Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Evaluation of IgG, IgM, CD4+ and CD8+ T cells during neoadjuvant chemotherapy with Tezio and Apatinib in gastric cancer patients

Zhe Cui[1], Jianjun Zhang[2], Jing Zhang[1], Lan Xu[1*]

[1] Department of Laboratory, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, 110042, China
[2] Department of Gastric Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, 110042, China

*Correspondence to: LanXu77777@163.com

Received March 15, 2020; **Accepted** May 15, 2020; **Published** June 5, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.3.17

Abstract: This experiment was carried out to study the effect the neoadjuvant chemotherapy with Tezio and Apatinib on the treatment of advanced gastric cancer and its impact on the postoperative immune function of patients' function. The patients with advanced gastric cancer who were treated in gastrointestinal surgery in our hospital from January 2017 to December 2018 were divided into two groups. The new chemotherapy and the traditional chemotherapy groups. The new chemotherapy group received neoadjuvant chemotherapy of Tezio combined with Apatinib before surgery, and the control group received the traditional first-line chemotherapy regimen of oxaliplatin combined with capecitabine. During the chemotherapy, the adverse complications of the two groups of patients were recorded, and the RECIST1.1 evaluation system was used to evaluate the chemotherapy effect of the patients after chemotherapy. At the same time, the R0 resection rate of the two groups of patients with gastric cancer radical surgery was recorded and compared. The fasting venous blood of the patients was collected before the chemotherapy, after the end of chemotherapy, and one week after the operation. The content of immunoglobulin G and M (IgG and IgM) was measured. The flow cytometry was used to detect $CD4^+$ T cells and $CD8^+$ T cells. A total of 64 patients were enrolled in this study, including 26 patients in the new chemotherapy group. Chi-square test showed that the incidence of bone marrow suppression (Leukopenia, thrombocytopenia and anemia) and liver dysfunction in the new chemotherapy group were lower than that in the traditional chemotherapy group (all $P < 0.05$), but the surgical R0 resection rate in the new chemotherapy group was higher than that in the traditional chemotherapy group ($P < 0.05$). Wilcoxon rank-sum test and chi-square test found that the chemotherapy effect of the new chemotherapy group was better than that of the traditional chemotherapy group, and the results of repeated measures analysis of variance showed that the IgG, IgM and $CD4^+$/$CD8^+$ T cell ratios of the patients in the new chemotherapy group were higher than that of traditional chemotherapy group (all $P < 0.05$). Apatinib combined with Tezio's preoperative neoadjuvant chemotherapy can improve the chemotherapy effect of advanced gastric cancer, increase the rate of surgical R0 resection, and reduce the patient's immunosuppressive status during treatment.

Key words: Apatinib; Advanced gastric cancer; Targeted therapy.

Introduction

In the world, gastric cancer causes 720000 deaths every year in the world, and the trend is increasing, and the new cases of gastric cancer in China can account for 42.5% of the new cases in the world every year (1-3). The early symptoms of gastric cancer are mild and lack of specificity, so it is difficult for early diagnosis and early treatment. Many patients have developed into the advanced stage or even metastasis at the time of treatment, which leads to the failure of radical gastrectomy (4-6). Before the operation, neoadjuvant chemotherapy is often used to reduce the tumor stage and then select an opportunity for surgery, so as to improve the surgical R0 resection rate and improve the prognosis of patients (7,8). Although a variety of non-specific chemotherapy drugs including paclitaxel, oxaliplatin and S-1 have the effect of killing tumor cells, they have serious side effects such as inhibiting the immune system and hematopoiesis of the body, affecting the prognosis of patients (9,10). Therefore, it is urgent to develop and try to use targeted chemotherapy drugs including Apatinib in the clinic. Vascular endothelial growth factor, VEGF) and its receptors play an important role in the angiogenesis of tumor development. Apatinib can competitively bind to vascular endothelial growth factor receptor-2 (VEGFR-2), block the downstream signal pathway and inhibit tumor angiogenesis, and play a role in inhibiting tumor growth (11,12). But up to now, the role of Apatinib in preoperative chemotherapy of advanced gastric cancer is still lack of sufficient medical evidence. Therefore, Tezio and Apatinib were used in this study before the operation to observe the effect of chemotherapy in the advanced stage and to study the influence of Tezio and Apatinib on the patients' immune function after the operation.

Materials and Methods

General information

From January 2017 to December 2018, 64 patients with advanced gastric cancer were selected from the gastrointestinal surgery of our hospital, with an average

age of (45.98 ± 7.94) years. Inclusion criteria: ① gastric cancer was first diagnosed and treated in our hospital by means of CT and gastroscopic biopsy; ② the stage of gastric cancer was (T3-4N0-3M0) and no distant metastasis occurred; ③ the patient was in the good physical condition and could tolerate preoperative chemotherapy (ECoG score was 0-2). Exclusion criteria: ① patients with HIV and other serious diseases affecting the immune system; ② patients with drug allergy used in this study; ③ patients with severe cardiovascular or endocrine diseases; ④ Nrs2002 scoring system shows patients with nutritional risk requiring intervention (NRS2002 ≥ 3 points). With the permission of the hospital's ethics committee, all patients and their families signed informed consent.

Research methods

Implementation of preoperative chemotherapy

The patients were divided into two groups: neochemotherapy group (n = 26) and traditional chemotherapy group (n = 38). Neochemotherapy group (n = 26) received neoadjuvant chemotherapy of Tezio combined with Apatinib before the operation, the control group received oxaliplatin + capecitabine conventional first-line chemotherapy. Common adverse complications were monitored during chemotherapy. Chemotherapy was suspended for 2-3 days or reduced the chemotherapy dose when the patient cannot tolerate chemotherapy.

New chemotherapy group: 500 mg/d Apatinib (H20140104, Jiangsu Hengrui Pharmaceutical) orally took (Day 1-14) + 60 mg/d Tezio (H20113281, Jiangsu Hengrui Pharmaceutical) orally took (Day 1-14). The new chemotherapy cycle was 28 days, and all patients received 2-3 cycles of chemotherapy.

Conventional chemotherapy group: 130 mg/m^2 oxaliplatin (H20094158, Jiangsu Yangzi Jiang Pharmaceutical) intravenous infusion (Day 1) + 1000 mg/m^2 capecitabine (H20073024, Shanghai Roche Pharmaceuticals) orally took 2 times/Day, (Day 1-14). The chemotherapy cycle was 28 days, and all patients received 2-3 cycles of chemotherapy.

At the end of chemotherapy, according to the actual situation of the patients, we choose to carry out radical gastrectomy, which is performed by senior doctors in our hospital.

Observation indicators

Collection of adverse complications and operation effect

During chemotherapy, the adverse complications of the two groups were recorded, including myelosuppression, diarrhea, hand-foot syndrome, malignant vomiting and other adverse reactions. CT was performed before chemotherapy and after 4 cycles of preoperative chemotherapy. According to the RECIST1.1 evaluation standard of solid tumor effect (13), the chemotherapy effect of the patients was evaluated: ① Complete response (CR): the lesion completely disappeared; ② Partial response (PR): the lesion diameter was more than 30% less than the preoperative baseline level; ③ Progressive Disease: the diameter of lesions increased by more than 20% or new lesions appeared; ④ Stable disease (SD): between the disease progress and partial remission. Postoperative specimens were sent to the department of pathology to evaluate the surgical effect: R0: no tumor cells were left under the microscope; R1: microscopically, there are residual tumor cells.

Comparison of serum antibody level and proportion of immune cells in patients

Five – ten ml (2 tubes) of fasting venous blood were collected from patients before chemotherapy, after chemotherapy and one week after operation respectively. One tube of the blood sample was centrifuged at 4 ℃ and 3000 rpm to separate serum. Then the content of immunoglobulin G and m (IgG and IgM) were measured by immunoturbidimetry. 200 L whole blood was collected from another tube of the blood sample. According to the instruction manual, FITC labeled anti-human CD4 antibody (Anti-CD4-FITC; ab59474; Abcam) and PE-labeled anti-human CD4 antibody (anti-CD8-PE; ab39853, Abcam) were added successively. The blood sample was beaten and mixed and incubated at room temperature away from light for 30 min. 200 μL of hemolysin to lyse the red blood cells were added. After centrifugation at 1000 RPM for 5min at 4℃, the supernatant was removed and washed with 1 mL sterile PBS for 3 times. At last, 500 μLPBS was added to the cell precipitation, and flow cytometer (EPICS-XL, Beckman counter) was used for detection, and Flow Jo software was used to analyze the results.

Statistical analysis

The counting data are expressed by rate or percentage (%), and the measurement data of normal distribution are expressed by mean ± standard deviation. T-test and chi-square tests were used to analyze the differences between the two groups in general clinical data. Wilcoxon rank-sum test was used to compare the difference in chemotherapy effect between the two groups, and the chi-square test was used to analyze the difference in surgical R0 resection rate and chemotherapy adverse reactions between the two groups. The serum antibody level and the ratio of CD4 + T / CD8 + T in the two groups were also measured by repeated ANOVA. When $p < 0.05$, the difference was statistically significant.

Results

Comparison of general data

The general clinical data of the two groups of patients are shown in Table 1. The results of the t-test and chi-square analysis showed that there were no statistical differences between the two groups in gender, age, postoperative pathological type and gastric cancer staging (all $P > 0.05$).

Comparison of adverse complications

The complications of chemotherapy in the two groups were shown in Table 2. The chi-square test showed that the incidence of bone marrow suppression (leukocyte, platelet and anemia) and abnormal liver function in the new chemotherapy group were lower than those in the traditional chemotherapy group (all $P < 0.05$). However, there was no statistical difference in the incidence of diarrhea, hand-foot syndrome and malignant vomiting

Table 1. Comparison of general clinical data.

	New (n=26)	Conventional (n=38)	Test statistics	P
Male [case (%)]	14 (53.85%)	21 (55.26%)	0.013	0.911
Age (year)	44.09±11.52	46.63±13.54	-1.020	0.310
Pathological type [case (%)]				
Highly differentiated adenocarcinoma	4 (15.38%)	7 (18.42%)		
Moderately differentiated adenocarcinoma	5 (19.23%)	7 (18.42%)	0.101	0.992
Poorly differentiated adenocarcinoma	10 (38.46%)	14 (36.84%)		
Mucous adenocarcinoma	7 (26.92%)	10 (26.32%)		
Gastric cancer stage [case (%)]				
T3	14 (53.85%)	20 (52.63%)	0.009	0.924
T4	12 (46.15%)	18 (43.37%)		
N0-1	15 (57.69%)	22 (57.89%)	1.523	0.217
N2-3	11 (42.31%)	16 (42.11%)		

Table 2. Comparison of chemotherapy complications between the two groups.

Complication	New (n=38)	Conventional (n=26)	$\chi 2$	p
Leukopenia [case (%)]				
I	6 (15.79%)	2 (7.69%)		
II	5 (13.16%)	1 (3.85%)	4.761	0.029
III	3 (7.89%)	1 (3.85%)		
IV	0(0.00%)	0 (0.00%)		
Thrombocytopenia [case (%)]				
I	5 (13.16%)	1 (3.85%)		
II	5 (13.16%)	2 (7.69%)	5.13	0.024
III	6 (15.79%)	1 (3.85%)		
IV	0(0.00%)	0 (0.00%)		
Anemia [case (%)]				
I	6 (15.79%)	1 (3.85%)		
II	4 (10.52%)	1 (3.85%)	6.91	0.009
III	6 (15.79%)	1 (3.85%)		
IV	0 (0.00%)	0 (0.00%)		
Abnormal liver function [case (%)]				
I	7 (18.42%)	2 (7.69%)		
II	8 (21.05%%)	1 (3.85%)	4.452	0.035
III	2 (5.26%)	2 (7.69%)		
IV	0 (0.00%)	0 (0.00%)		
Diarrhea [case (%)]				
I	4 (10.53%)	3 (11.54%)		
II	2 (5.26%)	2 (7.69%)	0.001	0.971
III	2 (7.69%)	1 (3.85%)		
IV	0(0.00%)	0 (0.00%)		
Hand-foot syndrome [case (%)]				
I	2 (7.69%)	2 (7.69%)		
II	5 (13.16%)	3 (11.54%)	0.143	0.705
III	1(2.63%)	2 (7.69%)		
IV	0 (0.00%)	0 (0.00%)		
Nausea and vomiting [case (%)]				
I	3 (7.89%)	2 (7.69%)		
II	6 (15.79%)	4 (15.38%)	0.005	0.944
III	1(2.63%)	2(7.69%)		
IV	0(0.00%)	0(0.00%)		

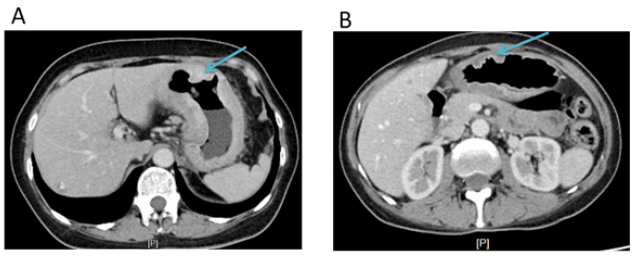

Figure 1. Typical CT imaging results of the two groups before and after chemotherapy. A. Typical CT before chemotherapy in neochemotherapy group; B. typical CT after chemotherapy in neochemotherapy group. Arrow indicates tumor location.

between the two groups (all $P > 0.05$).

Comparison of chemotherapy and surgical effects

AS shown in Figure 1A, B, Wilcoxon rank-sum test and chi-square test respectively showed that the chemotherapy effect of the new chemotherapy group was better than that of the traditional chemotherapy group, and the surgical R0 resection rate of the group was higher than that of the traditional chemotherapy group (all $P < 0.05$). Representative abdominal CT results of 2 patients in the new chemotherapy group before and after chemotherapy were shown in figure 2. After chemotherapy, gastric tumors in the new chemotherapy group significantly decreased in volume and tumor diameter.

Comparison of immune function of patients after operation

Serum antibody (IgM, IgG) and $CD4^+$ / $CD8^+$ were recorded in the traditional chemotherapy group and neochemotherapy group, respectively, as shown in Table 3 and Table 4. The serum antibody (IgM, IgG) and $CD4^+$ / $CD8^+$ in the conventional chemotherapy group and the new chemotherapy group showed a downward trend during the observation period, and the difference was statistically significant in different periods (all $P < 0.05$). The serum antibody (IgM, IgG) and $CD4^+$ / $CD8^+$ in the conventional chemotherapy group were significantly lower than those in the new chemotherapy group ($P < 0.05$). The analysis of interaction shows that there is an interaction between different chemotherapy schemes and treatment time, and the difference is statistically significant (all P interaction < 0.05), details are showed in Table 3 and Table 4.

Discussion

Lack of physical examination awareness and lack of specific symptoms are the main reasons for the development of advanced gastric cancer in some patients (15,16). Direct surgical treatment for advanced gastric cancer is not effective, some patients are difficult to achieve surgical R0 resection, so preoperative chemotherapy is often needed to reduce the stage of patients' tumor after elective surgery (17). Apatinib has a strong inhibitory effect on tumor angiogenesis and has been proved to have a therapeutic effect on a variety of tumors, including cervical cancer, gastric cancer and so on (18,19). In this study, Apatinib combined with Tezio was selected for preoperative chemotherapy, and it was found that compared with the conventional preoperative chemotherapy, Apatinib combined with Tezio could improve the chemotherapy effect of patients, and improve the chemotherapy effect and postoperative immunosuppression.

Tumor can stimulate neovascularization in the process of growth and provide nutrients for metabolism. In this process, vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-2 (VEGFR-2) on the endothelial cell membrane combine with and transfer cell proliferation signal, promote the generation of capillaries and participate in tumor growth (20, 21). Apatinib is a small molecular inhibitor targeting VEGFR-2. It can competitively bind to VEGFR-2, block the signal pathway related to the downstream cell proliferation after binding with VEGF, and play a role in inhibiting the growth of tumor cells (18). Previous studies have found that Apatinib can prolong the median survival time and reduce the risk of death in patients with gastric cancer who failed in the second-line chemotherapy, showing a good application prospect (22). This study also suggests that, compared with the conventional preoperative chemotherapy regimen of oxaliplatin combined with capecitabine, CT results after chemotherapy show that Apatinib combined with Tezio will increase the proportion of CP and PR after chemotherapy, and improve the surgical R0 resection rate of patients. Wilcoxon's rank-sum test showed that the incidence of myelosuppression (leukocytes, platelets and anemia) and liver dysfunction in the chemotherapy regimen of Apatinib combined with Tegio was low, but there was no advantage in diarrhea, hand-foot syndrome and malignant vomiting. It is speculated that the reason may be that VEGF is highly expressed only in the process of tumor growth. The chemotherapy plan of Apatinib combined with Tezio will target to inhibit neovascularization and kill tumor cells at the same time. The action of Apatinib targeting tumor cells will reduce the use of pan-specific chemotherapy drugs to some extent.

Table 3. Comparison of serum antibody IgG and IgM levels between the two groups.

Group		Before	After	After one week
IgG(g/L)	Conventional (n=38)	11.97±1.54	9.01±1.83	8.81±1.54
	New (n=26)	12.81±1.72	10.64±1.73	9.65±1.42
IgM(g/L)	Conventional (n=38)	1.24±0.21	0.96±0.24	0.92±0.28
	New (n=26)	1.35±0.34	1.10±0.21	1.12±0.19

Table 4. Comparison of $CD4^+$/$CD8^+$ between the two groups.

Group		Before	After	After one week
$CD4^+T/CD8^+T$	Conventional (n=38)	1.49±0.32	0.99±0.39	0.75±0.28
	New (n=26)	1.53±0.42	1.18±0.24	1.04±0.35

Therefore, it will have some advantages in reducing adverse complications during chemotherapy. However, small molecule targeted drugs also have diarrhea and hand-foot syndrome, so they cannot reduce the occurrence of some chemotherapy complications (23). In clinical practice, in order to ensure the smooth progress of chemotherapy, it is necessary to properly screen the patients with preoperative chemotherapy, to ensure that the general situation of patients can be tolerated and conduct preoperative chemotherapy, and to deal with the complications in time during the treatment process.

Oxaliplatin and capecitabine are both highly cytotoxic chemotherapy drugs. The former can inhibit tumor DNA replication by binding with G covalent bond in DNA, while the latter can play an anti-tumor role by generating 5-FU through metabolism in vivo (24, 25). However, these drugs can not only inhibit tumor growth, but also inhibit the immune system of the body, leading to the decline of humoral immunity and cellular immunity of patients, and affect the killing effect of the autoimmune system on tumor cells, which is not conducive to the prognosis of patients (26). IgM and IgA are produced by B-lymphocytes and participate in many important immune processes such as anti-infection and anti-virus immunity (27). The proportion of $CD4^+$ / $CD8^+$ T cells is also an important indicator of the immune state of the body. The decrease in the proportion indicates that the immune function of the body is in a state of inhibition. Severe immunosuppression will make it difficult for the body to remove the residual tumor cells after surgery and increase the risk of recurrence. The results of this study show that different chemotherapy regimens can lead to the decrease of IgM, IgA and $CD4^+$ / $CD8^+$ T cell ratio in the course of treatment, which suggests that the cytotoxic effect of chemotherapy drugs can inhibit the normal immune system of the body during the treatment. However, the decrease degree of each index of Apatinib combined with Tezio group was lower than that of oxaliplatin and capecitabine group, which further indicated that the targeting mechanism of molecularly targeted drugs could improve the inhibition effect of traditional cytotoxic drugs on the immune function of the body, which was conducive to the resistance of patients for pathogen infection and the reduction of postoperative tumor recurrence. In general, different aspects of gastric cancer treatment should be considered.

There are also deficiencies in this study. Due to the small number of people included in this study, this study did not discuss the differences in the therapeutic effect of different drug doses. In addition, due to the limitation of study time, the patients were not followed up after the surgery in this study. It is impossible to know whether Apatinib combined with Tezio can improve the long-term prognosis of patients.

In summary, the preoperative neoadjuvant chemotherapy regimen of Apatinib combined with Tezio can improve the chemotherapy effect of advanced gastric cancer, improve the R0 resection rate and reduce the immunosuppressive status of patients during treatment.

References

1. Strong VE. Progress in gastric cancer. Updates Surg. 2018; 70(2):157–159.
2. Song Z, Wu Y, Yang J, Yang D, Fang X. Progress in the treatment of advanced gastric cancer. Tumour Biol. 2017; 39(7):101-116.
3. Xiao S, Zhou L. Gastric cancer: Metabolic and metabolomics perspectives (Review). Int J Oncol. 2017; 51(1):5–17.
4. Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. World J Gastroenterol 2018; 24(26):2818–2832.
5. Zong L, Abe M, Seto Y, Ji J. The challenge of screening for early gastric cancer in China. Lancet. 2016; 388(10060):2600-2606.
6. Digklia A, Wagner AD. Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol. 2016; 22(8):2403–2414.
7. Reddavid R, Sofia S, Chiaro P, et al. Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake? World J Gastroenterol. 2018; 24(2):274–289.
8. Das M. Neoadjuvant chemotherapy: survival benefit in gastric cancer. Lancet Oncol. 2017;18(6): e307.
9. Skeel RT, Khleif SN, editors. Handbook of cancer chemotherapy. Lippincott Williams & Wilkins; 2011.
10. Kano M, Hayano K, Hayashi H, et al. Survival Benefit of Neoadjuvant Chemotherapy with S-1 Plus Docetaxel for Locally Advanced Gastric Cancer: A Propensity Score-Matched Analysis. Ann Surg Oncol. 2019; 26(6):1805–1813.
11. Li C, Zheng J, Xue Y. Effects of vascular endothelial growth factor and epidermal growth factor on biological properties of gastric cancer cells. Arch Med Sci. 2019; 15(6):1498–1509.
12. Li B, Qu G. Inhibition of the hypoxia-induced factor-1α and vascular endothelial growth factor expression through ginsenoside Rg3 in human gastric cancer cells. J Cancer Res Ther. 2019; 15(7):1642–1646.
13. Baidya Kayal E, Kandasamy D, Khare K, Bakhshi S, Sharma R, Mehndiratta A. Intravoxel incoherent motion (IVIM) for response assessment in patients with osteosarcoma undergoing neoadjuvant chemotherapy. Eur J Radiol. 2019; 119:108635.
14. Molina-Castro S, Pereira-Marques J, Figueiredo C, Machado JC, Varon C. Gastric cancer: Basic aspects. Helicobacter. 2017; 22 Suppl 1:10.1111/hel.12412.
15. Kim SJ, Choi CW. Common Locations of Gastric Cancer: Review of Research from the Endoscopic Submucosal Dissection Era. J Korean Med Sci. 2019;34(35): e231. Published 2019 Sep 9.
16. Aoyama T, Yoshikawa T. Adjuvant therapy for locally advanced gastric cancer. Surg Today. 2017;47(11):1295–1302.
17. Miao ZF, Liu XY, Wang ZN, et al. Effect of neoadjuvant chemotherapy in patients with gastric cancer: a PRISMA-compliant systematic review and meta-analysis. BMC Cancer. 2018; 18(1):118.
18. Scott LJ. Apatinib: A Review in Advanced Gastric Cancer and Other Advanced Cancers [published correction appears in Drugs. 2018 May 4]. Drugs. 2018; 78(7):747–758.
19. Ding J, Cheng XY, Liu S, et al. Apatinib exerts anti-tumour effects on ovarian cancer cells. Gynecol Oncol. 2019; 153(1):165–174.
20. Siveen KS, Prabhu K, Krishnankutty R, et al. Vascular Endothelial Growth Factor (VEGF) Signaling in Tumour Vascularization: Potential and Challenges. Curr Vasc Pharmacol. 2017; 15(4):339–351.
21. Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell. 2019; 176(6):1248–1264.
22. Li J, Qin S, Xu J, et al. O-0029 * Phase III Study Of Apatinib in advanced gastric cancer: a randomized, double-blind, placebo-controlled trial. Annals Oncology, 2014; 25(suppl 2):ii117-ii117.
23. Geng R, Song L, Li J, Zhao L. The safety of Apatinib for the treatment of gastric cancer. Expert Opin Drug Saf. 2018; 17(11):1145–1150.

24. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019; 393(10184):1948–1957.
25. Yu X, Wang QX, Xiao WW, et al. Neoadjuvant oxaliplatin and capecitabine combined with bevacizumab plus radiotherapy for locally advanced rectal cancer: results of a single-institute phase II study. Cancer Commun (Lond). 2018; 38(1):24.
26. Stojanovska V, Prakash M, McQuade R, et al. Oxaliplatin Treatment Alters Systemic Immune Responses. Biomed Res Int. 2019; 2019:4650695.
27. Seifert M, Küppers R. Human memory B cells. Leukemia. 2016; 30(12):2283–2292.
28. Pels EJ. Oral mucositis and saliva IgA, IgG and IgM concentration during anti-tumor treatment in children suffering from acute lymphoblastic leukemia. Adv Clin Exp Med. 2017;26(9):1351–1358.
29. Kazemi E, Kahrizi D. Lack of association between gastric cancer and hopq alleles in Helicobacter pylori. Genetika 2016; 48(3): 893-902
30. Kazemi E, Kahrizi D, Moradi MT, Sohrabi M, Yari K. Gastric Cancer and Helicobacter pylori: Impact of hopQII Gene. Cell Mol Biol 2016; 62(2): 107-110.
31. Kazemi E, Kahrizi D, Moradi MT, Sohrabi M, Amini A, Mousavi SAR, Yari K. Association between Helicobacter pylori hopQI genotyping and human gastric cancer. Cell Mol Biol 2016; 62(1): 6-9.
32. Kazemi E, Kahrizi D, Moradi MT, Sohrabi, M, Amini S, Mousavi S.A.R., Yari K. Association between Manganese Superoxide Dismutase (MnSOD Val-9Ala) genotypes with the risk of generalized aggressive periodontitis disease. Cell Mol Biol 2016; 61(8): 49-52.