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β-Tubulin is a Predictive Marker of Docetaxel Combined with S-1 in Recurrent or Metastatic Gastric Cancer

Yuehong Cui, Rongyuan Zhuang, Qian Li, Shan Yu, Yiyi Yu, Yi Feng, Yan Wang, Xi Guo and Tianshu Liu*

Medical Oncology Department, Zhongshan Hospital, Fudan University, China

***Corresponding author:** Tianshu Liu, Medical Oncology Department, Zhongshan Hospital, Fudan University, Fenglin Road 180#, Shanghai, China, Tel: 86-21-13681973996, 86-21-64041990-7289; Fax: 86-21-52303355; E-mail: liutianshu@188.com, liu.tianshu@zs-hospital.sh.cn

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Abstract

Aim: The aim of this study was to evaluate efficacy and toxicity of low dose of docetaxel in combination with standard dose of S-1 for patients with recurrent or metastatic gastric cancer, and to investigate whether β-tubulin protein expression level is a predictive or prognostic factor.

Methods: From March 2010 to December 2011, 90 patients from Medical Oncology Department of Shanghai Zhongshan Hospital, Fudan University, were enrolled in this study. Patients with recurrent or metastatic gastric adenocarcinoma were treated with docetaxel of 40 mg/m^2 intravenously on day 1 and S-1 of 80 mg/m^2 orally for 14 days with one-week intermission as first-line chemotherapy. The chemotherapeutic effects were evaluated every 3 cycles using the Response Evaluation Criteria In Solid Tumors (RECIST1.1). The tumor tissues and the serum of peripheral blood were obtained at the start of the study to analyze the protein expression level of β-tubulin, which were estimated using immunohistochemistry(IHC) and enzyme-linked immunosorbent assay (ELISA), respectively. Response and toxicity were analyzed. All the patients were followed-up until the time of progression, death, or the censored time, to calculate progression-free survival (PFS) and overall survival (OS) time.

Results: In total, 90 patients (median age: 60.5 years [range: 28–76 years]) received a total of 491 treatment cycles (median: 6 [range: 2–9]) of docetaxel combined with S-1 chemotherapy, and 291 cycles of single S-1-maintenance treatment. Three complete response (CR) and thirty-eight partial responses (PR) were observed, with an overall response rate (ORR) of 45.1%. Median OS was 12.5 months, and median PFS was 7.0 months. PFS and OS in patients with peritoneal metastases were significantly longer compared to patients with other metastatic loci. β-tubulin protein expression levels in tumor tissue and in serum were significantly lower in responders than in non-responders. Lower expression of β-tubulin protein in serum but not in tumor tissues was associated with more serious toxicities.There was significant correlation between tumor tissues and peripheral blood about the expression of β-tubulin. Peritoneal metastasis was an independent prognostic factor by COX regression. PFS and OS were not correlated with β-tubulin expressive level.

Conclusion: This combination of standard dose of S-1 and low dose of docetaxel is effective and well tolerated in patients with recurrent or metastatic gastric cancer. Peritoneal metastasis is treated more effectively by this regimen than other forms of metastases. Baseline expression levels of β-tubulin could predict the response. β-tubulin is a predictive marker.

Keywords: Stomach neoplasm; Chemotherapy; β-Tubulin; Docetaxel; Metastasis

Introduction

Docetaxel is a taxane anti-mitotic agent that binds to free tubulin and leads to the assembly of stabilized microtubule bundles, inhibition of the cell cycle, and cell death due to apoptosis. Phase II trials have shown that single-agent docetaxel, which inhibits microtubule depolymerization and is widely used for the treatment of metastatic gastric cancer, has response rates of 16–24% [1-3]. Docetaxel in gastric cancer is considered effective in the pivotal study of V325. In the V325 study, the dose of docetaxel was 75 mg/m^2 with TTP (time to progression) of 5.6 months and OS of 9.2 months, but the grade 3~4 hematologic toxicity was severe, especially the incidence of neutropenia was as high as 82% [4]. In 2012 ESMO (European Society of Medical Oncology) congress, the results of modified DCF (docetaxel-cisplatin plus fluorouracil) regimen in Chinese patients reported that 60 mg/m^2 docetaxel got 7.2 months PFS and 10.15 months OS with 60.5% incidence of grade 3~4 neutropenia. Therefore, whether low dose docetaxel is appropriate for Asian patients, with high effectiveness and less toxicity is a question needed to be answered. In 2014, Japanese START clinical trial published the final results that standard dose of S-1 (80 mg/m^2) combined with low dosage of docetaxel (40 mg/m^2) got the median OS of 12.5 months [5].

Fundamental studies have shown that high levels of β-tubulin are associated with taxane resistance in several human cancer cell lines, including lung, ovarian, prostate, and pancreatic cancers [6-9]. However, there are conflicting data. It has been found that the target components microtubules, which are thought to mediate refractoriness through alterations of the expression pattern of tubulins or microtubule associated proteins and the expression of alternative tubulin isoforms, failed to confirm such association in breast cancer

[10]. Some research have reported that β-tubulin expression is a simple and useful marker for predicting the clinical response of gastric cancer patients to docetaxel-based chemotherapy [11-13], yet clinical data have been limited and inconsistent, such as difference in clinical endpoints measured and in methods of tissue collection preparation and storage. Whether β-tubulin can become a valid practical biomarker deserves further confirmation.

Predictive biomarkers indicate the likely benefit of treatment, whereas prognostic biomarkers are associated with survival that is independent of the treatment effect. Based on the previous results, we did a pilot study to practice the low-dosage regimen of docetaxel combined with standard-dosage of S-1 in advanced gastric cancer. The aim of this study was to investigate ORR, PFS, and OS, as well as to ascertain whether β-tubulin protein expression level is a predictive or prognostic factor for patients with advanced gastric cancer to S-1 combining docetaxel chemotherapy.

Patients and Methods

Patient eligibility

Between March 2010 and December 2011, 90 patients administered in the Department of Medical Oncology of Shanghai Zhongshan Hospital, Fudan University, were enrolled in this study. The last follow-up was in March 2014. All the recruited patients were clinically inoperable, recurrent or metastatic gastric cancer patients .The following criteria should be met. First, the patient must have no prior chemotherapy, or one adjuvant regimen (completed >6 months previously) that did not include a taxane or S-1. The patients were also required to have an Eastern Cooperative Oncology Group performance status of 0–2; an age of at least 20 years; sufficient hematological, renal, and hepatic functioning; and last, a life expectancy of at least 12 weeks. The institutional ethical review board of Shanghai Zhongshan Hospital, Fudan University approved the study, and written informed consent was obtained from all patients.

Tumor response and toxicity assessment following chemotherapy

For this regimen, docetaxel 40 mg/m^2 was administered as a 1-h infusion on the morning of day 1 of each cycle, and S-1 80 mg/m^2 was administered orally for two weeks, followed by a drug-free interval of one week. Dexamethasone was added to the infusion to reduce the risk of a hypersensitivity reaction, according to the manufacturer's instructions. Six to eight cycles of S-1/docetaxel treatment followed by S-1 single agent maintenance till disease progression or untolerance.

RECIST 1.1 was used to assess tumor response. Tumor size was determined from all measurable lesions in the week preceding treatment using CT or MRI. These imaging studies were repeated, and tumor response was confirmed at 4 weeks for CR or PR or 6 weeks for SD (stable disease). In this study, we also enrolled the patients who had only peritoneal metastasis. These patients' non-measurable lesions were evaluated by CT, MRI or clinical manifestation. For the final analysis, these patients were divided into 2 groups according to tumor response: a responder group and non-responder group. The responder group comprised of patients with CR or PR. The responder group of peritoneal metastasis with non-measurable lesions included CR, non-CR/ non-PD.

Toxicity was graded at each cycle according to the National Cancer Institute Common Toxicity Criteria version 3.0.The dose of S-1 alone was to be reduced to 60 mg/m^2 in any event of grade 3 to 4 toxicities and there was no dose reduction for docetaxel. Treatment with both agents was discontinued if recovery did not occur within 14 days.

Measurement of β-tubulin protein expression level

IHC analysis: The tumor tissues from the samples of surgery or endoscopy were detected by IHC. For antigen retrieval, retrieval solution was automatically poured onto the sections, and was heated for 20 minutes at 100. Endogenous peroxide activity was blocked via 10 minutes of immersion in 3% hydrogen peroxide. With diluted primary antibodies for β-tubulin (rabbit monoclonal antibody, product No.#3124-1, 1:250, Epitomics, Burlingame, CA 94010-1303, U.S.A.), the sections were incubated for 60 minutes at 37. Immunoperoxidase staining was conducted using the DAB system (Shanghai Sango Biotech Co., Ltd. #PW017) and the sections were counterstained lightly with hematoxylin.

Interpretation of immunohistochemical staining: The staining intensity was graded as follows: no staining, weak staining, strong staining and very strong staining, which were scored from 0 to 3. The staining square was graded by the presence of positively stained tumor cells: no specific staining, 0-5% tumor cells, 5% to 10% tumor cells, 11% to 50% tumor cells and >50% tumor cells, which were also scored from 0 to 4. The immunohistochemical value was acquired as the score of staining intensity multiplied the score of staining square [14,15].

ELISA: Serum specimens were obtained from the patients' peripheral blood before the first session of chemotherapy and then after every 3 cycles of chemotherapy. The specimens were assigned with anonymous marks, and the protein expression level of β-tubulin in the serum was determined by ELISA following the human beta-tubulin Elisa kit (1231 Campanile Drive San Diego, CA92156). First, the sample was diluted and added to standard solution. This mixture was placed into the wells of the ELISA kit, and the plate was closed using a closure-plate membrane and incubated for 30 min at 37°C. The next steps involved configuration of the liquid, washing, addition of the enzyme, incubation, and another washing, before chromogen solutions A and B were added to each well. The wells were then kept out of light for 15 min at 37°C. The reaction was terminated using a stop solution and the absorbance was calculated for each well at 450 nm within 15 min of reaction termination. A blank well was used as standard.

Statistical analysis: The correlation between baseline β-tubulin and the toxicity/anti-tumor effects of docetaxel-based chemotherapy was evaluated. The Independent-sampls T test was used to compare protein expression levels and various factors. Multivariate analysis was from COX regression model. PFS and OS were estimated using the Kaplan-Meier survival analysis by log rank test. The association of β-tubulin expression in tumor tissues and peripheral blood was evaluated by correlated analysis. SPSS software (version 11.5) was used in all analyses, and a P-value of less than 0.05 was considered significant.

Results

Patient characteristics

Patient characteristics were shown in Table 1. All the patients (51 males and 39 females; median age: 60.5 years [range: 28–76 years]) had

recurrent or metastatic gastric cancer. With regard to the histologic type, 25 patients had high- and moderate- differentiated adenocarcinoma, and 65 patients had low- and poor- differentiated adenocarcinoma. In total, 61 patients (67.0%) received second-line chemotherapy. After a median follow-up of 13.0 months (range: 5.00–45.00 months), 7 out of the 90 patients (7.8%) were alive.

Characteristic	No. of patients (%)
Age, years old	
Median	60.5
Range	28-76
Gender	
Male	51 (56.0)
Female	39 (42.9)
ECOG PS	
0	12 (13.2)
1	64 (70.3)
2	14 (15.4)
Lauren type	
High-/moderate-differentiated adenocarcinoma	65 (71.4)
Low-/poor-differentiated adenocarcinoma	25 (27.5)
No. of organs involved	
1	55 (60.4)
2	20 (22.0)
3	15 (16.5)
Prior therapy	
Surgery only	5 (5.5)
Surgery + adjuvant chemotherapy	26 (28.6)
None	59 (64.8)
Metastasis	
Lymph nodes	39 (43.3)
Liver	23 (25.6)
Lung	5 (5.6)
Bone	6 (6.7)
Peritoneum	51 (56.7)

Table 1: Patient characteristics (N=90).

Clinical efficacy: response, toxicity, and survival

In total, 90 patients could be assessed for tumor response at least once during the study. PFS was analyzed in all patients and OS was analyzed in 83 patients. Thirty-eight patients had PR and three patient had CR; hence, the overall response rate (ORR=CR + PR) was 45.1%. Of all the patients, 42 (46.2%) patients had stable disease; therefore, the overall disease control rate (DCR=CR + PR + SD) was 91.3%. In 7 patients (7.7%), progressive disease was obtained after the first evaluation.

Most of grade 3-4 toxicities were hematologic. Grade 3-4 neutropenia was observed in 11 patients (12.2%), 1 patient (1.1%) got anemia, and 3 patient (3.3%) was diagnosed with thrombocytopenia. Grade 3-4 febrile neutropenia was not observed. All toxicities could be controlled by granulocyte colony-stimulating factor administration. Nonhematologic toxicities were generally mild in severity, and no grade 4 toxicities of this type were observed. All the toxicities were listed in Table 2. The treatment-related toxicities could be managed with appropriate medical care, and there were no treatment-related mortalities during the study.

Toxicities	No. of patients (%)	
	Grade 1-2	Grade 3-4
Hematologic		
Leukopenia (including neutropenia)	28 (31.1)	11 (12.2)
Anemia	18 (20.0)	1 (1.1)
Thrombocytopenia	5 (5.6)	3 (3.3)
Nonhematologic		
Fatigue	25 (27.8)	3 (3.3)
Anorexia	25 (27.8)	4 (4.4)
Nausea	14 (15.6)	6 (6.7)
Vomitting	2 (2.2)	2 (2.2)
Diarrhea	4 (4.4)	1 (1.1)
Alopecia	4 (4.4)	0 (0)
Neurosensory	6 (6.7)	0 (0)
Abnorma liver function	4 (4.4)	0 (0)
Hand-foot syndrome	5 (5.6)	0 (0)

Table 2: Toxicities for 90 assessable patients.

The median survival time was 12.5 months (95% CI: 11.47–13.53 months) and the median PFS was 7.0 months (95% CI: 6.19–7.81 months; Figure 1). Patients with peritoneal metastasis had longer PFS and OS than patients with other metastases (9.77 ± 5.29 vs 6.36 ± 3.40 months, P=0.001 for PFS; 16.36 ± 8.92 vs 12.74 ± 6.42 months, P=0.035 for OS).

Relationship of protein expression levels of β-tubulin with response and toxicity

ELISA was used to measure the protein expression levels of β-tubulin in 84 patients at the time point of baseline. The mean β-tubulin in serum was 376.16 ± 216.89 pg/mL. The β-tubulin protein expression level was not related to patients' gender, age, performance status, or pathological type. β-Tubulin protein expression levels were significantly lower in responders (321.02 ± 190.21 pg/mL) than in non-responders (426.29 ± 229.32 pg/mL; P=0.028). IHC method was used to detect β-tubulin expression in 68 patients' tumor tissues. The

expression of β-tubulin protein was obviously lower in responders (IHC score 5.00 ± 3.86) than that in non-responders (IHC score 7.27 ± 4.50; P=0.030) (Figure 2).

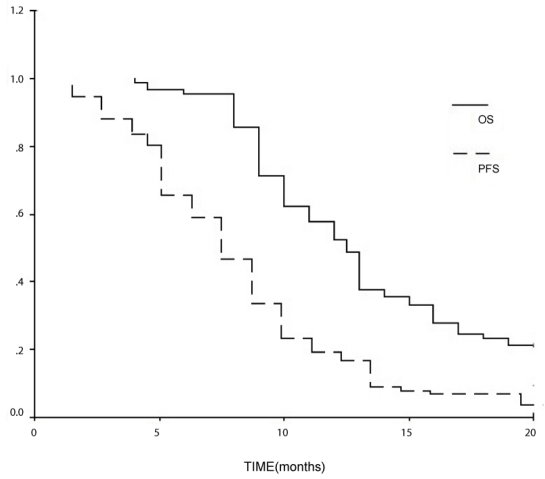

Figure 1 : Median OS was12.5 months [95% CI, 11.47-13.53 months], and median PFS was 7.0 months [95% CI, 6.19-7.80 months] for all patients.

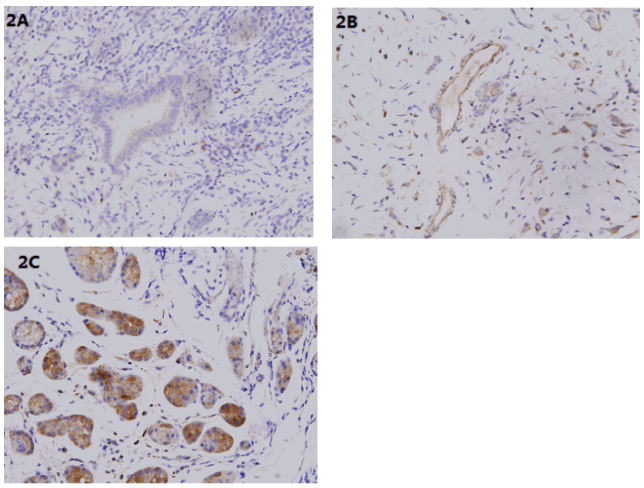

Figure 2 : Representative staining for β-tubulin in gastric cancer: absence of staining (2A), moderate staining (2B), strong staining (2C). Photomicrographs are taken at ×20 objective magnification (A–C).

In total, 21 patients (23.1%) developed grade 3-4 toxicities. β-Tubulin baseline expression level in these patients with severe toxicities was 258.68 ± 112.93 pg/mL. However, in patients without grade 3-4 toxicities, β-tubulin expression level was 415.32 ± 229.41 pg/mL (P=0.004). Therefore, low expression level of β-tubulin in patients indicated that they were more likely to develop severe toxicity. However, β-tubulin expression in tumor tissues could not predict the toxicity (Table 3).

Correlation of β-tubulin protein expression in tumor tissues and the serum of peripheral blood with survival time and prognosis

There was significant correlation between tumor tissues and peripheral blood about the expression of β-tubulin (Pearson's R=0.647, P<0.05). The median values of β-tubulin in serum and tumor tissues were 333.81 pg/ml and score 6.0, respectively. Whether β-tubulin expression level higher or lower than the median value was not associated with PFS and OS (Table 4). By COX regression analysis, peritoneal metastasis was an independent prognostic factor. Therefore, the patients with peritoneal metastases could benefit from this regimen maximally. Baseline β-tubulin was a predictive but not a prognostic marker.

	β-Tubulin	**P**
In serum (pg/ml)		
Response		
Responders (n=40)	321.02 ± 190.21	
Non-responders (n=44)	426.29 ± 229.32*	0.028
Toxicity		
Grade 1-2 toxicity (n=63)	415.32 ± 229.41	
Grade 3-4 toxicity (n=21)	258.68 ± 112.93*	0.004
In tumor tissues (score)		
Response		
Responders (n=31)	5.00 ± 3.86	
Non-responders (n=37)	7.27 ± 4.50 *	0.030
Toxicity		
Grade 1-2 toxicity (n=52)	6.62 ± 4.50	
Grade 3-4 toxicity (n=16)	5.00 ± 3.61	0.195

Table 3 : The expression of β-tubulinin serum and tumor tissues at baseline was in relation to response, and β-tubulin in serum but not in tumor tissues could predict severe toxicity.

*p<0.05, with statistical difference

	≥ median	**< median**	**P value**
In serum (pg/ml)			
median (333.81)	n=42	n=42	
PFS(months)	8.43 ± 4.22	8.63 ± 5.59	0.852
OS(months)	16.05 ± 8.08	14.44 ± 8.31	0.372
In tumor tissues (score)			
median (6.0)	n=39	n=29	
PFS(months)	7.59 ± 3.57	8.78 ± 5.80	0.336

OS(months)	14.32 ± 7.05	16.10 ± 10.43	0.403

Table 4 : The expression of β-tubulinin serum and tumor tissues at baseline was not in relation to PFS and OS.

Discussion

Based on the results of V325 study, docetaxel was often drawn into treating gastric cancer, but the DCF regimen has been widely criticized and held under scrutiny for its toxicity profile. Thus, strategies to control treatment-related side effects without compromising efficacy were proposed, including changes in the dose and schedule, such as weekly dosing schedules or low-dose regimen. Phase I and II studies have explored docetaxel 20~40 mg/m^2 of weekly dosing schedules to minimize the frequency of side-effects [16-20]. Therefore, docetaxel 40 mg/m2, even less than 40 mg/m^2, in several schedules has been verified to be effective with tolerable toxicities [21,22]. Phase II studies on S-1 administered at a dose of 40 mg/m^2 twice daily for two weeks in combination with docetaxel administered in doses ranging from 35 to 60 mg/m^2 have indicated that the rates of grade 3 and 4 neutropenia were between 29.4% and 67%. The ORRs in these studies ranged from 46% to 87% [23-26]. Therefore, a dose of S-1 80 mg/m^2 for two weeks and one dose of docetaxel 40 mg/m^2 on day 1 were selected as first-line regimen in this pilot study.

Previous studies have reported that the three-week S-1/docetaxel chemotherapy was an effective and accepted regimen for the treatment of advanced gastric cancer (DCR: 93.8%; median OS: 14.3 months; TTP: 7.3 months) [26]. Although OS and ORR were greater in patients on this regimen than that of other regimens, the trials were done just in Japan with small sample size and there was a lack of data from other countries. The patients in our study receiving S-1 (80 mg/m2)/ docetaxel (40 mg/m^2) chemotherapy exhibited very good tumor DCR (91.3%), ORR (45.1%), median PFS (7.0 months; 95% CI: 6.19-7.81 months), and median OS (12.5 months; 95% CI: 11.47-13.53 months), which was comparable to the OS of patients on other regimens, such as docetaxel–cisplatin–5-FU (10 months), epirubicin–cisplatin–5-FU (10 months), and oxaliplatin–folinic acid–5-FU (11 months) [27,28]. Nonhematologic toxicities were generally mild and all were grade 3 or less. Anorexia and nausea that were the most common grade 3 nonhematologic toxicities were observed in 11.0% patients. The predominant hematologic toxicity was grade 3-4 myelosuppression, although this only occurred in 16.6% patients which was much lower than that in V325 study (80%), also lower than that in the modified DCF regimen of Chinese population which had the dosage of docetaxel of 60 mg/m^2, but with 60.5% of grade 3-4 hematological toxicity. All the hematologic and nonhematologic toxicities could be well-controlled in this study. 50 patients (55.56%) received single S-1 maintenance therapy and 61 patients (67.0%) received second-line chemotherapy. It was concluded that the S-1/docetaxel regimen resulted in few toxicities and increased the possibility for further therapy.

Gastric cancer with peritoneal metastasis, which is caused by the dissemination of free tumor cells from the primary gastric cancer site, is one of the most common types of cancer spreading and results in death of the patients. Operative treatment of peritoneal metastasis is inadvisable and it is the most difficult type of cancer spreading to treat [29]. The standard care for gastric cancer with peritoneal metastasis is chemotherapy. However, there is no chemotherapy regimen with a sufficient level of evidence. Taxanes such as paclitaxel and docetaxel, have been studied as promising intraperitoneal drugs for peritoneal metastasis by maintaining a high concentration in the peritoneal cavity [30,31]. It was rarely reported the relationship between intravenous taxanes and peritoneal metastasis. However, the Japanese START trial compared the administration of single agent S-1 with S-1 plus docetaxel for the treatment of advanced gastric cancer. This trial stratified non-measurable patients, such as peritoneal metastatic patients. In these patients, OS was 12.5 vs. 10.8 months, respectively (P=0.032). Among patients with non-measurable lesions, OS was significantly longer in the docetaxel plus S-1 group (17.9 month) than in the S-1 alone group (12.0 months; HR 0.65; P = 0.013) [5]. It was concluded that S-1 plus docetaxel was a superior treatment option for peritoneal metastatic patients. Why was S-1/taxane regimen effective in peritoneal metastasis? Japanese researchers investigated S-1 for the treatment of peritoneal metastasis by using a mouse peritoneal metastasis model from colon cancer. Colon cancer cells were transplanted intraperitoneally into mice. S-1 was orally administrated on day 20 post-transplantation. The AUC 0-8h values of both 5-FU and gimeracil(a strong dihydropyrimidine dehydrogenase inhibitor) were greater in the peritoneal tumor tissue than in the normal peritoneal tissue. The AUC of 5-FU in the peritoneal tumor tissue was 2. 9 times higher than that in plasma [32]. It was found that low-dose docetaxel, which did not induce G2/M arrest, increased p53 and p21 and resulted in down-regulation of thymidylate synthase(TS), and down-regulation of TS was considered to be responsible for the synergistic effect of S-1 [33]. In this study, we also stratified the peritoneal metastatic patients, and found that peritoneal metastasis wasn't related with gender, age and histological type. Survival analytic results showed that PFS and OS were longer in these patients than that in patients with other metastases. The patients with peritoneal dissemination has usually not yet evaluated and explored from clinical study because of disease risk and having no measurable disease. In this study, we evaluated the response of peritoneal metastasis not only by CT or MRI, but also by clinical symptom, such as abdominal discomfort improvement, ascites disappearance and without drainage of ascites. Therefore, patients with peritoneal metastases benefited more from this regimen than those with other metastases.

In this study, we tested the β-tubulin expression level in tumor tissues and the serum of peripheral blood before chemotherapy. We used IHC method to detect β-tubulin expression in tumor tissues and ELISA to test it in the serum of peripheral blood. It is known that the sample from peripheral blood is a convenient way to get and to be investigated. In the present study, we just got the tumor tissue samples and the peripheral blood samples simultaneously in 67 patients, the baseline protein expression levels of β-tubulin made an obvious difference between the responders and non-responders both in serum and in tumor tissues. We also found that low baseline β-tubulin protein expression in serum was associated with high grade of toxicity, but that was not in tumor tissues. In addition, the expression of β-tubulin in serum of patients' peripheral blood reflects its metabolic situation in liver, so we took into consideration that it was not only affected by the chemotherapeutic drug, but also influenced by the metabolic enzyme in the liver. Thus, we investigated β-tubulin expression in tumor tissues. We found that β-tubulin expression in serum and in tumor tissues was significantly correlated. Based on the results of this study, we can suggest that the response of patients with low protein expression levels of β-tubulin undergoing docetaxel-based chemotherapy can be determined, and might have longer survival time. Therefore, the protein expression level of β-tubulin might be considered a predictive factor for the response of S-1/docetaxel

chemotherapy at the individual level. β-tubulin was a prognostic factor in non-small cell lung cancer and breast cancer [34,35]. In head and neck squamous cell carcinoma, β-tubulin was a predictive and prognostic factor, because it not only could predict outcome of chemotherapy, but also was associated with PFS and OS [36]. Hwang and his colleagues reported that β-tubulin is a predictive marker for taxane-based chemotherapy in recurrent and metastatic gastric cancer [37], which was consistent with our study.

The activity and tolerability of the S-1/docetaxel regimen, as well as the convenience of oral S-1 dosing, meant that this new regimen was highly promising and had the potential to improve the survival of gastric cancer patients with peritoneal metastasis. Based on the results of START trial, we tested this regimen in Chinese patients. It deserves further study in other races. The true role of β-tubulin in the prognosis of recurrent or metastatic gastric cancer needs to be indentified in randomized trials of large sample.

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