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Original Article

Evaluation of the effect of ultrasound interventional injection of cisplatin in the treatment of liver cancer

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Abstract: Objective: To evaluate the effect of ultrasound interventional injection of cisplatin in the treatment of hepatocellular carcinoma (HCC). Methods: 68 patients with HCC admitted to our hospital from February 2016 to February 2018 were enrolled. According to the different treatment methods, they were divided into a study group and a control group. The control group was treated with hepatic artery embolization chemotherapy (n=34), the study group adopted interventional ultrasound injection of cisplatin (n=34). The clinical treatment effects of the two groups of patients were compared; the liver function and the occurrence of adverse reactions were compared; all patients were followed up for 24 months, and their progressive-free survival (PFS) was also compared. Results: The study group had higher total effective rate compared with the control group (91.18% vs 67.65%) (P<0.05); the AST, ALT, T-BIL and D-BIL levels of the two groups decreased remarkably after treatment, and the reduction in the study group was more obvious (P<0.05); the levels of VEGF, AFP and CEA of the two groups reduced noticeably after treatment, and the decrease in the study group was more significant (P<0.05); the total incidence of adverse reactions in the study group and the control group was 2.94% and 23.53% respectively, (P<0.05); the two groups were followed up for 24 months, and the disease control rate (DCR) of the control group was 58.82%, significantly lower than 85.29% in the study group; the PFS time of the control group was (15.68±4.23) lower than that of the study group (18.12±5.42) (P<0.05). Conclusion: Interventional ultrasound injection of cisplatin in the treatment of HCC has a definite effect. It can effectively relieve liver damage, reduce adverse reactions, improve serum tumor marker levels, and boost the DCR and PFS time of tumor patients.

Keywords: Ultrasound intervention, cisplatin, liver cancer, effect

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. The epidemiological survey revealed [1] that HCC has become the fifth most common type of cancer and takes up 54% of the total cancers. HCC also shows an increasingly rising every year, which seriously threatens the lives of patients. At present, the surgical treatment is the primary option for clinical treatment of HCC. But due to its insidious onset, most patients have progressed to the middle and advanced stages when diagnosed [2]. In addition, the surgical resection rate is low and the recurrence rate is high, with about two-thirds of patients are prone to recurrence after surgery, and low long-term survival rate. Non-surgical hepatic artery chemotherapy and embolization are also common methods for clinical treatment of HCC, but the efficacy is not satisfactory as expected [3]. Therefore, it is extremely urgent to seek more effective treatments for controlling tumor recurrence and prolonging the survival time of patients. In recent years, with the continuous progress of research, as an in situ inactivation method, ultrasound-guided interventional therapy for HCC has become a new type of clinical non-surgical treatment [4]. For instance, the application of ultrasonic interventional injection of absolute alcohol therapy, microwave coagulation, radiofrequency ablation and other therapeutic methods are of the emerging options of ultrasonic interventional therapy for HCC. As a first-line treatment for advanced cancer, cisplatin is commonly used in clinical chemotherapy for patients with HCC, and its therapeutic effect is remarkable [5].

Studies have shown [6] that ultrasound can continuously monitor the patient's liver conditions and understand the local lesions by displaying the results. Interventional injection of cisplatin for HCC can effectively reduce the complications and improve the long-term survival. At present, there are few reports on the ultrasound interventional injection of cisplatin in the treatment of HCC. Therefore, we selected 68 patients with primary HCC admitted to our hospital from February 2017 to February 2020 to evaluate the clinical efficacy of ultrasound interventional injection of cisplatin in the treatment of HCC.

Materials and methods

General information

68 patients with primary HCC admitted to our hospital over a period of February 2016 to February 2018 were selected as the research objects. Inclusion criteria: (1) Patients who met the *Specifications for the Diagnosis and Treatment of Primary HCC* [7], and confirmed as primary HCC by histopathology, CT, MRI imaging, etc.; (2) Child-Pugh classification of liver function before treatment was grade A and B; (3) With complete clinical data; Exclusion criteria: (1) With organs function deficit such as kidney, lung, heart, brain, etc.; (2) With coagulation dysfunction or obvious ascites; (3) With mixed HCC or other malignant tumors; (4) With mental or speech communication disorders.

According to different treatment methods, they were equally divided into study group and control group. Among them, there were 19 males and 15 females in the study group; aged 40-78 (57.52±9.74) years; disease course was 1-5 (3.01±0.78) years; tumor diameter was 3.11-5.96 (4.45±1.24) cm; Child-pugh classification: 15 cases of grade A, 19 cases of grade B. In the control group, there were 18 males and 16 females; aged 41-77 (57.60±9.80) years old; disease course was 1.2-5 (3.05±0.80) years; tumor diameter was 3.04-5.92 (4.42±1.27) cm; Child-pugh classification: 14 cases of grade A, 20 cases of grade B. They were comparable in general data (P>0.05). The approval has been obtained from the ethics committee of our hospital, and the patients and their families knew the purpose of the study and agreed to participate to the study.

Instruments and drugs

Mindray DC-N6 color Doppler ultrasound [Guangdong FDA No. 2230509], transvaginal probe 7.5 MHz puncture frame, manual 16G puncture needle (U.S. Bard), cisplatin injection (Jiangsu Haosen Pharmaceutical Co., Ltd., batch number: H20090521) were used in this study.

Methods

Patients in the control group were treated with hepatic artery embolization chemotherapy. The patients received Sedinger puncture. The patients' lesions were understood by arteriography, and superselective intubation was performed based on the results of the angiography, and the catheters were sent to the patients' corresponding lesions for chemotherapy at the arterial site, and the specific drugs were fluorouracil 0.5 g, epirubicin 30 mg, and oxaliplatin 150 mg.

The study group used ultrasound interventional injection of cisplatin for treatment. The Mindray DC-N6 color Doppler ultrasound diagnostic apparatus was applied, and the probe frequency was 5-12 MHz. American Bard manual 16G puncture needle was used for the puncture treatment. Before surgery, ultrasound positioning was performed to observe the location and path of the tumor, the sonographic appearance of the tumor and its relationship with surrounding tissues, and the blood supply in the tumor. Under the guidance of ultrasound intervention, the posterior part of the central axis of the tumor was punctured, and then the chemotherapy drug cisplatin (Jiangsu Haosen Pharmaceutical Co., Ltd., SFDA approval number: H20090521) was slowly injected, and the injection was carried out by points, from shallow to deep. If there is a strong echo that gradually increases from the tip of the needle to the surroundings, and the strong echo completely covers the tumor and is larger than 0.5 cm from the edge of the tumor, the injection should be stopped. In the meantime, the needle should be rotated during the injection to ensure that the cisplatin is evenly dispersed. If the drug enters the blood vessel, the puncture should be adjusted to avoid the blood vessel and then inject it. Then the puncture needle was withdrawn to 1.0 to 1.5 cm of the liver capsule to observe whether there is drug overflow, and

Table 1. Comparison of clinical efficacy of two groups

Groups	CR	PR	SD	PD	Total effective rate
Study group (n=34)	5 (14.71)	15 (44.12)	11 (32.35)	3 (8.82)	31 (91.18)
Control group (n=34)	2 (5.88)	8 (23.53)	13 (38.24)	11 (32.35)	23 (67.65)
t					5.757
P					0.016

after no drug overflow was confirmed, the puncture needle was withdrawn from the patient's body. Each tumor was treated once a week. After 20-40 minutes of treatment, whether the patients have fever, nausea, vomiting, pain, fatigue and other discomfort was observed.

Observation indicators and efficacy evaluation

(1) Efficacy evaluation: ① Complete response (CR): After treatment, the patient's lesions disappeared completely and lasted longer than one month; ② Partial response (PR): After treatment, the total volume of the patient's lesions was reduced by more than 50%, and lasted at least one month; ③ Stable disease (SD): After treatment, the total volume of the patient's lesion is slightly reduced or reduced below 25%; ④ Progressive disease (PD): After treatment, the patient has a new lesion or the original lesion has an increase in total volume. (2) Comparison of liver function between the two groups of patients before and after treatment; 5 ml of fasting venous blood was collected before and two months after the operation, and centrifuged to separate the serum. The American Beckman DXC800 automatic biochemical analyzer was used to detect the changes in liver function index levels of the two groups of patients, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum total bilirubin (T-BIL) and direct bilirubin (D-BIL); (3) Comparison of serum tumor marker levels before and after treatment between the two groups of patients; the Swiss Tecan Infinite F50 multifunctional microplate reader was used to detect the serum tumor marker levels of the two groups before and after treatment, including vascular endothelial growth factor (VEGF), carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP); kits was purchased from Jiangsu Feiya Biological Technology Co., Ltd., and the specific operation was carried out in strict accordance with the instructions; (4) Adverse reactions of the two groups of patients were compared; (5) Long-term survival between the two groups was compared. All were followed up for 24 months, and the long-term survival prognosis of patients was carried out according to the standards formulated by the National Comprehensive Cancer Network [8]; ① disease control rate (DCR): the results of CT or MRI examination showed that the tumor did not shrink or increase, and the tumor size was maintained at about 5 cm; ② progression-free survival time (PFS): the time from the beginning of treatment to the secondary appearance of the tumor.

Statistical methods

All data were processed using SPSS 18.0 software. The count data was expressed as n (%) and the χ^2 test was used; the rank data was tested by the rank sum; the measurement data was expressed in form of ($\bar{x} \pm s$) and the t test was performed. A *P* value of <0.05 was considered statistically significant.

Results

Comparison of clinical efficacy

The study group showed higher total effective rate compared to the control group (91.18% vs 67.65%) (P<0.05). See **Table 1**.

Comparison of liver function

The AST, ALT, T-BIL and D-BIL levels of the two groups of patients before treatment were similar (P>0.05); the AST, ALT, T-BIL and D-BIL levels of the two groups of patients decreased remarkably after treatment, and the reduction of the study group was more significant (P<0.05). See **Table 2**.

Comparison of serum tumor marker levels

No marked difference was observed in VEGF, AFP and CEA levels in the two groups before treatment (P>0.05); the VEGF, AFP, and CEA levels of the two groups of patients after treat-

Table 2. Comparison of liver function between the two groups before and after treatment

Groups	AST (U/L)		ALT (U/L)		T-BIL (μmol/L)		D-BIL (μmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n=34)	73.52±13.81	35.32±7.38[a]	65.16±14.56	26.44±7.05[a]	43.15±9.29	31.17±5.26[a]	35.34±7.03	13.26±3.03[a]
Control group (n=34)	73.46±13.73	44.29±8.68[a]	64.60±14.58	39.56±8.79[a]	43.23±9.25	38.47±6.83[a]	35.40±7.10	20.18±4.16[a]
t	0.018	4.591	0.159	6.789	0.036	4.938	0.035	7.840
P	0.870	<0.001	0.970	<0.001	0.985	<0.001	0.975	<0.001

Note: Compared with the same group before treatment, [a]P<0.05.

Table 3. Comparison of serum tumor marker levels before and after treatment in the two groups

Groups	VEGF (mg/mL)		AFP (mg/mL)		CEA (μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n=34)	13.43±2.81	5.72±1.27[b]	276.26±64.38	121.57±23.29[b]	12.36±3.80	4.52±1.21[b]
Control group (n=34)	13.52±2.78	8.03±2.14[b]	274.87±65.08	146.20±26.34[b]	12.27±3.83	6.83±1.81[b]
t	0.133	5.413	0.089	4.085	0.097	6.187
P	0.895	<0.001	0.930	<0.001	0.922	<0.001

Note: Compared with the same group before treatment, [b]P<0.05.

Table 4. Comparison of adverse reactions between the two groups of patients

Groups	diarrhea	nausea and vomiting	acute cholecystitis	Total incidence rate
Study group (n=34)	0 (0.00)	1 (2.94)	0 (0.00)	1 (2.94)
Control group (n=34)	2 (5.88)	5 (14.71)	1 (2.94)	8 (23.53)
χ^2				6.275
P				0.012

Table 5. Comparison of long-term survival of two groups of patients

Groups	DCR	PFS (month)
Study group (n=34)	29 (85.29)	18.12±5.42
Control group (n=34)	20 (58.82)	15.68±4.23
χ^2/t	5.916	2.069
P	0.015	0.042

ment decreased noticeably, and the decrease in the study group was more significant (P<0.05). See **Table 3**.

Comparison of adverse reactions

The study group exhibited lower total incidence of adverse reactions compared to the control group (2.94% vs 23.53%) (P<0.05). See **Table 4**.

Comparison of long-term survival

Both groups were followed up for 24 months. The DCR of the control group was 58.82%, significantly lower than that of the study group (85.29%). The PFS time of the control group was (15.68±4.23), lower than that of the study group (18.12±5.42) (P< 0.05). See **Table 5** and **Figure 1**.

Discussion

HCC is a malignant tumor with a high mortality rate worldwide, and its incidence is rising on a yearly basis. The symptoms of the disease are rather insidious in the early stage, and most of them are in the middle to late stages when they are diagnosed [9]. Surgical resection is a frequently used option for the treatment of HCC and some metastatic HCC. If the tumor can be found early, liver transplantation or resection of the tumor can effectively improve the survival rate of patients [10]. However, due to the rapid development of the disease, the hidden and complex location of the lesion, the high degree of malignancy, the multi-center lesion and the difficulty of resection, most patients have missed the best opportunity for radical surgical treatment at the time of diagnosis. The advanced stage is no longer sensitive to radiotherapy and chemotherapy, so palliative treatment is the main method for the treatment of HCC. Its purpose is to control tumor growth, reduce symptoms, improve the quality of life of patients, and prolong their survival [11, 12].

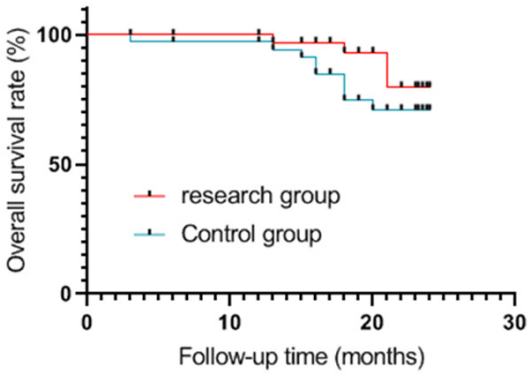

Figure 1. Long-term survival comparison of the two groups of patients.

Cisplatin injection is one of the main methods of palliative treatment for patients with HCC. Cisplatin is a class of anticancer drugs containing inorganic platinum, with the structure of Cis-Dichlorodiamineplatinum. The drug is a cell cycle non-specific drug and has cytotoxicity. It can bind to DNA and cause cross-reaction and damage DNA functions and further inhibits cancer cells from mitosis, and can be used clinically to treat a variety of cancers [13, 14]. The concentration of cisplatin in the treatment of HCC is generally much greater than that of intravenous administration. Injecting cisplatin into the tumor can cause cell protein degeneration, coagulation, necrosis, fixation and dehydration of the lesion tissue. The destruction of local endothelial cells in the lesion can cause thromboembolism, thereby blocking the blood supply to the tumor, leading to cell death [15]. The concentration of cisplatin injected into the tumor is much greater than that of intravenous administration. The injection of cisplatin into the liver cancer tumor can cause the tumor tissue to be dehydrated, fixed, cell protein coagulation, degeneration, and necrosis, and the local endothelial cells of the tumor blood vessels are destroyed, which can form thrombus and blood vessels. Occlusion or twist of blood vessels blocks the blood supply of the tumor, leading to cell death and fibrosis, in turn makes the tumor shrink or no longer increase [16]. Ultrasound interventional injection of chemotherapy drugs for the treatment of HCC is a new type of local minimally invasive treatment, which can effectively prolong the long-term survival of patients with advanced HCC. Ultrasound-guided injection of chemotherapeutic drugs in the treatment of advanced liver cancer can achieve satisfactory long-term curative effects, which can be comparable to surgical treatment to a certain extent, and has become the main treatment or first choice for advanced liver cancer. For recurrent liver cancer, metastatic liver cancer, liver cancer with portal vein tumor thrombus, and liver cancer growing near large blood vessels that are difficult to remove by surgery, ultrasound-guided injection of chemotherapy drugs is also an ideal alternative treatment option [16, 17]. At present, this treatment method has become the first choice for patients with advanced HCC. We found that the total effective rate of the study group was higher; it indicated that the effect of ultrasound interventional injection of cisplatin was satisfactory, and ensures the tumor shrink or no longer increase. Because the normal immune function of patients with HCC is destroyed, the immune function of the patient becomes low. Moreover, our study revealed that the AST, ALT, T-BIL, and D-BIL levels of the two groups of patients after treatment decreased significantly, and the study group was smaller than the control group, indicating that ultrasound interventional injection of cisplatin can relieve liver damage. VEGF is a glycoprotein that can specifically promote vascular endothelial cell division and angiogenesis, and can maintain the normal state and functional integrity of blood vessels [18]. Most of the HCC cells are multivascular lesions, which have rich blood supply and play an important role in angiogenesis. During the growth of HCC, the secretion of VEGF will gradually increase, which can not only cause local increase in lesions, but also angiogenesis can enhance the growth of tumors. Moreover, VEGF enters the blood, and serum VEGF will be highly expressed [19]. AFP is a special protein, produced by embryonic stem cells, and gradually disappears after the fetus is born [9]. When suffering from HCC or other cancers, AFP synthesis genes can be activated in the corresponding tumor cells, so that AFP will be produced in large quantities, and the concentration in the blood will increase. Therefore, AFP can be used as a tumor marker for detecting primary HCC. CEA is a common antigen of fetal cells and cancer tissues. During the development of tumors, due to the disappearance of the polarity of tumor cells, CEA refluxes into the blood or lymph liquid, and serum CEA will be highly expressed. In recent years, many malignant tumors have been found

to have a certain positive detection rate, such as gastric cancer, lung cancer, breast cancer and colon cancer [9].

The results of this study showed that the levels of VEGF, AFP, and CEA of the two groups reduced notably after treatment, and the study group was more significant, indicating that ultrasound interventional injection of cisplatin can improve the level of serum tumor markers. In addition, we found that the total incidence of adverse reactions in the study group was much lower; it indicated that the use of ultrasound interventional injection of cisplatin in patients with HCC can reduce the incidence of adverse reactions and is safe for use. Moreover, we have shown that during a 24-month follow-up, the DCR and the PFS time of the control group was lower. Ultrasound interventional injection of cisplatin in the treatment of HCC may improve the DCR and PFS time. This study presents several limitations such as the research object selected was from our hospital, and the included sample size is small, which may lead to selection bias. Further studies including larger sample size and more clinical data is needed to refine the research conclusion.

In summary, ultrasound interventional injection of cisplatin has a desirable effect in the treatment of HCC. It can effectively alleviate liver damage, reduce adverse reactions, improve the serum levels of tumor marker, and improve the DCR and PFS time of tumor patients.

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Disclosure of conflict of interest

None.

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References

[1] Qiu J, Peng B, Tang Y, Qian Y, Guo P, Li M, Luo J, Chen B, Tang H, Lu C, Cai M, Ke Z, He W, Zheng Y, Xie D, Li B and Yuan Y. CpG methylation signature predicts recurrence in early-stage hepatocellular carcinoma: results from a multicenter study. J Clin Oncol 2017; 35: 734-742.

[2] Zeng DX, Wang CG, Lei W, Huang JA and Jiang JH. Efficiency of low dosage apatinib in post-first-line treatment of advanced lung adenocarcinoma. Oncotarget 2017; 8: 66248-66253.

[3] Tak WY, Lin SM, Wang Y, Zheng J, Vecchione A, Park SY, Chen MH, Wong S, Xu R, Peng CY, Chiou YY, Huang GT, Cai J, Abdullah BJJ, Lee JS, Lee JY, Choi JY, Gopez-Cervantes J, Sherman M, Finn RS, Omata M, O'Neal M, Makris L, Borys N, Poon R and Lencioni R. Phase III HEAT study adding lyso-thermosensitive liposomal doxorubicin to radiofrequency ablation in patients with unresectable hepatocellular carcinoma lesions. Clin Cancer Res 2018; 24: 73-83.

[4] Lai JP, Conley A, Knudsen BS and Guindi M. Hypoxia after transarterial chemoembolization may trigger a progenitor cell phenotype in hepatocellular carcinoma. Histopathology 2015; 67: 442-450.

[5] Feng F, Jiang Q, Cao S, Cao Y, Li R, Shen L, Zhu H, Wang T, Sun L, Liang E, Sun H, Chai Y, Li X, Liu G, Yang R, Yang Z, Yang Y, Xin S and Li BA. Pregnane X receptor mediates sorafenib resistance in advanced hepatocellular carcinoma. Biochim Biophys Acta Gen Subj 2018; 1862: 1017-1030.

[6] Shen Q, Eun JW, Lee K, Kim HS, Yang HD, Kim SY, Lee EK, Kim T, Kang K, Kim S, Min DH, Oh SN, Lee YJ, Moon H, Ro SW, Park WS, Lee JY and Nam SW. Barrier to autointegration factor 1, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3, and splicing factor 3b subunit 4 as early-stage cancer decision markers and drivers of hepatocellular carcinoma. Hepatology 2018; 67: 1360-1377.

[7] Kasajima M, Igawa S, Ishihara M, Otani S, Takakura A, Yokoba M, Kubota M, Sasaki J, Katagiri M and Masuda N. Correlation between the efficacy of amrubicin and the previous chemotherapy regimen for relapsed small cell lung cancer. Oncol Lett 2017; 13: 1719-1724.

[8] Sun Y, Cheng Y, Hao X, Wang J, Hu C, Han B, Liu X, Zhang L, Wan H, Xia Z, Liu Y, Li W, Hou M, Zhang H, Xiu Q, Zhu Y, Feng J, Qin S and Luo X. Randomized phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small-cell lung cancer. BMC Cancer 2016; 16: 265.

[9] Lu W, Jin XL, Yang C, Du P, Jiang FQ, Ma JP, Yang J, Xie P and Zhang Z. Comparison of efficacy between TACE combined with apatinib and TACE alone in the treatment of intermediate and advanced hepatocellular carcinoma: a single-center randomized controlled trial. Cancer Biol Ther 2017; 18: 433-438.

[10] Wang G, Zhao J, Song Y, Zhang W, Sun Y, Zhou A, Huang J, Du F and Yang L. Phase II study of adjuvant chemotherapy with S1 plus oxaliplatin for Chinese patients with gastric cancer. BMC Cancer 2018; 18: 547.

[11] Lyu N, Kong Y, Mu L, Lin Y, Li J, Liu Y, Zhang Z, Zheng L, Deng H, Li S, Xie Q, Guo R, Shi M, Xu L, Cai X, Wu P and Zhao M. Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma. J Hepatol 2018; 69: 60-69.

[12] Baba H, Yamada Y, Takahari D, Matsumoto H, Yoshida K, Nakamura M, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y and Sugihara K. S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study. ESMO Open 2017; 2: e000135.

[13] Wang RK, Shao XM, Yang JP, Yan HL and Shao Y. MicroRNA-145 inhibits proliferation and promotes apoptosis of HepG2 cells by targeting ROCK1 through the ROCK1/NF-κB signaling pathway. Eur Rev Med Pharmacol Sci 2019; 23: 2777-2785.

[14] Casaccia M, Santori G, Bottino G, Diviacco P and Andorno E. Laparoscopic resection vs laparoscopic radiofrequency ablation for the treatment of small hepatocellular carcinomas: a single-center analysis. World J Gastroenterol 2017; 23: 653-660.

[15] He L, Xiao D, Feng J, Yao C and Tang L. Induction of apoptosis of liver cancer cells by nanosecond pulsed electric fields (nsPEFs). Med Oncol 2017; 34: 24.

[16] Chen F, Liu AH, Zhang Y and Yao XS. Clinical significance of interventional injection of cisplatin in the treatment of liver cancer by color Doppler ultrasound. Chin J Coal Indust Med 2012; 15: 1555-1556.

[17] Tan HY, Gong JF, Yu F, Tang WH and Yang K. Long-term efficacy of laparoscopic radiofrequency ablation in early hepatocellular carcinoma: a systematic review and meta-analysis. J Laparoendosc Adv Surg Tech A 2019; 29: 770-779.

[18] Lin Y, Zhai E, Liao B, Xu L, Zhang X, Peng S, He Y, Cai S, Zeng Z and Chen M. Autocrine VEGF signaling promotes cell proliferation through a PLC-dependent pathway and modulates Apatinib treatment efficacy in gastric cancer. Oncotarget 2017; 8: 11990-12002.

[19] Yin L, Wang J, Huang FC, Zhang YF, Xu N, Wen ZQ, Li WL and Dong J. Inhibitory effect of apatinib on HCT-116 cells and its mechanism. Nan Fang Yi Ke Da Xue Xue Bao 2017; 37: 367-372.