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ORIGINAL ARTICLE

Clinical study of docetaxel plus S-1 as neoadjuvant therapy for advanced gastric cancer

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Abstract

Objective To evaluate the efficacy, toxicity, and operative complications of docetaxel in combination with S-1 for treating patients with advanced gastric cancer.

Methods From July 2013 to December 2014, 30 patients with advanced gastric cancer were treated with i.v. docetaxel 75 mg/m^2 on day 1 and oral S-1 60 mg/m^2 bid on days 1–14 every 3 weeks. The efficacy and toxicity were evaluated after two chemotherapy cycles.

Results The overall treatment response (complete response [CR] + partial response [PR]) was 76.6% (23/30), CR was 6.7% (2/30), PR was 70.0% (21/30), SD was 23.3% (7/30), and progression disease was 0% (0/30). All patients were treated surgically. Twenty-six patients received radical surgery; of them, 23 received D2 lymph node dissection. The other four patients received exploratory celiotomy. No patients died in the group, and the adverse reactions included neutropenia, diarrhea, nausea, and vomiting.

Conclusion Docetaxel/S-1 combination is highly active, safe, and well tolerated in patients with advanced gastric cancer. Further investigations in randomized studies are warranted.

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Key words: advanced gastric cancer; neoadjuvant chemotherapy; surgery; curative operation

For most patients with advanced gastric cancer, even if radical surgery and lymph node dissection are performed, it remains difficult to achieve a biological radical cure, while a high risk of recurrence persists post-surgery [1]. In recent years, with improvements in our understanding of tumor biological behavior, therapy for gastric cancer has changed from surgery only to a new mode of neoadjuvant therapy followed by a standard surgery for advanced gastric cancer. Gastric cancer is relatively sensitive to chemotherapy, but a unified efficient gold standard drug or treatment is currently lacking. Ajani from America MD Anderson Cancer Center reported that docetaxel-based chemotherapy may be the most important progress in treatment of gastric cancer [2]. Subsequently, scholars in many countries have made multiple improvements to docetaxel-based chemotherapy regimens to achieve high efficacy and low toxicity. Patients in the current study received a combination of docetaxel and S-1 since neoadjuvant therapy is highly active and well tolerated.

Patients and methods

Clinical data

The study included 30 patients with gastric cancer who were in the hospital between July 2011 and December 2012 (–60% men; median age, 58 years; age range, 32–73 years) (Table 1). Eligibility criteria included: (1) stomach cancer diagnosed by preoperative gastroscopic biopsy pathology; (2) advanced gastric cancer diagnosed by gastroscopy, ultrasound, computed tomography (CT) and without liver, lung, brain, or bone metastases with TNM staging using the 7th edition of the American Joint Committee on Cancer and International Union for Control TNM staging criteria [3]; (3) chemotherapy-naive; (4) normal hepatorenal, blood, and cardiopulmonary function on preoperative examinations as well as no surgical or chemotherapy contraindications; and (5) relatives informed of the study objective and regimens as well as the possible adverse reactions of neoadjuvant therapy and signed an informed consent from. Exclusion criteria included: (1) history of severe heart or lung disease; (2) history of congestive heart failure, frequent episodes of an-

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Table 1 Patient characteristics

Characteristic	No. of patients (n = 30)
Sex	
Male	18
Female	12
Age (years)	
Median	58
Range	32–73
ECOGPS	
0–1	30
2	0
Disease status	
Locally advanced disease	30
Metastatic disease	0
Histology	
Adenocarcinoma, moderately differentiated	9
Adenocarcinoma, signet-ring cell carcinoma and mucinous adenocarcinoma, poorly differentiated	21
Tumor location	
Upper	5
Middle	7
Lower	18
TNM-staging	
cT3N + M0	14
cT4N + M0	16
The histological grading of G	
I	5
II	7
III	12
IV	6

gina pectoris, or myocardial infarction in the preceding 6 months; (3) resistant hypertension; (4) lung dysfunction or severe pulmonary infection; (5) history of mental illness; and (6) distant metastasis precluding surgery.

Methods

Patients were treated with i.v. docetaxel (Batch Number: 20100127a; QiLu Pharmaceutical Co., Ltd.) 75 mg/m^2 on day 1 and oral S-1 (Batch Number: 101101; ShanDong New Era Pharmaceutical Co., Ltd.) 60 mg/m^2 bid on days 1–14. After 1 week of rest, the next cycle was started. We treated the patients with oral dexamethasone 8 mg q12h for 3 days before the day of chemotherapy to prevent a docetaxel allergic reaction and fluid retention as well as 5-hydroxytryptamine-3 routinely to prevent vomiting. Patients underwent twice-weekly blood and hepatorenal function tests and used granulocyte colony stimulating factor as needed accordingly. Patients rested for 2 weeks after two cycles of chemotherapy, underwent a second CT examination, and ultimately underwent surgery 4 weeks after chemotherapy.

Efficacy evaluation

The following were performed to evaluate the regimen's efficacy: clinical observation, in which we used the Response Evaluation Criteria in Solid Tumors to identify complete tumor remission (CR), partial remission (PR), tumor stability (SD), progression disease (PD), and response rate (RR) [4]; and observed postoperative complications using Common Terminology Criteria for Adverse Events v3.0 [5].

Surgery

All of the patients underwent surgery under general anesthesia 4 weeks after the completion of chemotherapy. Nasogastric and nutrition tubes were placed preoperatively. The modus operandi was decided according to the intraoperative situation and abdominal drainage tubes were routinely placed prior to abdominal closure.

Statistical method

We used SPSS 12.0 for the statistical analyses.

Results

Treatment response to neoadjuvant chemotherapy

After neoadjuvant chemotherapy, all patients underwent a radiologic exam to assess tumor response. The treatment RR (CR + PR) was 76.7% (23/30), CR was 6.7% (2/30), PR was 70.0% (21/30), SD was 23.3% (7/30), and PD was 0% (0/30). The physical condition of patients with varying degrees of symptom remission, such as better appetite or increased weight, improved significantly.

Neoadjuvant therapy toxicity

The patients' adverse reactions primarily included hematology toxicity (evidenced by decreases in white blood cell count) and non-hematologic toxicity mainly for nausea and vomiting, mostly at level 1–2. Table 2 shows the toxicity noted in the 30 assessable patients.

Surgery

Twenty-six patients received radical surgery (86.7%); of them, 23 (88.5%) received D2 lymph node dissection. The other four (13.3%) underwent an exploratory celiotomy. Two patients who underwent radical surgery did not receive D2 lymph node dissection because of the surgical bleeding caused by body fat. Another patient developed anesthesia-induced arrhythmia during the operation, so the D2 lymph node dissection was not performed to reduce the surgical time. The rest of the patients who underwent exploratory celiotomy had an identified pancreatic neoplasm or the tumor on Vaterian cancer for which they could not undergo radical surgery.

Table 2 Toxicity noted in the 30 assessable patients

Toxicity	No. of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Neutropenia	7	2	1	0
Anemia	4	0	0	0
Thrombocytopenia	3	2	0	0
Nonhematologic ~~gastrointestinal~~				
Nausea and vomiting	9	5	2	0
Diarrhea	2	0	0	0
~~Nonhematologic, other~~				
Neurosensory ~~and~~ ~~Neuromotor~~	2	0	0	0
Liver damage	3	1	0	0
Alopecia	3	1	0	0

Table 3 Pathological condition of new adjuvant chemotherapy after surgery and tumor downstaging

Category	Cases
The postoperative pathology	
Pathological complete remission (pCR)	1
Pathological partial remission (pPR)	24
No pathological changes (nPC)	5
Pathological downstaging after surgery	
pT0N0M0	1
pT1N0M0	1
pT2N0M0	12
pT2N1M0	5
pT3N1M0	4
pT3N2M0	2
pT4N1M0	5

cTNM, clinical stage; pTNM, pathological stage

Postoperative pathology

In the current study, there were seven cases of medium-differentiated adenocarcinoma, eight of poorly differentiated adenocarcinoma, five of signet ring cell carcinoma, and 10 of myxoadenocarcinoma. The postoperative pathological analysis showed that the tumor cells of most patients had differing degrees of degeneration, liquefaction, and necrosis. Fibrous tissue in tumors had hyperplasia, small blood vessels inflammatory occlusion, and thrombosis (Table 3).

Postoperative complications

Four patients had postoperative complications, including one with anastomotic leakage, two with a surgical site infection, and one with a lung infection. The median hospital stay was 12.3 days, and no patients died perioperatively.

Discussion

Surgery remains the dominant treatment for advanced gastric cancer. The postoperative 5-year overall survival for advanced gastric cancer is approximately 30%–50%. Much research has been performed over many years in an effort to improve the treatment effect. The effect of surgery alone is very limited, and patients with gastric cancer can often receive only palliative surgery. In fact, even if such patients receive R0–R1 resection, their prognosis is not always satisfactory. Thus, it is necessary to explore more effective treatments to improve gastric cancer outcomes.

Frei postulated the concept of presurgical neoadjuvant chemotherapy [6] in 1982. Since gastric cancer is relatively sensitive to chemotherapy, its use prior to surgery has gained consensus approval. The histological examination of patients treated with two cycles of chemotherapy revealed significant tumor necrosis. Tumors do not shrink obviously after more than three cycles of chemotherapy and even tend to increase in size after four cycles [7]. There is currently no gold standard for neoadjuvant chemotherapy regimen or number of cycles, so conclusions must be drawn by the histological comparison of morphological changes in tumors among different numbers of regimens. If a chemotherapy therapy is too long, adverse reactions, especially bone marrow suppression, the operation time will be delay. Therefore, cycle length should be limited; in fact, scholars in many countries have proposed a 2–3-week limit [8–9].

Neoadjuvant chemotherapy has the following known advantages: (1) prevents postoperative tumor blood supply changes that affect chemotherapy efficacy; (2) prevents stimulation of residual tumor growth by primary tumor resection; (3) reduces tumor clinical stage and improves resection success rate; (4) reduces intraoperative spread, eliminates potential micrometastases, effectively blocks the free cancer cells, and reduces postoperative metastasis and recurrence; and (5) enables the use of chemotherapy sensitivity tests to understand tumor sensitivity to chemotherapy drugs and maximize efficacy [10]. Docetaxel is a new kind of cytotoxic drug that gained approval for treating advanced gastric cancer in the past 10 years. V325 research showed that the survival data of the docetaxel, cisplatin, and fluorouracil regimen were superior to those of the cisplatin and fluorouracil regimen for advanced gastric cancer. However, its severe adverse reactions, especially granulocytopenia level 3/4, are not well tolerated.

S-1 is a kind of compound capsule in which tegafur, gimeracil, and potassium oxonate play an anti-tumor role to enable patients to maintain higher longer-term serum fluorouracil concentration as well as improve the drug's antitumor activity and reduce its digestive tract toxicity.

Compared with fluorouracil, S-1 enable to maintain higher blood drug concentration to improve the antitumor activity, and reduce the toxicity obviously. S-1 is a safe and convenient oral medication. Maehara and Minagawa also proved that the docetaxel + S-1 (DS) combination has good efficacy and is well tolerated as second-line treatment of elderly patients with advanced gastric cancer and multiple liver and ovarian metastases [11–13]. Kunisaki proved that the RR of DS chemotherapy was 56% for advanced gastric cancer. The main adverse reactions were bone marrow suppression and gastrointestinal tract reactions, but the symptoms were mild and easily corrected after symptomatic treatment [14].

Based on the above theory, we evaluated the curative effect after two cycles of DS as neoadjuvant chemotherapy for advanced gastric cancer and operated 4 weeks after the chemotherapy ended. The treatment RR (CR + PR) was 76.6% (23/30), and every patient tolerated it well. Levels 1–2 hematological and non-hematological toxicity were noted. The treatment RR and toxicity were better than those of related studies. Some data showed that the RR of S-1 with docetaxel and cisplatin was 40.4% [15], while that of S-1 in combination with cisplatin was 55.6% [16].

The adverse reactions of these two regimens mainly consisted of bone marrow suppression and the severe gastrointestinal tract reaction, side effects that might have been caused by the cisplatin. Surgeons pay more attention to whether neoadjuvant chemotherapy increases surgical difficulty and leads to more postoperative complications. In this study, 26 patients received D2 radical surgery (86.6%); of them, 23 also underwent a D2 lymph node dissection (88.8%). Both rates are higher than those reported in the MAGIC study (69.3% and 42.5%, respectively) [14]. Four patients had postoperative complications, including one with anastomotic leakage, two with a surgical site infection, and one with a lung infection. The median hospital stay was 12.3 days. No cases of perioperative mortality were observed.

Twenty-six patients who underwent radical surgery received DS as an adjuvant therapy, while the other four patients who underwent an exploratory celiotomy received docetaxel, oxaliplatin, and S-1 to prolong survival time. This study showed that docetaxel in combination with S-1 as neoadjuvant therapy followed by surgery for the treatment of advanced gastric cancer is both safe and effective and improves the resection and radical surgery success rates. However, further randomized studies to confirm the present findings are warranted.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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