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ORIGINAL ARTICLE

Two therapeutic regimens for advanced gastric carcinoma: DOS chemotherapy alone *vs.* trastuzumab combined with DOS

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Summary

Purpose: *The purpose of this study was to explore the efficacy and safety of trastuzumab combined with docetaxel, oxaliplatin and S-1 (DOS regimen) in neoadjuvant chemotherapy for advanced gastric carcinoma.*

Methods: *A total of 106 patients with advanced gastric carcinoma were divided into Trastuzumab + DOS group (n=53) and DOS group (n=53). The HER-2-positive patients were treated with trastuzumab combined with DOS regimen, while the HER-2-negative patients were treated with DOS regimen alone. The imaging examination was performed to evaluate the efficacy every 2 cycles. Moreover, the short-term clinical efficacy, related adverse reactions and tumor pathological grade were observed and recorded in both groups, and the surgical resection rate, radical resection rate and postoperative complications were compared between the two groups.*

Results: *In Trastuzumab + DOS group and DOS group, the objective response rate (ORR) was 66.0% and 52.8%, respectively, and the disease control rate (DCR) was 94.3% and 90.6%, respectively. Besides, the surgical resection rate was 94.3% and 90.6%, respectively, in the two groups, while the R0 resection rate in Trastuzumab + DOS group was significantly higher than that in DOS group. The pathological response rate (≥ grade 1b) was 80.0% and 60.4%, respectively, in the two groups, which was obviously higher in Trastuzumab + DOS group than that in DOS group. Besides, there was 1 case of pathological complete response (pCR) in Trastuzumab + DOS group, and 0 case of pCR in DOS group.*

Conclusion: *Compared with DOS chemotherapy alone, trastuzumab combined with DOS regimen can significantly improve the pathological response rate and R0 resection rate without increasing the risk of surgery in neoadjuvant chemotherapy for advanced gastric carcinoma, and the patient's tolerance is good, so it is worthy of clinical popularization and application.*

Key words: *trastuzumab, docetaxel, oxaliplatin, S-1, gastric carcinoma, neoadjuvant chemotherapy*

Introduction

According to the report of the International Agency for Research on Cancer in 2014, the morbidity rate of gastric carcinoma ranks 5th in the world, which is a major cause of cancer-related deaths [1]. In China, the morbidity rate of gastric carcinoma ranks 2nd in those of systemic malignant tumors in males and 4th in females, and the 5-year survival rate of patients with gastric carcinoma is <28% [2]. Gastric carcinoma has no early typical symptoms, and it is difficult to be diagnosed, so most patients are not definitely diagnosed until the middle and late stage, missing the optimal opportunity of surgical resection. Even though surgical resection is performed, the postoperative recurrence and metastasis rates reach up to 40-60%. The effects of radiotherapy and chemotherapy are

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not satisfactory, resulting in poor prognosis [3]. S-1 combined with platinum-based chemotherapeutic drugs is one of the standard chemotherapy regimens for advanced gastric carcinoma [4]. Studies have demonstrated that the overexpression of human epidermal growth factor receptor-2 (HER-2) protein can be found in gastric carcinoma tissues, which is positively correlated with the prognosis of patients [5]. It has been confirmed via randomized controlled clinical studies that the combination chemotherapy of HER-2 monoclonal antibody trastuzumab has significantly superior efficacy to chemotherapy alone in the advanced gastric carcinoma with HER-2 overexpression [6,7].

In the present study, the clinical data of 106 patients with advanced gastric carcinoma treated in our department from December 2016 to December 2018 were retrospectively analyzed, and the clinical efficacy and safety were compared between trastuzumab combined with docetaxel, oxaliplatin and S-1 (DOS regimen) and DOS neoadjuvant chemotherapy alone, so as to provide more bases for selecting the therapeutic regimen for such patients.

Methods

General data

A total of 106 patients with advanced gastric carcinoma were selected as objects of study, including 61 males and 45 females aged 26-73 years old. According to the HER-2 expression, economic conditions and physical conditions of patients, HER-2-positive patients were treated with trastuzumab combined with DOS neoadjuvant chemotherapy (Trastuzumab + DOS group, n=53), including 33 males and 20 females aged 58.13 years old on average. Before chemotherapy, there were 24 cases of moderate-to-high differentiation of tumors and 29 cases of poor differentiation. In terms of the tumor stage, 21 cases were in stage II and 32 cases in stage III. Besides, the remaining 53 HER-2-negative patients only underwent the DOS neoadjuvant chemotherapy (DOS group), including 28 males and 25 females aged 56.93 years old on average. Before chemotherapy, there were 31 cases of moderate-to-high differentiation of tumors and 22 cases of poor differentiation. In terms of the tumor stage, 26 cases were in stage II and 27 cases in stage III. There were no statistically significant differences in such baseline data as age, gender, tumor type, clinical stage, degree of tumor differentiation and Eastern Cooperative Oncology Group (ECOG) score between the two groups ($p>0.05$), and they were comparable (Table 1).

Inclusion criteria: patients diagnosed with gastric adenocarcinoma through preoperative gastroscopy and biopsy, those with locally advanced gastric carcinoma confirmed by CT (depth of tumor invasion > cT2 or cN+, cM0) and at least one measurable lesion, those meeting the TNM staging criteria of the International Union Against Cancer/American Joint Committee on Cancer (Version 7) in 2010 [8], HER-2$^+$ [immunohistochemistry (IHC3$^+$ or IHC2$^+$ and FISH$^+$)] patients (the HER-2 staining criteria were based on the HER-2 detection guideline for gastric carcinoma in 2016) [9], newly-treated patients with the left ventricular ejection fraction (LVEF) >50%

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

	Trastuzumab + DOS group (n=53) *n (%)*	*DOS group (n=53)* *n (%)*	*p*
Age, years	58.13±10.63	56.93±9.89	0.549
Gender			0.172
Male	33 (58.3)	28 (64.6)	
Female	20 (41.7)	25 (35.4)	
Tumor type			0.623
Intestinal type	39 (16.7)	43 (20.8)	
Diffuse type	9 (20.8)	7 (22.9)	
Mixed type	5 (62.5)	3 (56.2)	
Histologic differentiation degree			0.174
Moderate-to-high differentiation	24 (43.8)	31 (37.5)	
Low differentiation (signet ring cell, undetermined)	29 (25.0)	22 (29.2)	
TNM stage			0.328
II	21 (14.6)	26 (16.7)	
III	32 (10.4)	27 (6.2)	
ECOG score			0.541
0	33 (12.5)	36 (20.8)	
1	20 (33.3)	17 (35.4)	

DOS: docetaxel, oxaliplatin plus S-1; TNM: Tumor, lymph node, metastasis; ECOG: Eastern Cooperative Oncology Group.

shown in echocardiogram, those without congestive heart failure, a history of myocardial infarction, obvious abnormalities in blood routine, hepatic and renal functions, and severe complications, and those with the ECOG score of 0-1 point and an estimated survival time >3 months. All patients enrolled conformed to the *Declaration of Helsinki*, and signed the informed consent. This study was approved by the Ethics Committee of Zhuji Affiliated Hospital of Shaoxing University.

Treatment methods

In Trastuzumab + DOS group, trastuzumab (8 mg/m^2) was intravenously infused in the first cycle, as well as docetaxel (60 mg/m^2) intravenously infused at 0 d, oxaliplatin (130 mg/m^2) intravenously infused at 1 d, and S-1 at 1 d orally taken twice a day after morning and evening meal at a dose based on the patient's body surface area (40 mg/time in the case of body surface area <1.25 m^2, 40 mg in the morning and 60 mg in the evening in the case of body surface area of 1.25-1.50 m^2, and 60 mg/time in the case of body surface area >1.50 m^2). The first cycle of treatment lasted for 14 d every 3 weeks. In the second cycle, the dose of trastuzumab was adjusted to 6 mg/m^2, and the remaining operations were the same as above.

In DOS group, the DOS chemotherapy regimen was adopted as above. The gastroscopy and CT were reviewed every 2 cycles, and the efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The multidisciplinary discussion was made to determine whether to perform the surgery for patients. Neoadjuvant chemotherapy was conducted for 4 cycles at most [10], during which the changes in hemogram and cardiac function were monitored.

Observation indexes

The efficacy was evaluated through performing routine CT and MRI QWN DWDFCV CDE at the specified time according to RECIST 1.1, as follows. Complete response (CR): The tumor completely shrinks, and tumor markers return to normal for ≥4 weeks. Partial response (PR): The sum of the longest diameters of all target lesions declines by ≥30% for ≥4 weeks. Stable disease (SD): Between PR and progressive disease (PD). PD: The sum of the longest diameters of all target lesions increases by ≥20% or there are new metastases. Objective response rate (ORR)=CR+PR, and disease control rate (DCR)=CR+PR+SD. Each patient should finish the examination to determine the baseline of the tumor lesions before enrollment, and the efficacy was evaluated once every 2 cycles. If the patient had discomfort, he should be examined promptly in the hospital. Adverse reactions were observed during chemotherapy, and they were evaluated and recorded in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.0). The severity could be classified into grade I-IV.

The surgery-related indexes in both groups were recorded, and the differences in the surgical resection rate and radical resection rate were compared. The postoperative specimens in both groups were pathologically diagnosed by more than two experienced pathologists, and the pathological response rate was calculated. The pathological evaluation was based on the criteria for pathological changes of the Japanese Gastric Cancer Association, and the response of tumor to treatment was classified into the following grades: grade 0 (no tumor tissue necrosis is observed), grade 1a (residual viable tumor cells >67%), grade 1b (residual viable tumor cells of 33-67%), grade 2 (residual viable tumor cells <33%), and grade 3 (complete necrosis of tumor). ≥grade 1b indicates the pathological response, and grade 3 indicates the pathological CR (pCR) [11].

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for the intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was employed for the intergroup comparison. P<0.05 suggested statistically significant difference.

Results

Comparison of short-term efficacy

All of the 106 patients finished neoadjuvant chemotherapy for 2-3 cycles, with an average of 2.55 cycles, and the efficacy in them could be evaluated. In Trastuzumab + DOS group, there were 4 cases of CR, 31 cases of PR, 15 cases of SD and 3 cases of PD. In DOS group, there were 2 cases of CR,

Table 2. Comparison of clinical efficacy between the two groups of patients

	Trastuzumab+DOS group (n=53)	*DOS group (n=53)*	*p*
CR	4	2	
PR	31	26	
SD	15	20	
PD	3	5	
ORR (%)	35 (66.0)	28 (52.8)	0.166
DCR (%)	50 (94.3)	48 (90.6s)	0.462

DOS: docetaxel, oxaliplatin plus S-1; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

26 cases of PR, 20 cases of SD and 5 cases of PD. In the two groups, the ORR was 66.0% (35/53) and 52.8% (28/53), and the DCR was 94.3% (50/53) and 90.6% (48/53), respectively. The results revealed that there were no statistically significant differences in ORR and DCR between the two groups (p=0.166, p=0.462) (Table 2).

Comparison of adverse reactions

During chemotherapy, adverse reactions, mainly including myelosuppression, gastrointestinal reaction, liver function damage, neurotoxicity and hand-foot syndrome occurred in 106 patients to varying degrees. Among the hematologic adverse reactions, leukopenia had the highest incidence rate in the two groups (67.9% and 73.6), and the incidence rates of anemia and thrombocytopenia were 49.1% and 45.3%, 54.7% and 62.3%, respectively, mostly in grade I-II. Adverse reactions were all improved after timely and appropriate dose reduction of chemotherapy drugs and leukocyte-increasing symptomatic treatment, without affecting subsequent chemotherapy. In Trastuzumab + DOS group, there were 2 cases of grade III-IV nausea and vomiting, 3 cases of grade III-IV liver function damage and 3 cases of grade III-IV hand-foot syndrome. In DOS group, there were 5 cases of grade III-IV nausea and vomiting, 1 case of grade III-IV liver function damage and 1 case of grade III-IV hand-foot syndrome. The incidence of chemotherapy adverse reactions had no statistically significant differences between the two groups (p>0.05) (Table 3).

Surgical resection of tumor

In Trastuzumab + DOS group, 3 out of 53 cases gave up the surgery due to PD, and 50 cases (94.3%) underwent surgical resection, including 39 cases (78.0%) undergoing R0 resection. Among the 50 patients, 35 cases (35/50, 70%) received D2 lymph node dissection, and 15 cases (15/50, 30%) only received D1 lymph node dissection due to late stage. In DOS group, 5 out of 53 cases gave up the surgery due to PD, and 48 cases (90.6%) finished chemotherapy and underwent surgery, including 26 cases (54.2%) undergoing R0 re-

Table 3. Comparison of adverse reactions between the two groups of patients

	Grade I-IV			*Grade III-IV*		
	T+DOS group n (%)	*DOS group n (%)*	*p*	*T+DOS group n (%)*	*DOS group n (%)*	*p*
Hematological						
Anemia	26 (49.1)	24 (45.3)	0.560	3 (5.7)	2 (3.8)	0.647
Thrombocytopenia	29 (54.7)	33 (62.3)	0.430	4 (7.5)	6 (11.3)	0.506
Leukopenia	36 (67.9)	39 (73.6)	0.522	5 (9.4)	8 (15.1)	0.374
Non-hematological						
Nausea, vomiting	22 (41.5)	31 (58.5)	0.080	2 (3.8)	5 (9.4)	0.241
Diarrhea	14 (26.4)	19 (35.8)	0.294	0 (0)	2 (3.8)	0.153
Hepatic dysfunction	24 (45.3)	18 (34.0)	0.234	3 (5.7)	1 (1.9)	0.308
Neurotoxicity	7 (13.2)	10 (18.9)	0.427	1 (1.9)	2 (3.8)	0.558
Anorexia	9 (17.0)	6 (11.3)	0.403	1 (1.9)	0 (0)	0.315
Hand-foot syndrome	18 (34.0)	11 (20.8)	0.127	3 (5.7)	1 (1.9)	0.308

T: trastuzumab; DOS: docetaxel, oxaliplatin plus S-1.

Table 4. Comparison of postoperative pathologic grade between the two groups of patients

	Trastuzumab+DOS group (n=53) n (%)	*DOS group (n=53) n (%)*	*p*
Grade 0	0	0	
Grade 1a	10 (20.0)	19 (39.6)	
Grade 1b	17 (34.0)	23 (47.9)	
Grade 2	22 (44.0)	6 (12.5)	
Grade 3(pCR)	1 (2.0)	0 (0)	
Pathological response rate (≥ Grade 1b)	40 (80.0)	29 (60.4)	0.034

DOS: docetaxel, oxaliplatin plus S-1; pCR: pathologic complete response.

Table 5. Comparison of postoperative clinical and pathologic tumor stage between the two groups of patients

	CR	*I*	*II*	*III*	*IV*
		n (%)	*n (%)*	*n (%)*	*n (%)*
Trastuzumab+DOS group (n=50)					
Clinical TNM stage	4	0 (0)	21 (42.0)	29 (58.0)	0 (0)
Pathologic TNM stage	1	9 (18.0)	20 (40.0)	19 (38.0)	2 (4.0)
DOS group (n=48)					
Clinical TNM stage	2	0 (0)	25 (52.1)	23 (47.9)	0 (0)
Pathologic TNM stage	0	3 (6.3)	29 (60.4)	11 (22.9)	5 (10.4)

DOS: docetaxel, oxaliplatin plus S-1; TNM: tumor, lymph node, metastasis; CR: complete response.

section. Among the 48 patients, 31 cases (31/48, 64.6%) received D2 lymph node dissection, and 17 cases (17/48, 35.4%) only received D1 lymph node dissection due to late stage. The surgical resection rate showed no statistically significant difference between the two groups (p=0.462), while the R0 resection rate in Trastuzumab + DOS group was significantly higher than that in DOS group (p=0.013). Besides, no statistically significant differences were found in the incidence of postoperative complications between the two groups (4.0% *vs.* 8.3%), and there were no perioperative deaths. There were 2 cases of duodenal stump fistula in Trastuzumab + DOS group, and 1 case of duodenal stump fistula, 2 cases of wound infection and 1 case of pulmonary infection in DOS group.

Comparison of postoperative pathological grade

According to the criteria for pathological changes of the Japanese Gastric Cancer Association, the postoperative pathological changes were dominated by grade 1b and 2 in 50 patients receiving surgery in Trastuzumab + DOS group, including 1 case of pCR, while they were dominated by grade 1a and 1b in 48 patients receiving surgery in DOS group, and there was no pCR. No grade 0 patients were found in the two groups. The pathological response rate (≥ grade 1b) was 80.0% (40/50) and 60.4% (29/48), respectively, in the two groups, displaying a statistically significant difference, which was obviously higher in Trastuzumab + DOS group than that in DOS group (p=0.034) (Table 4).

Comparison of postoperative clinical stage and pathological stage of tumor

After 2.55 cycles of neoadjuvant chemotherapy for the 106 patients, 8 cases gave up the surgery due to PD, and the remaining 98 cases finished the surgery and received the biopsy, followed by pathological staging. The pathological results of postoperative biopsy revealed that Trastuzumab + DOS group had 9 cases in stage I, 20 cases in stage II, 19 cases in stage III and 2 cases in stage IV, including 1 case of pCR after operation, while DOS group had 3 cases in stage I, 29 cases in stage II, 11 cases in stage III and 5 cases in stage IV, without pCR after operation. Moreover, the clinical stage and pathological stage of 98 patients after neoadjuvant chemotherapy were compared, and it was found that there were 6 cases of CR. However, it was pathologically confirmed that only 1 case was pCR in Trastuzumab + DOS group, not true for the remaining 5 cases, suggesting the inconsistency between clinical stage and pathological stage. The tumor stage evaluated clinically before operation and the tumor stage confirmed pathologically after operation in both groups are shown in Table 5.

Discussion

Trastuzumab is a kind of humanized monoclonal antibody that has a potent antagonistic effect on HER-2-mediated biological functions, which can inhibit cell proliferation, induce apoptosis, control cell cycle progression and retard local neovascularization in tumors. Trastuzumab has been initially combined with conventional chemotherapy for the treatment of HER-2-positive patients with breast cancer, and it has been confirmed to play a positive role in inhibiting breast cancer development and optimizing chemotherapeutic efficacy [12,13].

As molecular biological research has been constantly deepened in recent years, trastuzumab has become the most effective and widely used targeted drug in the anti-HER-2 targeted therapy for gastric cancer. A landmark ToGA study confirmed that in patients with advanced gastric carcinoma (HER-2 IHC2$^+$ and FISH$^+$ or IHC3$^+$), the median overall survival (mOS) in trastuzumab + chemotherapy group was significantly prolonged compared with that in chemotherapy group, and there was no difference in the safety between the two groups [6]. A study released in the American

Society of Clinical Oncology (ASCO) meeting in 2013 explored the efficacy of trastuzumab combined with paclitaxel in the treatment of HER-2-positive gastric cancer, and the results showed that in experimental group, the ORR and median progression-free survival (mPFS) were 37.2% (95% CI: 23.0-53.3%) and 5.2 months (95% CI: 3.9-6.6), indicating that trastuzumab combined with paclitaxel has better efficacy in the second-line treatment of advanced gastric carcinoma [14]. Moreover, several phase II clinical studies have demonstrated that in the first-line treatment of HER-2-positive gastric cancer, trastuzumab combined with capecitabine + oxaliplatin, S-1 + cisplatin, docetaxel + oxaliplatin + capecitabine, docetaxel + cisplatin + S-1 have the similar efficacy to that in ToGA study, and the mPFS and mOS were 6.0-14.1 months and 14.6-21.0 months [15-18]. In two phase II studies (HER-FLOT and NEOHX) on anti-HER-2 neoadjuvant therapy for gastric carcinoma or gastroesophageal adenocarcinoma in the perioperative period released by ASCO, certain curative effects are achieved, and the pCR of surgical specimens is 23% and 8%, respectively. In addition, a phase II study involving 16 cases of inoperable advanced gastric carcinoma manifested that after application of trastuzumab combined with docetaxel + cisplatin + S-1, the response rate and surgical conversion rate are 100% and 56.3% [18].

In the present study, the clinical data of 106 patients with advanced gastric carcinoma treated in our department were retrospectively analyzed, and the clinical efficacy and safety were compared between trastuzumab combined with DOS regimen and DOS neoadjuvant chemotherapy alone. It was found that in Trastuzumab + DOS group and DOS group, the ORR was 66.0% (35/53) and 52.8% (28/53), respectively, and the DCR was 94.3% (50/53) and 90.6% (48/53), respectively, indicating that there were no statistically significant differences in ORR and DCR between the two groups (p=0.166, p=0.462). The main adverse reactions included myelosuppression, gastrointestinal reaction, liver function damage, neurotoxicity and hand-foot syndrome, and the incidence of adverse reactions had no statistically significant differences between the two groups (p>0.05). The surgical resection rate displayed no statistically significant difference (p=0.462), while both R0 resection rate and pathological response rate in Trastuzumab + DOS group were significantly higher than those in DOS group (p=0.013, p=0.034).

The inconsistency between clinical stage and pathological stage was mentioned in this study. Professor RC Fields of MSKCC conducted 5 prospective studies on this issue from 1985 to 2009, and 2627 patients were enrolled, among which 714 cases underwent neoadjuvant therapy. The results showed that only 60 (30%) out of 200 clinical CR cases are pCR after treatment, and the recurrence rate is 23% in them, 36% of which is brain metastasis [19]. Biffi et al. [20] applied the docetaxel-based TCF regimen in preoperative chemotherapy for locally advanced resectable gastric carcinoma, and it was confirmed pathologically after operation that the pCR is only 11.7%. Therefore, CR does not means cure, so it is necessary to be particularly careful in the interpretation of CR, and whether the CR patients still need active surgery should be carefully considered. In terms of the therapeutic method after pCR, it is recognized that the surgery should continue based on the stage before treatment, and full-cycle adjuvant therapy should be performed after operation, without blindly adjusting the therapeutic regimen based on the clinical efficacy.

There are still many deficiencies in this study. For example, the sample size is small, the different operation methods may cause deviation in results, and the patients are not followed up for a long time to understand the effect of treatment on the long-term survival of them. Therefore, further large-sample multicenter randomized controlled trials are needed in the future to verify the conclusions made in this study.

Conclusions

Compared with chemotherapy alone, trastuzumab combined with DOS regimen can significantly improve the pathological response rate and R0 resection rate without increasing the risk of surgery in neoadjuvant chemotherapy for advanced gastric carcinoma, and the patient's tolerance is good, so this regimen is worthy of clinical popularization and application.

Conflict of interests

The authors declare no conflict of interests.

References

1. Herrero R, Park JY, Forman D. The fight against gastric cancer - the IARC Working Group report. Best Pract Res Clin Gastroenterol 2014;28:1107-14.
2. Zygogianni A, Fotineas A, Platoni K et al. A five split-field three dimensional conformal technique versus an anterior-posterior on in postoperative radiotherapy for gastric carcinoma: a multicenter comparative study using quality of life measurements as well as clinical and dosimetric parameters. JBUON 2018;23:1020-8.
3. Goksoy B, Bozkurt H. Social attention of the top 50 scientific articles on gastric cancer: Bibliometric and altmetric analysis. J BUON 2020;25:2322-31.
4. Digklia A, Wagner AD. Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol 2016;22:2403-14.
5. Boku N. HER2-positive gastric cancer. Gastric Cancer 2014;17:1-12.
6. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
7. Nishikawa K, Takahashi T, Takaishi H et al. Phase II study of the effectiveness and safety of trastuzumab and paclitaxel for taxane- and trastuzumab-naive patients with HER2-positive, previously treated, advanced, or recurrent gastric cancer (JFMC45-1102). Int J Cancer 2017;140:188-96.
8. Shi GD, Luo ZL, Fu MY, Tian D, Zhang L, Zhang KP. [Evaluation of the value of 7th editions of UICC-AJCC esophageal and gastric cancer TNM staging systems for prognostic prediction of adenocarcinoma of esophagogastric junction (Siewert type II)]. Zhonghua Zhong Liu Za Zhi 2014;36:916-21.
9. Wang YK, Wang SN, Li YY et al. Methods and significance of the combined detection of HER2 gene amplification and chemosensitivity in gastric cancer. Cancer Biomark 2018;21:439-47.
10. Watanabe H, Okada M, Kaji Y et al. [New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1)]. Gan To Kagaku Ryoho 2009;36:2495-501.
11. Fujimoto M, Matsuzaki I, Nishino M, Iwahashi Y, Warigaya K, Kojima F, Ono K, Murata SI. HER2 is frequently overexpressed in hepatoid adenocarcinoma and gastric carcinoma with enteroblastic differentiation: a comparison of 35 cases to 334 gastric carcinomas of other histological types. J Clin Pathol 2018; 71: 600-7.
12. Maximiano S, Magalhaes P, Guerreiro MP, Morgado M. Trastuzumab in the Treatment of Breast Cancer. Biodrugs 2016;30:75-86.
13. Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017;389:1195-205.
14. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
15. Ryu MH, Yoo C, Kim JG et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer 2015;51:482-8.
16. Kurokawa Y, Sugimoto N, Miwa H et al. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). Br J Cancer 2014;110:1163-8.
17. Chua C, Tan IB, Yamada Y et al. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol 2015;76:397-408.
18. Mitsui Y, Sato Y, Miyamoto H et al. Trastuzumab in combination with docetaxel/cisplatin/S-1 (DCS) for patients with HER2-positive metastatic gastric cancer: feasibility and preliminary efficacy. Cancer Chemother Pharmacol 2015;76:375-82.
19. Fields RC, Strong VE, Gonen M et al. Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. Br J Cancer 2011;104:1840-7.
20. Biffi R, Fazio N, Luca F et al. Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer. World J Gastroenterol 2010;16:868-74.