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ORIGINAL ARTICLE

Efficacy of endostatin combined with continuous transcatheter arterial infusion and chemoembolization on gastric cancer with liver metastasis and analysis of prognosis

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Summary

Purpose: *To explore the efficacy and safety of Endostatin combined with continuous transcatheter arterial infusion (TAI) and transcatheter arterial chemoembolization (TACE) in the treatment of gastric cancer with liver metastasis, and analyze the prognosis.*

Methods: *96 gastric cancer patients with liver metastasis treated in our hospital from September 2013 to September 2016 were collected and randomly divided into TAI+TACE group (n=48) and Endostatin+TAI+TACE group (n=48). The clinical efficacy, changes in the level of vascular endothelial growth factor (VEGF) before and after treatment, adverse reactions, postoperative tumor recurrence and patient survival were observed and recorded, and the possible influencing factors for prognosis were analyzed.*

Results: *In the Endostatin+TAI+TACE group and TAI+TACE group, the objective response rate (ORR) was 70.8% (34/48) and 47.9% (23/48), and the disease control rate (DCR) was 91.7% (44/48) and 83.3% (40/48), respectively. After treatment, the concentration of VEGF declined significantly in both groups compared with that before treatment, more obviously in the Endostatin+TAI+TACE group than in the TAI+TACE group. According to the follow-up results, both overall survival (OS) and progression-free survival (PFS) in the Endostatin+TAI+TACE group were evidently higher than those in the TAI+TACE group. The Cox regression analysis revealed that the grade of tumor differentiation and Endostatin combination therapy were independent factors influencing the prognosis of patients.*

Conclusion: *Endostatin combined with TAI and TACE can obtain good short-term clinical efficacy in the treatment of gastric cancer with liver metastasis. Compared with those treated with chemotherapy alone, patients receiving Endostatin+TAI+TACE have significantly improved OS and PFS, a reduced level of VEGF and a lower incidence rate of adverse reactions, so Endostatin+TAI+TACE is worthy of clinical popularization and application.*

Key words: *gastric cancer, liver metastasis, Endostatin, transcatheter arterial infusion, chemoembolization, prognosis*

Introduction

Gastric cancer is a clinically common malignant tumor, its morbidity rate ranks 3rd among malignant tumors, and about 50% of gastric cancer cases occur in Asian patients [1,2]. Most patients have had metastasis of gastric cancer when diagnosed, 4-14% of which is liver metastasis, with a 5-year survival rate ≤10% [3-5]. The therapeutic effect on gastric cancer with liver metastasis is extremely poor, and fewer than 20% of patients can undergo surgical excision due to other non-

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curative factors [6]. Gastric cancer with liver metastasis is characterized by diffuse distribution, thus increasing the difficulty of treatment without an effective clinical regimen. It is recommended in the guidelines for the diagnosis and treatment of primary gastric cancer of the National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) (2017, V1), and the Japanese guidelines for the treatment of gastric cancer (2014, V4) that gastric cancer with metastasis be treated with chemotherapy, radiotherapy and local treatment, such as radiofrequency ablation and infusion chemotherapy [3,7].

It is reported that continuous transcatheter arterial infusion (TAI) combined with transcatheter arterial chemoembolization (TACE) has prominent advantages over traditional chemotherapy in the treatment of localized gastric cancer with liver metastasis [8]. Recombinant human Endostatin is an anti-tumor vascular targeting drug, and its anti-tumor effect has been confirmed in numerous studies [9,10]. In the present study, the clinical data of 96 gastric cancer patients with liver metastasis treated in our hospital from September 2013 to September 2016, who underwent TAI+TACE and Endostatin+TAI+TACE, were retrospectively analyzed, the safety and efficacy of such a therapeutic method were explored, and the influencing factors for prognosis were analyzed, so as to provide references for the treatment of gastric cancer patients with liver metastasis

Methods

General data

A total of 96 gastric cancer patients with postoperative liver metastasis treated in our hospital from September 2013 to September 2016 were collected and randomly divided into TAI+TACE group (n=48) and Endostatin+TAI+TACE group (n=48). There were 55 males and 41 females aged 24-73 years old (mean 60.64±10.71). The number of liver metastatic tumor was 1 in 15 cases, 2 in 39 cases, and 3 and above in 42 cases.

Inclusion criteria

Patients diagnosed with gastric cancer with liver metastasis via MRI and CT or liver biopsy, those aged 21-73 years old, those with estimated survival time >3 months, those with the Eastern Cooperative Oncology Group (ECOG) score 0-1, those with normal renal function, blood routine and electrocardiographic examina-

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

Characteristics	*Endostatin+TAI+TAE group (n=48)* *n (%)*	*TAI+TAE group (n=48)* *n (%)*	*p value*
Age, years	59.58±10.74	61.36±10.63	0.416
Gender			0.680
Male	26 (54.2)	29 (60.4)	
Female	22 (45.8)	19 (39.6)	
Number of metastatic sites			0.712
1	8 (16.7)	7 (14.6)	
2	21 (43.7)	18 (37.5)	
3 or more	19 (39.6)	23 (47.9)	
Histologic differentiation grade			0.739
High	3 (6.3)	2 (4.2)	
Moderate	9 (18.7)	11 (22.9)	
Poor	22 (45.8)	25 (52.1)	
Undifferentiated carcinoma	14 (29.2)	10 (20.8)	
T stage			0.399
T1-2	6 (12.5)	9 (18.8)	
T3-4	42 (87.5)	39 (81.2)	
N stage			0.695
N0	4 (8.3)	3 (6.3)	
N+	44 (91.7)	45 (93.7)	
ECOG score			0.302
0	23 (47.9)	18 (37.5)	
1	25 (52.1)	30 (62.5)	

TAI: Transcatheter arterial infusion; TAE: Transcatheter arterial embolization; T: Tumor; N: Lymph node; ECOG: Eastern Cooperative Oncology Group

tions before treatment, those with the Child-Pugh classification of liver function < grade C, those without cancer embolism at the main portal vein and with less formation of collateral vessel, and those with the volume ratio of tumor in the whole liver <70%.

Exclusion criteria

Patients with peritoneal cancer lesions or diffuse liver invasion, those allergic to the drugs used in this study, those complicated with other tumors, those with severe infectious diseases, those complicated with HIV infection or other autoimmune diseases, those with widespread distant metastasis of tumor, dyscrasia or multiple organ failure, or those with hypovascular liver metastasis.

There were no statistically significant differences in the age, gender, number of metastatic tumors, grade of tumor differentiation, T stage, N stage and preoperative ECOG score between the two groups (p>0.05), and they were comparable (Table 1). All patients enrolled adhered to the *Declaration of Helsinki* and the study was approved by the Ethics Committee of Gansu Provincial Hospital. Signed informed consents were obtained from all participants before the start of the study.

Treatment methods

Routine preparation: Under horizontal position, the right femoral artery was punctured using the Seldinger method, the hepatic catheter was inserted into the celiac trunk, and the catheter and catheter sheath were fixed after the correct catheter position was confirmed. The catheter was sealed with 500 U heparin and 20 mL of normal saline, and the patient was returned to the ward. In the ward, oxaliplatin (85 mg/m^2), calcium folinate (200 mg/m^2) and fluorouracil (400 mg/m^2) on day 1, and fluorouracil (1200 mg/m^2) on day 2 were continuously pumped for 48 h, during which whether there was exudation at the femoral artery catheter and pressure alarm in the artery pump was closely observed. At the same time, routine antiemetic therapy, gastric mucosal protective agents and nutritional support therapy were given, as well as pneumatic therapy for both lower extremities to prevent the lower extremity deep venous thrombosis. After the pumping of fluorouracil, the feeding artery of tumor, namely the target vessel, was determined via digital subtraction angiography, followed by target vessel embolization using polyvinyl alcohol or gelfoam particles with 300-500 μm in particle size. After operation, the catheter was withdrawn, followed by pressure bandaging.

On the above basis, recombinant human Endostatin was combined in Endostatin+TAI+TACE group. Fifteen mg of Endostatin were perfused through the infusion pump for 8-10 h continuously on days 1-14. The treatment was performed 4 times, once every 4 weeks.

Observation indexes

The clinical efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (V1.1). Complete response (CR): The lesions completely disappear after treatment for >1 month. Partial response (PR): The product of maximum diameter and maximum vertical diameter of lesion declines by >50% for >1 month. Stable disease (SD): The product of maximum diameter and maximum vertical diameter of lesion declines by <50% or increases by <25%, and there are no new lesions. Progressive disease (PD): The product of maximum diameter and maximum vertical diameter of lesion increases by ≥25%, or there are new lesions. The objective response rate (ORR) = (CR+PR)/total cases × 100%, and the disease control rate (DCR) = (CR+PR+SD)/total cases × 100%.

The patients were reexamined once every 3 months with general laboratory examination (hepatic and renal function, tumor markers and coagulation function), upper abdominal CT or MRI scan, till the patient's death. The level of vascular endothelial growth factor (VEGF) was measured via enzyme-linked immunosorbent assay before and after treatment. During chemotherapy, the adverse reactions were observed, evaluated and recorded based on the National Cancer Institute-Common Terminology Criteria Adverse Events (NCI-CTCAE) (V4.0), and they were classified into grade I-IV. The patient's survival and tumor progression status were recorded. The progression-free survival (PFS) refers to the time from initial chemotherapy to non-confirmed PD or death for any reason, while the overall survival (OS) refers to the time from initial chemotherapy to death for any reason. The patients were followed up till May 2019.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. P<0.05 suggested statistically significant difference. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was used to assess statistically significant differences in survival between the two groups. The possible influencing factors for the prognosis of patients were analyzed through the Cox regression model, and p<0.05 suggested statistically significant difference.

Results

Evaluation of short-term efficacy

In Endostatin+TAI+TACE group (n=48), there were 11 cases of CR, 23 cases of PR, 10 cases of SD, and 4 cases of PD. The ORR was 70.8% (34/48), and the DCR 91.7% (44/48). In TAI+TACE group (n=48), there were 7 cases of CR, 16 cases of PR, 17 cases of SD, and 8 cases of PD. The ORR was 47.9% (23/48), and the DCR 83.3% (40/48). It can be seen that the ORR in Endostatin+TAI+TACE group was significantly superior to that in TAI+TACE group (p=0.037), while the DCR had no statistically significant difference between the two groups (p=0.355) (Table 2).

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

Parameters	*Endostatin+TAI+TAE group (n=48)*	*TAI+TAE group (n=48)*	*p value*
CR	11	7	
PR	23	16	
SD	10	17	
PD	4	8	
ORR (%)	34 (70.8)	23 (47.9)	0.037
DCR (%)	44 (91.7)	40 (83.3)	0.355

TAI: Transcatheter arterial infusion; TAE: Transcatheter arterial embolization; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective response rate; DCR: Disease Control Rate

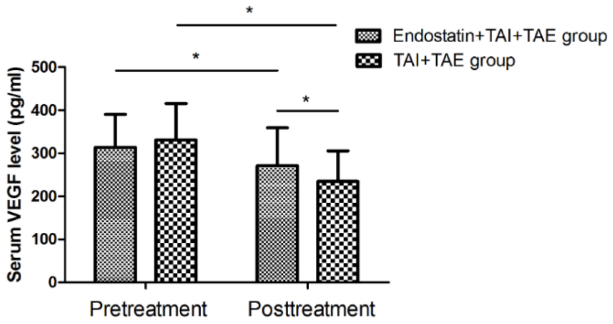

Figure 1. Comparison of serum VEGF level of patients in the two studied groups. The difference of pretreatment serum VEGF level of patients in Endostatin+TAI+TAE group and TAI+TAE group had no statistical significance (p=0.300). After treatment, serum VEGF level decreased dramatically in both groups (p=0.013,p<0.001). Posttreatment serum VEGF level of patients in Endostatin+TAI+TAE group was significantly lower than that of TAI+TAE group (*p=0.028).

Comparison of VEGF level between the two groups

Before and after treatment, the concentration of VEGF was 313.78±76.43 pg/mL and 271.13±88.36 pg/mL in Endostatin+TAI+TACE group, and 330.92±84.55 pg/mL and 234.71±70.79 pg/mL in TAI+TACE group. It can be seen that the concentration of VEGF had no statistically significant difference between the two groups before treatment (p=0.300), which was comparable. After treatment, the concentration of VEGF obviously declined in both groups compared with that before treatment, with statistically significant differences (p=0.013, p<0.001). The concentration of VEGF after treatment had a statistically significant difference between the two groups (p=0.028), and its decline was more obvious in Endostatin+TAI+TACE group than TAI+TACE group (Figure 1).

Adverse reactions and complications

After embolization, post-embolization syndromes in different degrees occurred in most patients, including fever in 20 and 27 cases, nausea and vomiting in 31 cases and 26 cases, and hepatalgia in 30 cases and 24 cases, mostly of grade I-II. Grade III nausea and vomiting occurred in 2 cases in each group, and relieved after symptomatic treatment. After treatment in the two groups, there were 29 cases and 24 cases of anemia, 18 cases and 20 cases of thrombocytopenia, and 25 cases and 30 cases of leukopenia, mostly of grade I-II. Besides, grade III myelosuppression occurred in 3 cases and 5 cases, and diarrhea in 13 cases and 8 cases, both of which were relieved after symptomatic treatment. Thirty-three cases and 28 cases of transaminase elevation were found in the two groups, mostly of grade I-II. One case of grade III transaminase elevation in TAI+TACE group was relieved after symptomatic treatment. Nine cases and 14 cases of hyperbilirubinemia were found in the two groups, also mostly of grade I-II. To sum up, there was no statistically significant difference in the incidence of adverse reactions between the two groups (p>0.05) (Table 3).

Follow-up results of patient survival

All patients were followed up for 9-46 months, with a median of 26.3 months and 25.4 months in the two groups. In Endostatin+TAI+TACE group, the mean OS and mean PFS were 24.3±2.2 months and 11.3±1.8 months, respectively. In TAI+TACE group, the mean OS and mean PFS were 21.6±2.4 months and 8.7±1.9 months, respectively. As shown in the Kaplan-Meier survival curves (Figure 2), OS and PFS had statistically significant differences between the two groups according to the log-rank test, and both OS and PFS in Endostatin+TAI+TACE group were evidently higher than those in TAI + TACE group (p=0.016, p=0.021).

Analysis of factors influencing prognosis

The related data of patients, such as age, gender, number of metastatic tumors, grade of tumor differentiation, T stage, N stage, ECOG score and whether patients received the Endostatin combination therapy, were collected. The univariate and multivariate Cox regression analyses were performed for the patient OS, and the clinical status

of all patients before enrollment and the possible effects on OS after different treatments were analyzed, so as to objectively reveal the predictive factors for OS of gastric cancer patients with liver metastasis. The univariate Cox regression analysis showed that the grade of tumor differentiation and whether the Endostatin combination therapy was conducted were influencing factors for the patient OS (p=0.019, p=0.029). The multivariate Cox regression analysis revealed that the grade of tumor differentiation and whether the Endostatin combination therapy was carried out were independent factors influencing the prognosis of patients (p=0.040, p=0.032) (Table 4).

Table 3. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Endostatin+TAI+TAE group (n=48)* *n (%)*	*TAI+TAE group (n=48)* *n (%)*	*p value*
Anemia	29 (60.4)	24 (50.0)	0.412
Thrombocytopenia	18 (37.5)	20 (41.7)	0.835
Leukopenia	25 (52.1)	30 (62.5)	0.409
Fever	20 (41.7)	27 (56.3)	0.828
Nausea, vomiting	31 (64.6)	26 (54.2)	0.100
Diarrhea	13 (27.1)	8 (16.7)	0.324
Hepatalgia	30 (62.5)	24 (50.0)	0.304
Elevated AST/ALT	33 (68.8)	28 (58.3)	0.397
Hyperbilirubinemia	9 (18.8)	14 (29.2)	0.339

TAI: Transcatheter arterial infusion; TAE: Transcatheter arterial embolization; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

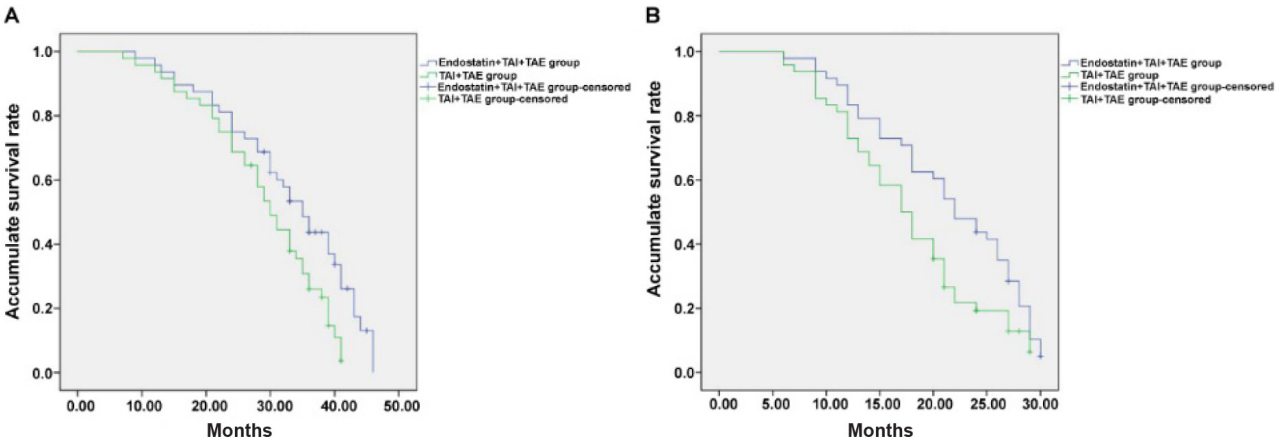

Figure 2. Kaplan-Meier survival curves of the studied patients. **A:** The overall survival rate of patients in Endostatin+TAI+TAE group was significantly higher than that of TAI+TAE group (p=0.016). **B:** The progression-free survival rate of patients in Endostatin+TAI+TAE group was significantly higher than that of TAI+TAE group (p=0.021).

Table 4. Univariate and multivariate Cox regression analysis of factors for overall survival in gastric cancer with liver metastasis

Parameters	*Univariate analysis*			*Multivariate analysis*		
	HR	*95%CI*	*p value*	*HR*	*95%CI*	*p value*
Age	0.94	0.91-1.10	0.225			
Gender	0.77	0.46-1.51	0.189			
Number of metastasis sites	1.14	0.54-1.87	0.080			
Histologic differentiation	0.36	0.21-1.05	0.019	0.44	0.26-1.34	0.040
T stage	1.52	0.62-3.39	0.411			
N stage	1.27	0.33-3.69	0.553			
ECOG score	0.98	0.41-2.35	0.789			
Endostatin	2.58	1.25-4.70	0.029	2.41	1.14-5.36	0.032

HR: Hazard ratio; CI: Confidence interval; T: Tumor; N: Lymph node; ECOG: Eastern Cooperative Oncology Group

Discussion

Studies have demonstrated that gastric cancer patients undergoing surgical resection will have metastasis in varying degrees within 3-30 months after operation, with liver metastases being the most common, increasing the difficulty of treatment [11,12]. The mechanism of liver metastasis after operation of gastric cancer is complicated, and the metastasis and growth of tumors depend on neovascularization. The more abundant the microvessels in lesions are, the greater the probability of tumor cell metastasis will be [13]. Surgical operation is the best therapeutic regimen for patients with single metastasis, but multiple liver metastases often occur in gastric cancer, in which case it is difficult to perform radical surgery. Systemic intravenous chemotherapy has significant adverse reactions and reduces the patient quality of life, and it is also prone to drug resistance. TAI can significantly increase the drug concentration in tumor lesions and surrounding lymphoid tissues up to 10-30 fold compared to oral and intravenous administration, which is also characterized by concentrated action, long-lasting effect and few adverse reactions [14]. TACE can effectively block the blood supply to tumor lesions, prolong the local retention time and concentration of drugs in tumor lesions, cause focal ischemia, and enhance the tissue sensitivity to chemotherapy drugs, accelerating tissue necrosis [15].

5-fluorouracil is the most commonly used chemotherapy drug for gastrointestinal tumors [16]. According to clinical studies, the efficacy upon drug administration for 24 h is better than that upon drug administration for 6 h [17]. However, continuous TAI of hepatic artery is rarely performed in the clinic today, and there have been no large-sample studies yet. The experience of continuous TAI of artery mainly comes from the treatment of colorectal cancer with liver metastasis and pancreatic cancer. In this study, the catheter was indwelt in the celiac trunk, and the chemotherapy drugs added with Oxaliplatin and Endostatin were continuously infused for intervention. Oxaliplatin is a third-generation platinum compound, and its gastrointestinal reaction and myelosuppression are milder than those of carboplatin and cisplatin [18]. The catheter indwelling in the artery can raise the concentration of chemotherapy drugs around the tumor, improve the tumor-killing ability, and accurately embolize the tumor vessels to block the access to nutrition in tumors [19]. Recombinant human Endostatin is an angiogenesis-inhibiting drug, which can effectively suppress the endothelial cell migration, prevent the tumor angiogenesis, and sever the nutrition supply to tumor cells, thereby inhibiting tumor metastasis [20].

In this study, the ORR in Endostatin+TAI+TACE group was significantly superior to that in TAI+TACE group after treatment (p=0.037), while the DCR had no statistically significant difference between the two groups (p=0.355). After embolization, post-embolization syndromes (fever, vomiting and hepatalgia) in different grades, grade III myelosuppression (an incidence rate of 8.3%), transaminase elevation and hyperbilirubinemia occurred in most patients. It can be seen that complications are mostly related to the embolism, and the incidence rate of adverse reactions in chemotherapy is lower. According to the follow-up results, both OS and PFS in Endostatin+TAI+TACE group were evidently higher than those in TAI+TACE group (p=0.016, p=0.021). The Cox regression analysis revealed that the grade of tumor differentiation and whether the Endostatin combination therapy were independent factors influencing the prognosis of patients (p=0.040, p=0.032).

VEGF is a major factor promoting tumor angiogenesis, which is closely related to the metastasis, prognosis and malignancy grade of gastric cancer. Enomoto et al studied and found that serum VEGF is mainly secreted and expressed by tumor cells, and its level is positively correlated with vascular proliferation of gastric cancer tissues, prognosis and metastasis [21]. In this study, the concentration of VEGF obviously declined after treatment in both groups compared with that before treatment (p=0.013, p<0.001), more obviously in Endostatin+TAI+TACE group than TAI+TACE group (p=0.028), which indicates that the mechanism of treatment of postoperative liver metastasis of gastric cancer with Endostatin+TAI+TACE may be related to the inhibition on the serum VEGF level in patients.

There are still many limitations in this study. For example, the sample size was small, the follow-up time was insufficient, the duration of disease, systemic complications and previous different surgery and treatment methods were not analyzed in groups, some patients were reexamined irregularly, and the accurate time of tumor progression had deviation, which all affected the prognostic analysis for patients. In the future, further large-sample multi-center randomized controlled trials are needed to verify the conclusions made in this study, hoping to provide a stronger basis for selecting the therapeutic regimen for gastric cancer patients with liver metastasis.

Conclusions

Endostatin combined with TAI and TACE can achieve good short-term clinical results in the treatment of gastric cancer with liver metastasis. Compared with those treated with chemotherapy alone, patients receiving Endostatin+TAI+TACE have significantly improved OS and PFS, a reduced level of VEGF and a lower incidence rate of adverse reactions, so Endostatin+TAI+TACE is worthy of clinical popularization and application.

Conflict of interests

The authors declare no conflict of interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Li K, Yuan D, Yan R, Meng L, Zhang Y, Zhu K. Stigmasterol exhibits potent antitumor effects in human gastric cancer cells mediated via inhibition of cell migration, cell cycle arrest, mitochondrial mediated apoptosis and inhibition of JAK/STAT signalling pathway. JBUON 2018;23:1420-5.
3. Ajani JA, D'Amico TA, Almhanna K et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14:1286-1312.
4. Xu D, Fang X, Li Y, Zhang Z, Li Q. Perioperative blood transfusion is one of the factors that affect the prognosis of gastric cancer. JBUON 2018;23:672-7.
5. Lin Y, Zhang CS, Li SJ, Li Z, Sun FB. LncRNA LOC554202 promotes proliferation and migration of gastric cancer cells through regulating p21 and E-cadherin. Eur Rev Med Pharmacol Sci 2018;22:8690-7.
6. Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. Br J Surg 2000;87:236-42.
7. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
8. Wang YY, Zhang W, Qian S, Liu R, Kan ZX, Wang JH. The effect of locoregional transarterial infusion chemotherapy on liver metastasis after gastric cancer resection. J Int Med Res 2012;40:1141-8.
9. Walia A, Yang JF, Huang YH, Rosenblatt MI, Chang JH, Azar DT. Endostatin's emerging roles in angiogenesis, lymphangiogenesis, disease, and clinical applications. Biochim Biophys Acta 2015;1850:2422-38.
10. Fu Y, Tang H, Huang Y, Song N, Luo Y. Unraveling the mysteries of endostatin. Iubmb Life 2009;61:613-26.
11. Wang W, Zhang R, Zhang H et al. [Risk factors in metachronous liver metastasis from gastric cancer]. Zhonghua Wei Chang Wai Ke Za Zhi 2014;17:121-3.
12. Feng F, Zheng G, Guo X et al. Impact of body mass index on surgical outcomes of gastric cancer. BMC Cancer 2018;18:151.
13. Simmet V, Noblecourt M, Lizee T et al. Chemotherapy of metastatic hepatoid adenocarcinoma: Literature review and two case reports with cisplatin etoposide. Oncol Lett 2018;15:48-54.
14. Suzuki E, Chiba T, Ooka Y et al. Transcatheter arterial infusion for advanced hepatocellular carcinoma: Who are candidates? World J Gastroenterol 2015;21:8888-93.
15. Takaki H, Sato Y, Yamakado K. Transcatheter arterial chemoembolization for hepatocellular carcinoma:current topics. Nihon Shokakibyo Gakkai Zasshi 2017;114:1602-10.
16. Kim DW, Talati C, Kim R. Hepatocellular carcinoma (HCC): beyond sorafenib-chemotherapy. J Gastrointest Oncol 2017;8:256-65.
17. Nagai H, Kanayama M, Higami K et al. Twenty-four hour intra-arterial infusion of 5-fluorouracil, cisplatin, and leucovorin is more effective than 6-hour infusion for advanced hepatocellular carcinoma. World J Gastroenterol 2007;13:280-4.
18. Bano N, Najam R, Qazi F, Mateen A. Clinical Features of Oxaliplatin Induced Hypersensitivity Reactions and Therapeutic Approaches. Asian Pac J Cancer Prev 2016;17:1637-41.
19. Liu X, Wang Z, Chen Z et al. Efficacy and Safety of Transcatheter Arterial Chemoembolization and Transcatheter Arterial Chemotherapy Infusion in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Oncol Res 2018;26:231-9.
20. Zhang K, Wang Y, Yu X et al. Recombinant human endostatin combined with radiotherapy inhibits colorectal cancer growth. BMC Cancer 2017;17:899.
21. Enomoto T, Mikami S, Kitajima M et al. [A Case in Which S-1 plus CDDP and S-1 Therapy Responded to Liver Metastasis Recurrence after Gastric Cancer Operation]. Gan To Kagaku Ryoho 2018;45:658-60.