu.

Data curation: long yan, Hongtao Li.

Formal analysis: Hongbin Liu, Chaoyang Wang, Gaitian Li.

Investigation: long yan, Xiaopeng Han, Tingbao Cao, Chaoyang Wang.

Methodology: long yan, Hongtao Li.

Project administration: Hongbin Liu.

Writing – original draft: long yan.

Writing – review & editing: Hongbin Liu.

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