Int J Clin Exp Med 2020;13(4):2527-2533
www.ijcem.com /ISSN:1940-5901/IJCEM0104172

Original Article

Comparative study of tegafur gimeracil and oteracil potassium (TS-1) plus docetaxel and oxaliplatin versus TS-1 plus oxaliplatin in postoperative adjuvant chemotherapy for gastric cancer

Ya Zhu, Zhenyong Zhang, Xinzhong Zou

Department of Oncology, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu Province, China

Received October 29, 2019; Accepted December 10, 2019; Epub April 15, 2020; Published April 30, 2020

Abstract: Objective: The objective of this study was to comparatively study the effect of tegafur gimeracil and oteracil potassium (TS-1) plus docetaxel and oxaliplatin versus TS-1 plus oxaliplatin in postoperative adjuvant chemotherapy for gastric cancer. Methods: A total of 121 advanced patients received chemotherapy after radical gastrectomy were enrolled in this study and randomly assigned to two groups. Sixty-three patients received the chemotherapy regimen of TS-1 plus oxaliplatin and docetaxel were in observation group, while 58 patients received the regimen of TS-1 plus oxaliplatin were in control group. The short-term efficacy, long-term efficacy, Karnofsky performance status (KPS) score and toxic side effects were observed in both groups. Results: The total effective rate was 58.73%, and the total control rate was 87.30% in the observation group, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical differences (both $P<0.05$). The progression-free survival and overall survival of the observation group were 5.73 and 11.18 months, respectively, which were not statistically significant from those of the control group (5.69 and 11.25 months; both $P>0.05$). The KPS scores of the observation group were higher than those of the control group after 3-week and 6-week chemotherapy (both $P<0.05$). There was no significant difference in the adverse reactions between the two groups after chemotherapy ($P>0.05$). Conclusions: The chemotherapy regimen of TS-1 plus docetaxel and oxaliplatin has significant effects in patients after gastrectomy, and improves patients' physical condition with reliable safety.

Keywords: Post-gastrectomy, adjuvant chemotherapy, tegafur gimeracil and oteracil potassium (TS-1), docetaxel, oxaliplatin

Introduction

Gastric cancer, as a common malignant tumor in clinic, ranks the third among tumors that cause death. In the year of 2015, there were 1.3 million patients with gastric cancer worldwide [1]. The mortality of gastric cancer is high among all cancers [2, 3]. China is a country with a high risk of gastric cancer in East Asia for the incidence here is the second highest among all cancers [4, 5]. To date, the main treatment for gastric cancer is surgery [6]. But the resection rate of advanced gastric cancer is low, with high risk of postoperative recurrence and metastasis, and low 5-year survival rate, so the efficacy of surgical treatment alone is not promising [7]. In order to improve clinical efficacy, postoperative adjuvant chemotherapy is frequently carried out to reduce recurrence and metastasis. However, its application in clinic is greatly limited due to the large difference in the efficacy of chemotherapy drugs in cells and animal experiments and in humans [8]. At present, the common chemotherapy regimen for gastric cancer is a combination of two cytotoxic drugs or three cytotoxic drugs [9]. The combination of two drugs is fluoropyrimidine (tegafur gimeracil and oteracil potassium (TS-1) or capecitabine) + oxaliplatin or cisplatin. The combination of three drugs is paclitaxel + oxaliplatin or cisplatin + fluoropyrimidine or its improved replacement [9]. But the optimum choice of chemotherapy

regimens is still controversial [10]. In this study, a double-drug regimen of TS-1 + oxaliplatin and a three-drug regimen of TS-1 + oxaliplatin + docetaxel were compared.

Materials and methods

Clinical data

A total of 128 patients with advanced gastric cancer received chemotherapy after radical gastrectomy from June 2017 to October 2018 were enrolled in our study and assigned to two groups using a random number table. Sixty-four patients received the chemotherapy regimen of TS-1 plus oxaliplatin and docetaxel were in the observation group, while 64 patients received the regimen of TS-1 plus oxaliplatin were in the control group. During the follow up, we lost 1 patient in the observation group and 6 patients in control group. Therefore, there were 121 patients included in the study analyses. All patients were 44-75 years old, with an average age of 53.4±8.9 years. Written informed consent form was obtained from all the subjects, and the study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Inclusion criteria

Patients were eligible if they were diagnosed with primary advanced gastric cancer of stage IIB-IIIC and received laparoscopic surgery [11]; had normal cardiopulmonary function; did not receive other tumor treatment before laparoscopic surgery and chemotherapy; had normal coagulation and bone marrow function; had complete clinical data.

Exclusion criteria

Patients who received or was receiving chemotherapy; patients with severe cardiopulmonary disease, other primary malignant tumors, or abnormal blood coagulation or bone marrow functions; patients with liver or kidney dysfunction; patients who were allergic to the chemotherapy drugs; patients who were not cooperative; patients with incomplete clinical data.

Clinical and pathological staging

Clinical staging and pathological staging were evaluated according to UICC/AJCC diagnostic criteria (version 7) [11].

Methods

The chemotherapy was given one week after surgery. The regimen for the observation group was as follows. During a chemotherapy period, which was 21 days, over 3 h of oxaliplatin (130 mg/m^2, from Nanjing-pharma, Jiangsu, China) and 1 h of docetaxel (75 mg/m^2, from Aosaikang, Jiangsu, China) were intravenously infused on day 1; TS-1 (40 mg/m^2, from Haiwangfu Pharma, Fujian, China) was orally taken from day 1 to day 14, 2 times a day. The regimen for the control group in a 21-day chemotherapy period was as follows. Over 3 h of oxaliplatin (130 mg/m^2) was intravenously infused on day 1; TS-1 (40 mg/m^2) was orally taken from day 1 to day 14, 2 times a day. In both groups, allergy prevention was given 12 h before chemotherapy with intravenous injection of 20 mg dexamethasone (Hasen-modern, Shanghai, China), and 30 min before chemotherapy with intramuscular injection of 25 mg promethazine (Shharvest, Shanghai, China). To protect the stomach, intravenous infusion of 300 mg cimetidine (Nanguo pharma, Guangdong, China) was given 30 min before chemotherapy. The efficacy in both groups was evaluated after 4 periods of chemotherapy.

Follow-up was performed monthly by reviewing the visit record or telephone. The disease-free survival (DFS) period was from the first day after surgery to the date of recurrence or progression. The overall survival (OS) was from the first day after clarifying of pathology after surgery to patient's death date or the last follow up.

Outcome measures

The short-term efficacy was evaluated after 4 periods of chemotherapy [12]. The treatment efficacy was divided into complete remission (CR), partial remission (PR), stability of disease (SD), and progression of disease (PD). Effective rate (%) = (CR + PR)/total number of patients × 100%. Disease control rate (%) = (CR + PR + SD)/total number of patients × 100%.

The long-term efficacy was evaluated according to progression-free survival (PFS) and overall survival (OS). PFS referred to the time during which the tumor progressed to other parts of the body in the study period. OS referred to the time from the start of chemotherapy treatment to the death of the patient or the end of the study period.

Table 1. Comparison of general and baseline data

Item	Observation group (n=63)	Control group (n=58)	χ^2/t	P
Sex (male: female)	35:28	34:24	0.116	0.734
Age (year)	53.2±9.1	53.6±8.8	0.243	0.808
Tumor size (cm)			0.167	0.683
>5 cm	36	31		
≤5 cm	27	27		
Pathological type			0.011	0.917
Differentiated	60	55		
Undifferentiated	3	3		
UICC stage			0.358	0.949
IIB	19	16		
IIIA	18	15		
IIIB	12	12		
IIIC	14	15		

Table 2. Comparison of clinical efficacy

Group	CR	PR	SD	PD	Total effective rate (%)	Total control rate (%)
Observation group (n=63)	5 (7.94)	32 (50.79)	18 (28.57)	8 (12.70)	37 (58.73)	55 (87.30)
Control group (n=58)	0 (0.00)	23 (39.66)	19 (32.76)	16 (27.59)	23 (39.66)	42 (72.41)
χ^2	8.975				4.395	4.210
P	0.030				0.036	0.040

Note: CR, complete remission; PR, partial remission; SD, stability of disease; PD, progression of disease.

The Karnofsky performance status (KPS) score was used to evaluate patients' condition before chemotherapy, after chemotherapy, and 3 weeks after surgery, with a total score of 100 points [13]. The higher the score was, the better the physical condition was. Score less than 60 points indicated poor physical condition, which was not conducive to the treatment.

Toxic reaction was recorded according to the NCI-CTC 4.0 classification after 4 cycles of chemotherapy [14]. The toxic reactions included toxic symptoms in blood system and other systems such as nausea and vomiting, diarrhea, constipation, abnormal liver function, abnormal renal function, abnormal cardiac function, alopecia, and toxicity in peripheral nervous system. The above toxic reactions were classified into grade 0-4 according to different conditions. Comparison was carried out between patients with grade 1-2 and with grade 3-4 in the two groups.

Statistical analyses

Statistical analyses were performed using SPSS 17.0 software. The continuous variables were expressed as mean ± standard deviation. The data conformed to normal distribution and homogeneity of variance were compared with the use of independent sample t test, denoted as t. The enumeration data were processed using Pearson chi-square test, denoted as χ^2. Survival analysis was performed using Kaplan-Meier analysis and Log-rank test. The difference was statistically significant at $P<0.05$.

Results

Comparison of general and baseline data

There were no differences in gender, age, tumor size, pathological type, and UICC stage between the two groups (all $P>0.05$), so the two groups were comparable. See **Table 1**.

Comparison of clinical efficacy

The total effective rate was 58.73%, and the total control rate was 87.30% in the observation group, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical differences (both $P< 0.05$). See **Table 2**.

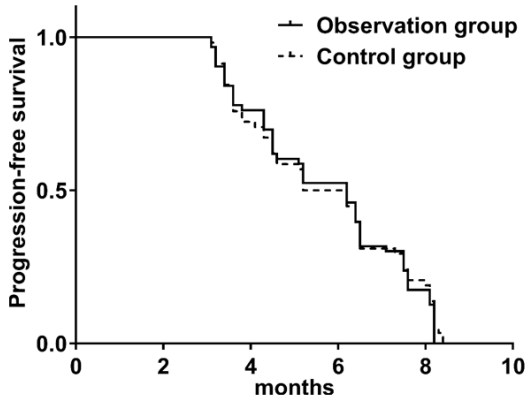

Figure 1. Comparison of progression-free survival.

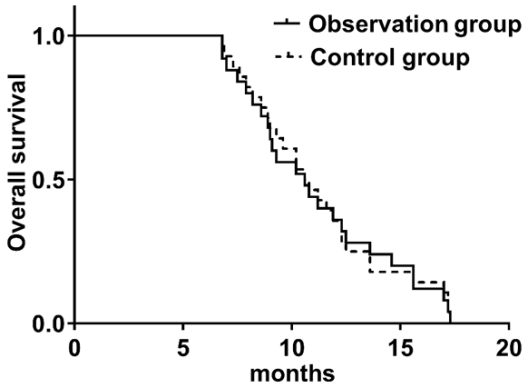

Figure 2. Comparison of overall survival.

Comparison of PFS

The PFS of the observation group was 5.73 months (95% CI: 5.290-6.180), and of the control group was 5.69 months (95% CI: 5.213-6.170), with no statistical difference between the two groups (χ^2=0.107, P=0.774). See **Figure 1**.

Comparison of OS

The OS in the observation group was 11.18 months (95% CI: 9.835-12.525), which was not significantly different from 11.25 months in the control group (95% CI: 10.043-12.471) (χ^2=0.008, P=0.928). See **Figure 2**.

Comparison of KPS score

A repeated measures analysis of variance in KPS scores between the two groups found that there were differences in KPS scores between the two groups at 3 weeks and 6 weeks postoperatively, and scores were higher in the observation group than those in the control group (P<0.05). See **Table 3**.

Comparison of adverse reactions

We compared the incidence of adverse reactions between patients with grade 1-2 and with grade 3-4 in the two groups and found no difference in the adverse reactions after chemotherapy between the two groups (all P>0.05). All the adverse reactions occurred were tolerable and properly treated. See **Table 4**.

Discussion

At present, it has become a research hotspot to optimize the radiotherapy and chemotherapy regimen for patients with advanced gastric cancer to reduce postoperative recurrence and metastasis and improve survival [12, 15]. With the advent of new chemotherapeutic drugs and protocols, the most commonly used drugs in the clinic now are fluoropyrimidines, platinum, taxanes, and trastuzumab, but the optimal chemotherapy regimen remains controversial [10]. The compound preparation composed of tegafur, gimeracil and oteracil potassium can inhibit the activity of orotate phosphoribosyltransferase in the gastrointestinal tract, thereby lessening its decomposition in the gastrointestinal tract, prolonging the action time *in vivo*, and maintaining the blood concentration, which promotes the transformation and absorption of the drug, and eventually achieves the purpose of inhibiting tumor growth [16]. A study found that the distribution of TS-1 was selective, mainly in the gastrointestinal tract, so the drug was able to alleviate gastrointestinal symptoms such as nausea and vomiting [17]. Additionally, TS-1 is an oral drug that can avoid or reduce the toxicity of intravenous injection on the heart and kidney [18]. Other study showed that the compound preparation of tegafur, gimeracil and oteracil potassium had a significant effect on advanced gastric cancer [19]. Oxaliplatin is a third-generation platinum drug that targets DNA and effectively prevents DNA replication and transcription [20]. Docetaxel is a taxol drug that has been shown to lead an improved effective rate for patients with advanced gastric cancer when combining with chemotherapy drugs [21].

In terms of efficacy, previous study showed that TS-1 combined with oxaliplatin regimen for the treatment of 41 patients with gastric cancer

Table 3. Comparison of KPS score

Group	At admission	3 weeks after operation	6 weeks after operation
Observation group (n=63)	68.48±5.27	85.43±5.10	90.00±2.84
Control group (n=58)	67.02±5.42	73.29±5.60	74.19±3.14
F		257.541	
P		0.000	

Note: KPS, karnofsky performance status.

Table 4. Comparison of adverse reactions (n, %)

Adverse reactions	Observation group (n=63)		Control group (n=58)		χ^2	P
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4		
Leukopenia	8 (12.70)	4 (6.35)	10 (17.24)	8 (13.79)	2.683	0.261
Hemoglobin reduction	12 (19.05)	5 (7.94)	15 (25.86)	5 (8.62)	0.890	0.641
Thrombocytopenia	13 (20.63)	4 (6.35)	12 (20.69)	6 (10.34)	0.653	0.721
Nausea and vomiting	20 (31.75)	5 (7.94)	19 (32.76)	4 (6.90)	0.054	0.974
Abnormal liver function	8 (12.70)	2 (3.17)	8 (13.79)	6 (10.34)	2.633	0.268
Alopecia	12 (19.05)	13 (20.63)	15 (25.86)	13 (22.41)	1.070	0.586
Neurotoxicity	5 (7.94)	7 (11.11)	8 (13.79)	4 (6.90)	1.564	0.457
Hand-foot syndrome	6 (9.52)	2 (3.17)	9 (15.52)	3 (5.17)	1.398	0.497

had a total effective rate of 53.7% and a median survival of 7.8 months [22]. Another study also used the combination of the two drugs for gastric cancer patients and showed an effective rate of 55.8% and PFS of 7 months [23]. Previous study that applied the three-drug combination of paclitaxel, oxaliplatin and TS-1 found an effective rate of 66.7% and PFS of 7.1 months [24]. In this study, the total effective rate of the observation group, using the combination of three drugs, was 58.73%, and the total control rate was 87.30%, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical difference. The PFS and OS of the observation group were 5.73 months and 11.18 months, which were not significantly different from 5.69 months and 11.25 months, respectively in the control group.

The KPS score was used to evaluate the physical condition of the patient after treatment, and the higher the score, the better the physical condition [13]. In the study, it was found that the KPS score of the observation group was higher than that of the control group after three-week and six-week chemotherapy, indicating that the combination of the three drugs was beneficial to the recovery of the patient's physical condition, which may be related to the higher effective rate and control rate of the observation group.

In terms of adverse reactions, the common reactions after chemotherapy in the two groups were symptoms in blood system and digestive system. Statistical comparison showed no significant difference between the two groups in leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, abnormal liver function, alopecia, neurotoxicity, and hand-foot syndrome. A study showed that the main adverse reactions in patients with gastric cancer treated with TS-1 combined with oxaliplatin were leukopenia and thrombocytopenia [23]. The reactions in patients treated with the three-drug regimen were leukopenia and alopecia [25]. The adverse reactions appeared in this study were tolerated, and the incidence was similar to the above studies.

The sample size of this study was small, so further expansion of the sample size is needed. Additionally, this study was a retrospective but not a prospective study, so a multicenter prospective study should be performed to further confirm the effect of three-drug chemotherapy regimen.

The chemotherapy regimen of TS-1 plus docetaxel and oxaliplatin has significant effects in patients after gastrectomy and improves the patient's physical condition, with reliable safety, so it is worthy of clinical investigation and promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Xinzhong Zou, Department of Oncology, Affiliated Hospital of Jiangnan University, No.585 Xingyuan North Road, Wuxi 214041, Jiangsu Province, China. Tel: +86-0510-82606510; Fax: +86-0510-82606510; E-mail: zouxinzhong25zxz@163.com

References

[1] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabé E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castañeda-Orjuela C, Catalá-López F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, G/Hiwot TT, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HMA, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Søreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BSC, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zenebe ZM, Murray CJL, Naghavi M. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017; 3: 524-548.

[2] Smith JP, Nadella S and Osborne N. Gastrin and gastric cancer. Cell Mol Gastroenterol Hepatol 2017; 4: 75-83.

[3] Torre LA, Siegel RL, Ward EM and Jemal A. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev 2016; 25: 16-27.

[4] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-32.

[5] Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, Esteve J, Ogunbiyi OJ, Azevedo ESG, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK and Coleman MP. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391: 1023-1075.

[6] Kim HS, Kim JH, Kim JW and Kim BC. Chemotherapy in elderly patients with gastric cancer. J Cancer 2016; 7: 88-94.

[7] Zhang H, Li H, Guo F, Zhang D, Yang H and Wang J. Screen and identification of serum protein biomarkers in gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2016; 19: 317-22.

[8] Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzen F and Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315-21.

[9] Qiu H and Zhou Z. Updates and interpretation on NCCN clinical practice guidelines for gastric cancer 2017 version 5. Zhonghua Wei Chang Wai Ke Za Zhi 2018; 21: 160-164.

[10] Matsusaka S, Kobunai T, Yamamoto N, Chin K, Ogura M, Tanaka G, Matsuoka K, Ishikawa Y, Mizunuma N and Yamaguchi T. Prognostic impact of KRAS mutant type and MET amplification in metastatic and recurrent gastric cancer patients treated with first-line S-1 plus cisplatin chemotherapy. Genes Cancer 2016; 7: 27-35.

[11] Ilhan E, Ureyen O and Meral UM. Ongoing problems concerning 7(th) TNM staging system and proposals for 8(th) TNM staging system of gastric cancer. Prz Gastroenterol 2016; 11: 223-225.

[12] Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Korn WM, Leong S, Linn C, Lockhart AC, Ly QP, Mulcahy MF, Orringer MB, Perry KA, Poultsides GA, Scott WJ, Strong VE, Washington MK, Weksler B, Willett CG, Wright CD, Zelman D, McMillian N and Sundar H. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016; 14: 1286-1312.

[13] Mor V, Laliberte L, Morris JN and Wiemann M. The karnofsky performance status scale. An examination of its reliability and validity in a research setting. Cancer 1984; 53: 2002-7.

[14] Lacouture ME. 5. Grading dermatologic adverse events in clinical trials using CTCAE v4.0. 2013.

[15] Wang C, Guo W, Zhou M, Zhu X, Ji D, Li W, Liu X, Tao Z, Zhang X, Zhang Y and Li J. The predictive and prognostic value of early metabolic response assessed by positron emission tomography in advanced gastric cancer treated with chemotherapy. Clin Cancer Res 2016; 22: 1603-10.

[16] Pietrantonio F, Caporale M, Morano F, Scartozzi M, Gloghini A, De Vita F, Giommoni E, Fornaro L, Aprile G, Melisi D, Berenato R, Mennitto A, Volpi CC, Laterza MM, Pusceddu V, Antonuzzo L, Vasile E, Ongaro E, Simionato F, de Braud F, Torri V and Di Bartolomeo M. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: implication for further clinical research. Int J Cancer 2016; 139: 2859-2864.

[17] De Vita F, Niger M, Vivaldi C, Giommoni E, Zaniboni A, Bozzarelli S, Tomasello G, Sava T, Spada M and Menatti E. B02*Ramucirumab as second line therapy in metastatic gastric cancer (MGC): results of the Italian compassionate-use named patients. The RAMoss study. Ann Oncol 2016; 27: iv17-iv17.

[18] Mielczarek E and Blaszkowska J. Trichomonas vaginalis: pathogenicity and potential role in human reproductive failure. Infection 2016; 44: 447-58.

[19] Gyurkovska V and Ivanovska N. Distinct roles of TNF-related apoptosis-inducing ligand (TRAIL) in viral and bacterial infections: from pathogenesis to pathogen clearance. Inflamm Res 2016; 65: 427-37.

[20] Wu DM, Wang YJ, Fan SH, Zhuang J, Zhang ZF, Shan Q, Han XR, Wen X, Li MQ, Hu B, Sun CH, Bao YX, Xiao HJ, Yang L, Lu J and Zheng YL. Network meta-analysis of the efficacy of first-line chemotherapy regimens in patients with advanced colorectal cancer. Oncotarget 2017; 8: 100668-100677.

[21] Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. J Clin Oncol 2006; 24: 4991-7.

[22] Oh SY, Kwon HC, Jeong SH, Joo YT, Lee YJ, Cho S, Kang MH, Go SI, Lee GW, Kim H and Kang JH. A phase II study of S-1 and oxaliplatin (SOx) combination chemotherapy as a first-line therapy for patients with advanced gastric cancer. Invest New Drugs 2012; 30: 350-6.

[23] Yang L, Song Y, Zhou AP, Qin Q, Chi Y, Huang J and Wang JW. A phase II trial of oxaliplatin plus S-1 as a first-line chemotherapy for patients with advanced gastric cancer. Chin Med J (Engl) 2013; 126: 3470-4.

[24] Zhou AP, Li YS, Yang L, Song Y, Sun YK, Zhang W, Cui CX, Chi Y, Yuan XH, Lu N and Wang JW. Phase II clinical trial of docetaxel, platinum and S-1 for advanced gastric cancer. Zhonghua Yi Xue Za Zhi 2012; 92: 1677-80.

[25] Amarantidis K, Xenidis N, Chelis L, Chamalidou E, Dimopoulos P, Michailidis P, Tentes A, Deftereos S, Karanikas M and Karayiannakis A. Docetaxel plus oxaliplatin in combination with capecitabine as first-line treatment for advanced gastric cancer. Oncology 2011; 80: 359-65.