Clinical Trial/Experimental Study

Medicine®

OPEN

Comprehensive evaluation of clinical efficacy and safety of celecoxib combined with chemotherapy in management of gastric cancer

Qinghong Guo, MM[a], Xiaojun Liu, MD[b], Linzhi Lu, MM[c], Hao Yuan, MD[a], Yuping Wang, MD[a], Zhaofeng Chen, MD[a], Rui Ji, MM[a], Yongning Zhou, MD[a,*]

Abstract

Background: To evaluate the clinical efficacy and safety of celecoxib combined with chemotherapy in the treatment of gastric cancer.

Methods: In total, 240 gastric cancer patients undergoing radical gastrectomy followed by adjuvant chemotherapy were randomly assigned into 2 groups. In the experimental group (n = 120), patients were administered with celecoxib-based chemotherapy, and chemotherapy alone was performed in the control group. Disease-free survival (DFS) and progression-free survival (PFS) were considered as the primary efficacy parameters, and objective response rate (ORR), overall survival (OS), quality of life (QOL), and safety as the secondary efficacy parameters.

Results: The 3-year OS did not significantly differ between the experimental (72%) and control groups (68%, $P = .67$). The 3-year DFS in the experimental group was 64%, which did not significantly differ from 51% in the control group ($P = .41$). In patients with positive cyclooxygenase-2 (COX-2) from the experimental group, the 3-year OS was 78%, significantly higher compared with 66% in the control group ($P = .02$), and the 3-year DFS was 70%, considerably >50% in the control group ($P = .01$). No statistical significance was identified in the incidence of nausea, neutropenia, anorexia, peripheral neurotoxicity, diarrhea, vomiting, asthenia, and thrombocytopenia, etc. The EORTC quality of life questionnaire (QLQ)-C30 questionnaire revealed that the global QOL in the experimental group was significantly higher than that in the control group ($P < .05$). No statistical significance was noted in the scores of functioning scale between 2 groups, whereas the scores of the symptom scale, especially pain and fatigue in the experimental group were remarkably higher than that in the control group ($P < .05$). The global score of EORTC QLQ-STO22 in the experimental group was considerably higher compared with that in the control group ($P < .05$). No statistical significance was identified in term of the domains of restrictions on feeding, dysphagia, anxiety, reflux, sense of taste, dry mouth, hair loss, and body shape between groups (all $P > .05$).

Conclusion: Celecoxib combined with chemotherapy yields clinical benefits for gastric cancer patients with positive COX-2, which not only enhances the OS, DFS, PFS, QOL, and short-term clinical efficacy, but also does not increase the risk of adverse events.

Abbreviations: CI = confidence interval, COX-2 = cyclooxygenase-2, DAB = diaminobenzidine, DFS = disease-free survival, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PBS = phosphate buffer solution, PFS = progression-free survival, QOL = quality of life.

Keywords: celecoxib, chemotherapy, disease-free survival, gastric cancer, progression-free survival

1. Introduction

Gastric cancer is the fifth most common malignancy worldwide. It is the most common malignant tumor in Asia, especially in China.[1,2] At present, the average prevalence and mortality rate of gastric cancer in China significantly exceed the average risk worldwide. A majority of cases are diagnosed with advanced gastric cancer upon admission. Surgical resection supplemented with postoperative chemotherapy remains the primary treatment, whereas the postoperative recurrence rate is alarmingly high.[3] Development of the molecular biological techniques unravels the mechanisms underlying the incidence and progression of malignant tumors. Cell receptor, cell cycle, signal conduction, and angiogenesis have been validated to act as the novel targets of clinical intervention of cancer. Previous studies[4–7] have demonstrated that cyclooxygenase-2 (COX-2) plays a pivotal role in the incidence and progression of malignant tumors. Our preliminary in vitro study has suggested that COX-2 can regulate the expression of E-cadherin through Snail/NF-kb signaling pathway and promote the proliferation, infiltration, and metastasis of gastric cancer cells. On this basis, celecoxib was applied as the

Editor: Yan Li.

Funding support: Science and Technology Foundation of Gansu (1606RJZA140); National key research and development plan, digital diagnosis and treatment equipment research and development special project (2016YFC0107006); Scientific and research Management Project of Gansu Healthy Profession (GWGL2010-19).

The authors have no conflicts of interest to disclose.

[a] Department of Gastroenterology, [b] Department of Oncology, the First Hospital of Lanzhou University, Lanzhou, [c] Department of Gastroenterology, Wuwei Tumor Hospital of Gansu Province, Wuwei, China.

[*] Correspondence: Yongning Zhou, Lanzhou University First Affiliated Hospital, Lanzhou, Gansu, China (e-mail: zhouyongning827@126.com).

Medicine (2017) 96:51(e8857)

Received: 11 September 2017 / Received in final form: 26 October 2017 / Accepted: 2 November 2017

http://dx.doi.org/10.1097/MD.0000000000008857

preoperative short-term intervention for gastric cancer patients, suggesting that elective COX-2 inhibitor could inhibit the proliferation, infiltration, and metastasis of malignant tumors. Recent investigations[8,9] have demonstrated that celecoxib, as an elective COX-2 inhibitor, possesses anti-tumor effect in tumor model studies and clinical trials. Celecoxib and chemotherapy agents exert a synergistic effect upon malignant tumors, whereas the conclusion remains to be further validated by multicenter and sample-size investigations. Moreover, gastric cancer is manifested with geographical pattern and influenced by genetics and environmental factors, which significantly affect the sensitivity and specificity of postoperative chemotherapy. In this case-control study, gastric cancer patients from Gansu province, a gastric cancer-prevalent region were recruited. The clinical efficacy and safety of celecoxib combined with chemotherapy in gastric cancer patients after undergoing radical gastrectomy were evaluated.

2. Materials and methods

2.1. Study subjects

The patients undergoing radical gastrectomy from 3 centers including the First Affiliated Hospital of Lanzhou University, Gansu Wuwei Tumor Hospital, and the General Hospital of Lanzhou Military Command between September 2010 and July 2016 were enrolled in this clinical trial. All patients were randomly assigned into the experimental and control groups. In the control group, a chemotherapy regime consisting of fluorouracil-type drugs (5-fluorouracil, capecitabine, and tegafur) in combination with oxaliplatin at a dosage of 130 mg/m^2 via intravenous drip for 3 hours. In the experimental group, the chemotherapy regime was similar to the control group. Celecoxib capsule (200 mg) was administered twice daily for approximately continuous 5 months until the day of final chemotherapy. According to the compliance and tolerance of gastric cancer patients, 6 cycles of adjuvant chemotherapy were delivered. The clinical efficacy and safety of adjuvant chemotherapy were assessed every 2 cycles. Written informed consents were obtained from all participants. The study procedures were approved by the ethics committee of our hospital.

2.2. Inclusion and exclusion criteria

Inclusion criteria were follows: aged 18 to 70 years; patients who had undergone radical gastrectomy; ECOG PS 0–2; estimated survival >12 weeks; no vital organ dysfunction; normal outcomes for liver, kidney, heart function tests; routine blood test: neutrophilic granulocyte count $\geq 1.5 \times 10^9$/L, hemoglobin ≥90 g/L, and platelet count $\geq 85 \times 10^9$/L. Liver function: total bilirubin <1.5 times of the upper limit of normal value; aspartate transaminase and alanine aminotransferase <2.5 times of the upper limit of normal value; kidney function: serum creatinine <1.25 times of the upper limit of normal value; electrocardiograph revealed no abnormality; no metastasis of malignant lesions. Exclusion criteria included uncontrollable hypertension, diabetes mellitus and digestive tract ulcer; serious allergic history; uncontrollable mental diseases; pregnant, and lactating women.

2.3. Immunohistochemical staining of OX-2

Immunohistochemical SP method: 5 μm-paraffin wax sections were subject to xylene deparaffin for 10 minutes, gradient ethanol dehydration, 3% hydrogen peroxide incubation at 37°C for 10 minutes, phosphate buffer solution (PBS) rinse for 5 minutes, 0.01 M citric acid buffer solution (pH = 6.0) at 95°C for 20 minutes, PBS for 5 minutes, normal goat serum working solution at 37°C for 10 minutes, supplemented with primary antibody mouse anti-human monoclonal antibody (ZSGB-bio company, Beijing, China), overnight incubation at 4°C, PBS rinse for 5 minutes, added with biotin-labeled secondary antibody, incubation at 37°C for 30 minutes, PBS rinse for 5 minutes, supplemented with horseradish peroxide enzyme-labeled streptomycin avidin working solution at 37°C for 30 minutes, diaminobenzidine (DAB), counterstained with hematoxylin for 3 minutes and observed under the microscope. Almost no staining was graded as 0, slight staining as 1, and dark staining as 2. The percentage of positive cells ≤5% was regarded as 0, 6% to 25% as 1, 26% to 50% as 2, and ≥51% as 3. The product of section staining score and the percentage of positive cells was calculated as the final score. A score of 0 to 1 was graded as negative (–), 2 to 3 as weakly positive (+), 4 to 6 as positive (++), >6 as strongly positive (+++), and ≥4 represented high expression of COX-2.

2.4. Clinical efficacy assessment

Disease-free survival (DFS) is defined as the period from patient enrollment to the recurrence or disease progression until death. The postoperative follow-up was delivered every 3 months. The clinical efficacy of chemotherapy was assessed every 2 cycles after the treatment. OS refers to the period from patient enrollment to the death. Postoperative follow-up was initiated from the beginning of the chemotherapy every 2 months until the death of patients. After the treatment, postoperative follow-up was delivered every 3 months until the death of patients. Quality of life questionnaire (QLQ) was assessed by EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires. The follow-up was initiated from the beginning of treatment every 2 months. The follow-up was continuously performed every 3 months until the death of patients.

2.5. Therapeutic safety assessment

Common adverse events included nausea, anorexia, vomiting, abdominal pain, diarrhea, constipation, neutropenia, peripheral neurotoxicity, asthenia, thrombocytopenia, and dizziness, etc. The severities of these symptoms were classified and statistically compared between 2 groups. Postoperative follow-up was initiated from the beginning of the chemotherapy every 2 months until the death of patients. After the treatment, postoperative follow-up was delivered every 3 months until the death of patients.

2.6. Statistical analysis

The values of $\alpha = 0.05$ and $\beta = 0.10$ were considered as a level of significance. The ratio comparison was performed by using chi-squared test. Measurement data were statistically analyzed by analysis of variance. The survival data were statistically analyzed by log-rank test and Kaplan–Meier test.

3. Results

3.1. Baseline data

A total of 240 patients undergoing radical gastrectomy were recruited in this study. Three patients in the experimental group and 7 in control group rejected to receive treatment. Eventually, 230 cases were eligible for subsequent investigation (Fig. 1).

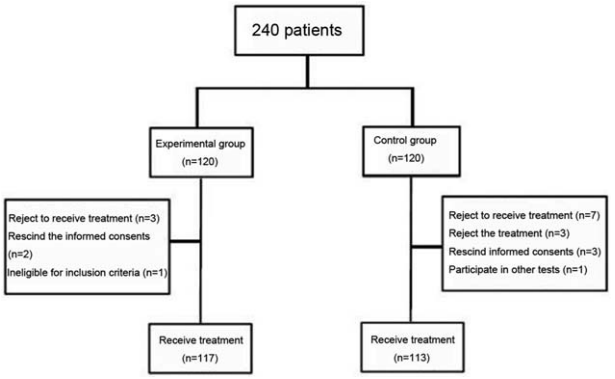

Figure 1. Flow chart of the screening and grouping of enrolled patients.

Among them, 155 cases were men and 75 women, aged 31 to 70 years, ECOG score of 0 to 1 in 187, ECOG score of 2 in 43, gastro-esophageal junction tumors in 63, gastric tumor in 167, 41 undergoing proximal gastrectomy, 123 with distal gastrectomy, and 66 undergoing radical gastrectomy. Fifty-four patients underwent D1 radical gastrectomy, 176 with D2 radical gastrectomy, Ib stage in 40, II stage in 125, III stage in 65, tubular adenocarcinoma in 138, mucinous adenocarcinoma in 57, signet-ring cell carcinoma in 35, intestinal type in 138, diffuse type in 39, mixed type in 53, COX-2 positive in 115, COX-2 negative in 107, specimen origin from gastroscope in 56, and specimen origin from surgery in 166 cases. No statistical significance was identified in the demographic and baseline data between the experimental and control groups.

3.2. COX-2 expression level

Immunochemical staining revealed that the positive rate of COX-2 in the experimental group was calculated as 49% (n = 57) and 51% (n = 58) in the control group with no statistical significance between 2 groups, as illustrated in the Fig. 2.

3.3. Postoperative survival

Kaplan–Meier survival curve of the OS and DFS in patients between 2 groups was delineated in Fig. 3. In the experimental group, the 3-year OS was 72% and 68% in the control group with no statistical significance (hazard ratio [HR] = 0.77, 95% confidence interval [CI] = 0.52–1.15, $P = .67$). In patients with positive COX-2 from the experimental group, the 3-year OS was 78%, significantly higher compared with 66% in the control group (HR = 0.57, 95% CI = 0.28–1.18, $P = .02$). In the experimental group, the 3-year DFS was 64% and 51% in the control group with no statistical significance (HR = 0.73, 95% CI = 0.48–1.09, $P = .41$). In patients with positive COX-2 from the experimental group, the 3-year DFS was 70%, significantly higher compared with 50% in the control group (HR = 0.50, 95% CI = 0.22–1.24, $P = .01$), as illustrated in Table 1 and Fig. 4.

3.4. Therapeutic safety evaluation

More adverse events induced by chemotherapy included nausea, appetite loss, vomiting, diarrhea, granulocytopenia, abdominal pain, and emaciation, etc. In the experimental group, the most common adverse event was nausea (36/117, 31%) including grade 3/4 in 3% (4/117), and 33 (29%) in the control group including grade 3/4 in (3/113). No statistical significance was

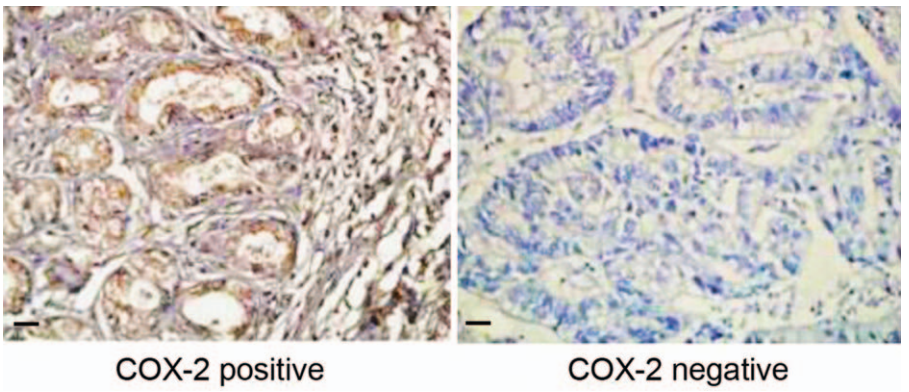

Figure 2. Immunohistochemical staining of COX-2 in gastric cancer tissues. COX-2 = cyclooxygenase-2.

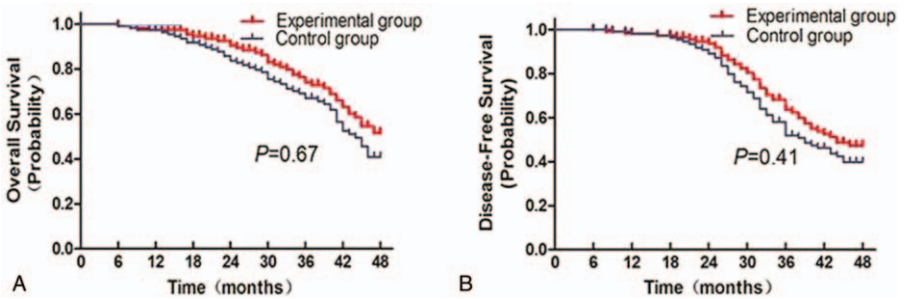

Figure 3. Comparison of OS (A) and DFS (B) in gastric cancer patients between 2 groups. DFS = disease-free survival, OS = overall survival.

Table 1

Comparison of survival analysis of patients between 2 groups.

	Celecoxib combined with chemotherapy (n = 117)	Chemotherapy (n = 113)	HR	95% CI	*P*
3-year OS	72%	68%	0.77	0.52–1.15	.67
3-year OS for COX-2 positive patients	78%	66%	0.57	0.28–1.18	.02
3-year DFS	64%	51%	0.73	0.48–1.09	.41
3-year DFS for COX-2 positive patients	70%	50%	0.50	0.22–1.24	.01

CI = confidence interval, COX-2 = cyclooxygenase-2, DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

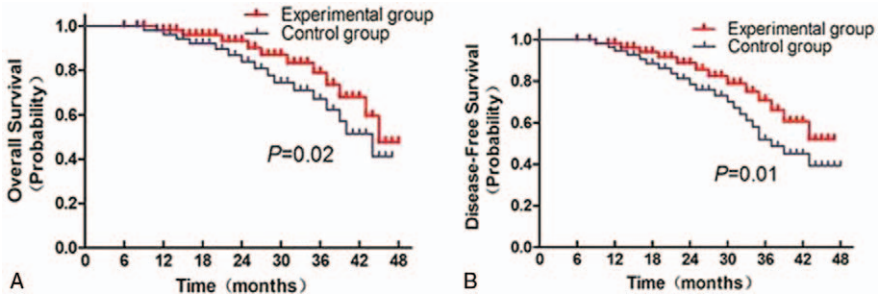

Figure 4. Comparison of OS (A) and DFS (B) in gastric cancer patients with positive COX-2 between 2 groups. COX-2 = cyclooxygenase-2, DFS = disease-free survival, OS = overall survival.

identified in the incidence of nausea between 2 groups. In addition, the incidence of neutropenia, anorexia, peripheral neurotoxicity, diarrhea, vomiting, asthenia, and thrombocytopenia did not significantly differ between 2 groups, as illustrated in Table 2.

3.5. QOL assessment

In both groups, QOL was evaluated by QLQ-C30 and QLQ-STO22 questionnaires. Prior to treatment, no statistical significance was identified in the scores of each scale of QOL between 2 groups (all $P > .05$). The scores of each scale of QLQ-C30 and QLQ-STO22 questionnaires did not significantly differ before and after chemotherapy in the control group (all $P > .05$). After chemotherapy, the global QOL of EORTC QLQ-C30 questionnaire in the experimental group was significantly higher compared with that in the control group ($P < .05$). No statistical significance was documented in the functioning scale scores between 2 groups (all $P > .05$). In the experimental group, the scores of symptom scale, especially pain and fatigue were considerably higher than those in the control group (all $P < .05$). In the experimental group, the global score of EORTC QLQ-STO22 questionnaire was significantly higher than that in the control group ($P < .05$), whereas no statistical significance was identified in the scores of the domains of restrictions on feeding, dysphagia, anxiety, reflux, sense of taste, dry mouth, hair loss, and body shape between 2 groups (all $P > .05$).

4. Discussion

Recent global statistics have revealed that stomach cancer is the fifth most common cancer worldwide, with 952,000 new cases

Table 2

Comparison of incidence of adverse events after treatment between 2 groups.

	Celecoxib combined with chemotherapy (n = 117)		Chemotherapy (n = 113)	
	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	36 (31%)	4 (3%)	33 (29%)	3 (3%)
Neutropenia	2 (2%)	1 (1%)	4 (4%)	1 (1%)
Anorexia	6 (5%)	1 (1%)	7 (6%)	1 (1%)
Peripheral neurotoxicity	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	11 (9%)	2 (2%)	8 (7%)	2 (2%)
Vomiting	5 (4%)	0 (0%)	6 (5%)	0 (0%)
Fatigue	5 (4%)	1 (1%)	7 (6%)	1 (1%)
Thrombocytopenia	1 (1%)	0 (0%)	2 (2%)	0 (0%)
Hand-foot syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Abdominal pain	1 (1%)	0 (0%)	2 (2%)	0 (0%)
Constipation	5 (4%)	0 (0%)	2 (2%)	0 (0%)
Dizziness	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Oral inflammation	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Emaciation	2 (2%)	0 (0%)	1 (1%)	0 (0%)

diagnosed in 2012.[10]*Helicobacter pylori* is an important cause of stomach cancer, particularly non-cardia cancer. Epstein-Barr virus, which is carcinogenic to humans, has also been linked to gastric cancer. Surgery, radiotherapy, and chemotherapy remain the primary interventions for the treatment of advanced gastric cancer.[11] Although radical gastrectomy and systemic lymph node dissection yield clinical efficacy, the risk of recurrence and metastasis of gastric carcinoma is still alarmingly high. Compared with the radical gastrectomy alone, radical gastrectomy combined with postoperative chemotherapy can significantly enhance the clinical prognosis, and prolong the median OS, DFS, and PFS of gastric cancer patients. Meta-analysis has revealed that combined chemotherapy exerts a higher clinical efficacy in the clinical prognosis of advanced gastric cancer patients compared with the chemotherapy alone. For patients diagnosed with middle- and advanced-stage gastric cancer, chemotherapy is still the primary option for gastric cancer treatment.[12] Chemotherapy combined with supporting therapy can mitigate the clinical symptoms, enhance the quality of life and improve clinical prognosis of gastric cancer patients. Nevertheless, the issues of insensitivity or drug resistance towards the chemotherapy drugs are urgently to be resolved. Previous clinical trials have reported that approximately 50% of patients are insensitive to platinum-based chemotherapy agents due to secondary multidrug resistance in China. Moreover, the use of chemotherapy is likely to cause severe injuries to the proliferation and activity of normal cells. Therefore, a targeted and harmless chemotherapy agent is urgently required to enhance the clinical efficacy and therapeutic safety of postoperative chemotherapy and non-surgical intervention.

Comprehensive therapeutic regime consisting of chemotherapy in combination with new drug is a novel orientation of current treatment of gastric cancer.[13] Multi-molecule target medication therapy has been proven to yield high clinical efficacy in clinical trials. The theoretical basis of targeted therapy depends upon the expression levels of tumor-specific biomarkers, which embodies the concept of individualized treatment of malignant tumors. The administration of celecoxib, a cyclooxygenase-2 inhibitor, is captivating widespread attention from oncologists. COX-2 has been proven to play a pivotal role in the incidence and progression of malignant tumors.[14] COX-2 is able to promote the growth and proliferation of tumors, inhibit the cellular apoptosis, up-regulate the expression level of vascular endothelial growth factor through prostaglandin E2.[15] Therefore, celecoxib has been recognized to exert anti-tumor effect by oncologists. United States Food and Drug Administration have approved the use of elective COX-2 inhibitor celecoxib to treat familial adenomatosis coli and prevent the incidence of colon cancer in clinical practice. Recent investigations[16–18] have demonstrated that high expression of COX-2 can upregulate the expression level of multidrug resistance proteins, which can be blocked by the use of COX-2 inhibitor. Consequently, administration of celecoxib can enhance the sensitivity of gastric cancer patients towards platinum-based chemotherapy drug and 5-Fu. Our preliminary in vitro research also found that COX-2 is capable of regulating the expression level of E-cadherin through Snail/NF-kb signaling pathway and promoting the growth, infiltration, and metastasis of gastric cancer cells. Therefore, celecoxib in combination with the first-line chemotherapy is a promising comprehensive treatment of gastric cancer.

The mortality rate of gastric cancer in Gansu province is reported up to 61.99/100,000, accounting for 39.75% of all malignant tumors. The incidence and mortality rate of gastric cancer in Gansu province is the highest nationwide. The prevalence of gastric cancer in Wuwei city of Gansu province is 90.71/100,000, almost 5 times higher compared with the average level in China. According to the annual report of the registered cancer patients in 2016, the incidence rate of gastric cancer in Wuwei city is calculated as 100.38/100,000, accounting for 41.56% among all types of malignant tumors, which is consistent with the incidence rate of 8% in the present investigation.

In this multicenter randomized case-control study, 230 patients diagnosed with advanced gastric cancer undergoing radical gastrectomy were recruited and randomly assigned into 2 groups. In the control group, chemotherapy regime consisting of fluorouracil in combination with oxaliplatin (5-Fu, capecitabine, and tegafur) alone was adopted. In the experimental group, chemotherapy combined with celecoxib was administered for almost 5 months until the final chemotherapy. According to the therapeutic compliance and tolerance, the adjuvant chemotherapy was delivered for 6 cycles.

In this study, DFS was considered as the primary efficacy parameter, and overall survival (OS), quality of life (QOL), and therapeutic safety were utilized as the secondary efficacy parameters. Postoperative follow-up endured for 3 years. In total, 117 gastric cancer patients underwent celecoxib combined with chemotherapy. The 3-year OS was calculated as 72% and 64% for the 3-year DFS. In the chemotherapy alone group, the 3-year OS was 68% and the 3-year DFS was calculated as 51%. No statistical significance was identified in terms of the 3-year OS and DFS between 2 groups. Interestingly, for patients with positive COX-2 in the celecoxib combined with chemotherapy group, the 3-year OS was 78% and the 3-year DFS was 70%, significantly higher compared with 66% and 50% of their counterparts in the control group. These comparative results indicate that celecoxib combined with chemotherapy can significantly prolong the 3-year OS and DFS in patients diagnosed with advanced gastric cancer. Although use of celecoxib fails to enhance the OS of all patients, it significantly prolongs the OS and DFS of gastric cancer patients with positive COX-2, suggesting that use of celecoxib target specific gastric cancer patients, and COX-2 is the molecular target of such specific effect. Previous studies have demonstrated that COX-2 is not expressed in all types of malignant tumors, and the expression rate of COX-2 in gastric cancer is estimated to 50% to 60%, which is consistent with the expression rate of COX-2 in gastric cancer patients enrolled in this clinical trial. Since use of celecoxib can enhance the clinical benefits for gastric cancer patients with positive COX-2, whether it is necessary to perform COX-2 detection before standard chemotherapy and screen the gastric cancer patients according to the status of COX-2 expression remain to be further elucidated.

Prior to corresponding treatment, the scores of QLQ-C30 and QLQ-STO22 did not significantly differ between 2 groups. In addition, no statistical significance was identified in the QLQ-C30 and QLQ-STO22 before and after chemotherapy alone. Nevertheless, the global QOL score, the scores of the pain and fatigue domains of QLQ-C30 questionnaire, and the score of the pain domain of QLQ-STO22 questionnaire in the experimental group were significantly higher after treatment. No statistical significance was noted in terms of alternative domains between 2 groups. These results suggest that administration of celecoxib can significantly enhance the QOL by mitigating the pain and fatigue symptoms of gastric cancer patients. In terms of the adverse events during treatment, 36 patients suffered from nausea in the experimental group, and 33 in the control group. The incidence

of grade 3–4 adverse events was lower compared with that of overall adverse events. No statistical significance was identified in terms of the adverse events during the period of treatment between 2 groups. These results indicate that celecoxib combined with chemotherapy is a relatively safe treatment of gastric carcinoma, which yields similar adverse events.

Taken together, celecoxib in combination with the first-line chemotherapy is an efficacious and safe treatment of advanced gastric cancer. The conclusion in this clinical trial should be validated by multicenter, large sample-size investigations.

References

[1] Chen M, Yu L, Gu CP, et al. Celecoxib antagonizes the cytotoxic effect of cisplatin in human gastric cancer cells by decreasing intracellular cisplatin accumulation. Cancer Lett 2013;329:189–96.

[2] Okano H, Shinohara H, Miyamoto A, et al. Concomitant overexpression of cyclooxygenase-2 in HER-2-positive on Smad4-reduced human gastric carcinomas is associated with a poor patient outcome. Clin Cancer Res 2004;10:6938–45.

[3] Cheng J, Fan XM. Role of cyclooxygenase-2 in gastric cancer development and progression. World J Gastroenterol 2013;19:7361–8.

[4] Song J, Su H, Zhou YY, et al. Cyclooxygenase-2 expression is associated with poor overall survival of patients with gastric cancer: a meta-analysis. Dig Dis Sci 2014;59:436–45.

[5] Zhang H, Sun K, Ding J, et al. Harmine induces apoptosis and inhibits tumor cell proliferation, migration and invasion through down-regulation of cyclooxygenase-2 expression in gastric cancer. Phytomedicine 2014;21:348–55.

[6] Yan WF, Sun PC, Nie CF, et al. Cyclooxygenase-2 polymorphisms were associated with the risk of gastric cancer: evidence from a meta-analysis based on case-control studies. Tumour Biol 2013;34:3323–30.

[7] Mrena J, Wikstein JP, Thiel A, et al. Cyclooxygenase-2 is an independent prognostic factor in gastric cancer and its expression is regulated by the messenger RNA stability factor HuR. Clin Cancer Res 2005;11:7362–8.

[8] Mrena J, Wikstein JP, Kokkola A, et al. COX-2 is associated with proliferation and apoptosis markers and serves as an independent prognostic factor in gastric cancer. Tumour Biol 2010;31:1–7.

[9] Li Y, Dai LP, Zhang JZ, et al. Cyclooxygenase-2 polymorphisms and the risk of gastric cancer in various degrees of relationship in the Chinese Han population. Oncol Lett 2012;3:107–12.

[10] Chimal-Ramírez GK, Espinoza-Sanchez NA, Fuentes-Panana EM. A role for the inflammatory mediators Cox-2 and metalloproteinases in cancer stemness. Anticancer Agents Med Chem 2015;15:837–55.

[11] Echizen K, Hirose O, Maeda Y, et al. Inflammation in gastric cancer: interplay of the COX-2/prostaglandin E2 and Toll-like receptor/MyD88 pathways. Cancer Sci 2016;107:391–7.

[12] Oshima H, Oshima M. The role of PGE2-associated inflammatory responses in gastric cancer development. Semin Immunopathol 2013; 35:139–50.

[13] Sheng HM, Shao JY, Washington MK, et al. Prostaglandin E2 increases growth and motility of colorectal carcinoma cells. J Biol Chem 2001; 276:18075–81.

[14] Leone V, di Palma A, Ricchi P, et al. PGE2 inhibits apoptosis in human adenocarcinoma Caco-2 cell line through Ras-PI3K association and cAMP-dependent kinase A activation. Am J Physiol Gastrointest Liver Physiol 2007;293:673–81.

[15] Tineke CTM, van der Pouw Kraan , René A.W. van Lier , et al. PGE2 and the immune response. A central role for prostaglandin E2 in down-regulating the inflammatory immune response. Mol Med Today 1995;1:61–5.

[16] Yan Y, Singh GK, Zhang F, et al. Comparative study of normal and rheumatoid arthritis fibroblast-likesynoviocytes proliferation under cyclic mechanical stretch: role of prostaglandin E2. Connect Tissue Res 2012;53:246–54.

[17] Liu N, Huang J, Sun S, et al. Expression of matrix metalloproteinase-9, cyclooxygenase-2 and vascular endothelial growth factor are increased in gastrointestinal tumors. Int J Clin Exp Med 2015;8:6495–501.

[18] Lu L, Huang F, Zhao Z, et al. CD44v6: a metastasis-associated biomarker in patients with gastric cancer?: A comprehensive meta-analysis with heterogeneity analysis. Medicine (Baltimore) 2016;95: e5603.