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Original Article

Effect of Lenvatinib and bevacizumab on hepatocellular carcinoma after hepatic arterial chemoembolization

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Abstract: Objective: Hepatocellular carcinoma is characterized by high morbidity and mortality, poor prognosis and many complications. Hepatic arterial chemoembolization (TACE) is the main treatment for patients with advanced hepatocellular carcinoma. The purpose of this study was to investigate the effect of Lenvatinib and bevacizumab on hepatocellular carcinoma after hepatic arterial chemoembolization, and to give full play to the advantages of dual-target chemotherapy. Method: A total of 30 patients with primary hepatocellular carcinoma treated by hepatic artery chemoembolization in our hospital from June 2020 to June 2021 were selected as the study subjects. The observation group was injected with bevacizumab (5 mg/kg) into the blood vessels supplying the tumor first. Then, lumvaritinib mesylate capsules were given orally, and the control group was injected with a mixture of lipiodol, and a pre-prepared chemotherapy drug into tumor blood vessels. The clinical efficacy, AFP, ACE, AST, albumin, platelet decline and liver pain were compared between the two groups. The adverse reactions were recorded and the clinical efficacy was evaluated. Results: After treatment, the levels of AFP, ACE, AST and albumin were significantly different between the two groups ($P < 0.001$), AFP level in the observation group (54.93±18.84 ng/mL) was significantly lower than that in the control group (216.53±28.66 ng/mL) ($P < 0.001$). The ACE level in the observation group (2.78±0.48 ug /L) was significantly lower than that in the control group (5.52±0.32 ug /L) ($P < 0.001$). The AST level in the observation group (30.13±3.85 U/L) was significantly lower than that in the control group (56.00±6.16 U/L) ($P < 0.001$). The albumin level in the observation group (45.00±3.21 g/L) was significantly lower than that in the control group (33.33±2.38 g/L) ($P < 0.001$). There was statistical difference in platelet level between the two groups after treatment ($P = 0.011$). In the observation group, the number of cases with decreased platelet after treatment was 11 (36.7%), which was significantly higher than that in the control group (13.3%). The pain relief and clinical efficacy of the observation group after treatment were significantly better than the control group ($P = 0.001$), with significant statistical significance. Conclusion: After hepatic arterial chemoembolization, Lenvatinib and bevacizumab can effectively improve the serum AFP, ACE, AST, albumin and platelet levels, improve liver pain, and improve the overall clinical treatment effect.

Keywords: Malignant tumors, hepatocellular carcinoma, hepatic arterial chemoembolization (TACE), Lenvatinib mesylate, bevacizumab, targeted therapy

Introduction

Hepatocellular carcinoma is a common malignant tumor of the digestive tract. The incidence of hepatocellular carcinoma in China is highest in the world, the incidence of hepatocellular carcinoma is third in malignant tumors, and the mortality rate from it is second, as such it has become a serious public health problem [1]. Hepatocellular carcinoma is characterized by high incidence, poor prognosis, many complications and high mortality. Early hepatocellular carcinoma has no obvious clinical symptoms, so that many patients with hepatocellular carcinoma are diagnosed in the middle and late stage, missing the best time for surgical treatment. Early hepatocellular carcinoma is mainly treated by surgery, and TACE is usually used to treat patients with intermediate and advanced hepatocellular carcinoma [2].

Hepatic arterial chemoembolization is a common treatment for patients with primary hepatocellular carcinoma, which can block the tumor aterial blood supply and reduce the tumor blood supply, thereby inhibiting the growth and proliferation of tumor cells and improving the survival prognosis of patients. TACE usually involves injecting chemotherapy drugs into the blood vessels to increase the effectiveness of the treatment and it kills tumor cells directly [3]. Bevacizumab is the most commonly used targeted chemotherapy drug, which can effectively inhibit tumor angiogenesis and specifically bind to VEGF, thereby inhibiting the formation of new blood vessels in tumors and normalizing abnormal blood vessels. Clinical studies have shown that bevacizumab can block the effect of VEGF on vascular endothelial cells, actively reshape the vascular structure of tumors, increase the sensitivity of tumors to chemotherapy drugs, and help prolong the survival of patients and promote the recovery of patients [4]. Clinical findings show that Lenvatinib as a multi-target receptor tyrosine kinase inhibitor, can block regulatory factors of tumor endothelial cells. It is recommended for early use for the treatment of invasive, locally advanced or metastatic differentiated malignant tumors [5]. In 2018, the US FDA approved the use of Lenvatinib in the treatment of unresectable hepatocellular carcinoma. However, there is no report on the treatment of hepatocellular carcinoma with Lenvatinib combined with bevacizumab after hepatic arterial chemoembolization.

This study aims to explore the effect of Lenvatinib and bevacizumab in the treatment of hepatocellular carcinoma after hepatic artery chemoembolization, to give full play to the advantages of dual-target chemotherapy, and better formulate the treatment plan of Lenvatinib and bevacizumab for hepatocellular carcinoma after hepatic artery chemoembolization, combined with scientifically optimized treatment drugs. As well as to provide more scientific clinical data and evidence for improving the efficacy of Lenvatinib and bevacizumab in the treatment of hepatocellular carcinoma after hepatic artery chemoembolization.

Methods

General information

In this study, 30 patients with primary hepatocellular carcinoma treated by hepatic artery chemoembolization in our hospital from June 2020 to June 2021 were selected as the research subjects, and were divided into the control group and observation group according to the order of admission, with 15 patients in each group. There was no statistical difference in age, gender and course of disease between the two groups, indicating comparability. This study was approved by the Ethics Committee of the Cangzhou Central Hospital (Cangzhou; Approval number: CCH20200305; Date of approval: 2020.02.09). Written informed consent was obtained from all patients.

Inclusion criteria

1. All patients met the diagnostic criteria for primary hepatocellular carcinoma, confirmed by histopathology, imaging and clinical symptoms and signs. All patients were treated with hepatic arterial chemoembolization.

2. Age: 18-75 years old.

3. Agree to this clinical trial and sign informed consent.

4. Approval of experimental studies through the hospital ethics Committee.

Exclusion criteria

1. Patients with renal dysfunction and abnormal coagulation.

2. Pregnant women and lactation patients were excluded.

3. Patients with malignant tumor metastasis.

4. Incomplete medical records and refusal to accept the clinical experiments.

Grouping and methods

All patients were treated with hepatic arterial chemoembolization. Femoral artery Seldinge puncture was selected for TACE surgery, and angiography was performed to determine tumor location and size, with ultrafine catheterization if necessary.

In the control group, the pre-prepared chemotherapy drug lipiodol mixture (oxaliplatin 200 mg, epirubicin 60 mg, superliquid lipiodol emulsion 15 ml) was injected into tumor blood vessels.

The observation group was injected with bevacizumab (5 mg/kg) into tumor blood vessels. Then the oral administration of Lenvatinib mesylate capsules (Eisai Europe Ltd., specification: 4 mg, Registration Number: J20180052) 8-12 mg/ time, once a day was given. The lower limbs were immobilized strictly for 8 h and they laid in bed strictly for 24 h. The changes of vital signs were closely observed. Routine blood examination and biochemical indexes were reviewed 3 d after surgery. CT examination was performed 4 weeks after surgery to observe the changes of tumor and determine whether to receive chemotherapy again. Both groups were treated for 2 months.

Evaluation indicators

The clinical efficacy, alpha-fetoprotein (AFP), angiotensin converting enzyme (ACE), glutamic oxalacetic transaminase (AST), albumin, platelet decline, liver pain were compared between the two groups, and the adverse reactions were recorded.

Evaluation criteria

We compared the clinical efficacy of the two groups, with improved as a standard of solid tumor curative effect evaluation, divided into complete remission (CR): target lesions disappeared in arterial enhancement period, partial response (PR): the total diameter of the lesions with arterial enhancement decreased ≥ 30%, stable disease (SD): the change of tumor between PR and PD, disease progression (PD): the total diameter of lesions enhanced in arterial phase increased ≥ 20% or new lesions appeared, the effective rate (RR) = CR + PD, the disease control rate (DCR) = CR + PR + SD.

Automatic biochemical analyzer was used to detect AFP, ACE, AST and albumin in the two groups, and the number of cases of platelet decline was recorded.

Comparison of pain in liver region: when pain disappeared, it was completely relieved. It was partial relief if the pain was significantly relieved without affecting sleep. Mild relief if the pain is slightly relieved but still interferes with sleep. If the pain was alleviated or intensified, it was invalid. Total effective rate = (complete remission + partial remission + slight remission)/ total number of people in the group × 100%.

Statistical analysis

SPSS 25.0 was used for statistical analysis. χ^2 test was used for counting data comparison. Analysis of variance and T test were used to compare measurement data. $P < 0.05$ was considered to be statistically significant.

Results

Basic information of the patients

There were 13 male patients and 17 female individuals. In addition, all patients included 16 cases with age < 65 years old, and 14 cases with age ≥ 65 years old. There were 17 individuals with tumor size < 5 cm, and 13 cases with tumor size ≥ 5 cm. Number of patients with pathologic grade I was 7, II was 10, III was 13. The number of patients with Ennenking stage I, II, III, IV was respectively 15, 11, 2, 2. There was no statistical significance between the control group and Lenvatinib + bevacizumab group ($P > 0.05$). (See **Table 1**).

Differences in AFP, ACE, AST and albumin between the two groups after treatment

After treatment, there were significant differences in AFP, ACE, AST and albumin levels between the two groups ($P < 0.001$). The AFP level in the observation group (54.93±18.84 ng/mL) was significantly lower than that in the control group (216.53±28.66 ng/mL) ($P < 0.001$). The ACE level in the observation group (2.78±0.48 ug /L) was significantly lower than that in the control group (5.52±0.32 ug /L) ($P < 0.001$). The AST level in the observation group (30.13±3.85 U/L) was significantly lower than that in the control group (56.00±6.16 U/L) ($P < 0.001$). The albumin level in the observation group (45.00±3.21 g/L) was significantly lower than that in the control group (33.33±2.38 g/L) ($P < 0.001$). (See **Table 2**).

Platelet changes in different groups after treatment

The chi-square test showed that there was a statistically significant difference in platelet levels between the two groups after treatment ($P = 0.011$). In the observation group, the number of cases with decreased platelet after treatment was 11 (36.7%), which was significantly

Table 1. Clinicopathological variables

			Groups		P
			Control (%)	Lenvatinib + bevacizumab	
Sex	Male	13	7 (23.3%)	6 (20.0%)	0.713
	Female	17	8 (26.7%)	9 (30.0%)	
Age	< 65 years	16	8 (26.7%)	8 (26.7%)	0.642
	≥ 65 years	14	7 (23.3%)	7 (23.3%)	
Tumor size	< 5 cm	17	9 (30.0%)	8 (26.7%)	0.713
	≥ 5 cm	13	6 (20.0%)	7 (23.3%)	
Pathologic grade	I	7	3 (10.0%)	4 (13.3%)	0.539
	II	10	4 (13.3%)	6 (20.0%)	
	III	13	8 (26.7%)	5 (16.7%)	
Tumor staging	I	15	8 (26.7%)	7 (23.3%)	0.984
	II	11	5 (16.7%)	6 (20.0%)	
	III	2	1 (3.3%)	1 (3.3%)	
	IV	2	1 (3.3%)	1 (3.3%)	

Pearson's chi-squared test was used.

Table 2. Comparison of AFP, ACE, AST and albumin between the two groups after treatment ($\bar{x} \pm s$)

	AFP (ng/mL)	ACE (ug/L)	AST (U/L)	albumin (g/L)
Control group	216.53±28.66	5.52±0.32	56.00±6.16	33.33±2.38
Observation group	54.93±18.84	2.78±0.48	30.13±3.85	45.00±3.21
P	< 0.001*	< 0.001*	< 0.001*	< 0.001*

*P < 0.05.

Table 3. Comparison of platelets between the two groups after treatment

	N	Post-treatment platelets		P
		Not dropped (%)	Dropped (%)	
Control group	15	4 (13.3%)	11 (36.7%)	0.011*
Observation group	15	11 (36.7%)	4 (13.3%)	

*P < 0.05.

higher than that in the control group (13.3%). (See **Table 3**).

Comparison of liver pain in different groups after treatment

Chi-square test showed that the two groups showed statistically significant difference in the efficacy of liver pain after treatment (P = 0.001). In the observation group, there were 9 (30.0%) patients with complete pain relief, 4 (13.3%) patients with partial pain relief, 1 (13.3%) patients with mild pain relief, and 1 (3.3%) patient with no pain relief. In the control group, 1 (3.3%) had complete, 1 (3.3%) had partial, 8 (26.7%) had mild, and 5 (16.7%) had no response. (See **Table 4**).

Comparison of clinical efficacy

The clinical efficacy of the two groups after treatment was compared, the difference was statistically significant (P = 0.001). The cases of complete remission in the observation group (10 (33.3%)) were significantly higher than that in the control group (1 (3.3%)). In the observation group, 3 (10.0%) had partial remission, 1 (3.3%) had disease stabilization, and 1 (3.3%) had disease progression after treatment. In the control group, the numbers for partial remission was 1 (3.3%), disease stabilization was 10 (33.3%), and progression was 3 (10.0%). (See **Table 5**).

Discussion

Hepatocellular carcinoma is a common malignant tumor of digestive tract. Statistics show that the number of individuals with primary hepatocellular carcinoma is rising all over the world, mainly in men over 60 [6]. Advanced hepatocellular carcinoma is mainly treated by chemotherapy, and interventional surgery of TACE is mainly used for treatment. However, there is no unified standard for drugs, and there are many treatment schemes, mostly metabolic resistance class, mooring class and fluorouracil [7]. Due to the expression of multidrug resistance genes in liver cells, they are not sensitive to conventional chemotherapy drugs, so targeted drugs are commonly used in clinical chemotherapy [8].

Table 4. Comparison of therapeutic effects of liver pain between the two groups after treatment

	N	Complete response	Partial remission	Mild remission	Inefficient	P
Control group	15	1 (3.3%)	1 (3.3%)	8 (26.7%)	5 (16.7%)	0.001*
Observation group	15	9 (30.0%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	

*P < 0.05.

Table 5. Comparison of clinical efficacy between the two groups after treatment

	N	Complete response	Partial remission	Disease stabilization	Disease progression	P
Control group	15	1 (3.3%)	1 (3.3%)	10 (33.3%)	3 (10.0%)	0.001*
Observation group	15	10 (33.3%)	3 (10.0%)	1 (3.3%)	1 (3.3%)	

*P < 0.05.

TACE "kill" tumor cells by reducing or effectively blocking blood supply to tumor vessels. However, TACE treatment in some patients easily causes damage to patients' liver function. Studies indicate that bevacizumab has a certain effect on hepatocellular carcinoma, and it has been reported that bevacizumab combined with TACE has been used in the treatment of intermediate and advanced hepatocellular carcinoma [9].

Bevacizumab is an anti-angiogenic drug that can inactivate vascular endothelial growth factor (VEGF) and inhibit new angiogenesis. It can also promote the change of vascular morphology, reduce the length and diameter of blood vessels, and reduce tumor nutrient absorption. In addition, the combination of bevacizumab and VEGF reduced the expression of matrix metalloproteinase 9, effectively improving the liver function of patients [10]. The results showed that the total effective rate and clinical benefit rate of bevacizumab combined with TACE in patients with advanced HCC were 16.67% and 77.78%, respectively, which were significantly higher than those treated with TACE alone, with statistically significant differences. The reason may be that the combination of bevacizumab can inhibit the highly expressed VEGF after the embolization of the tumor supplying artery, inhibit the formation of new blood vessels in the tumor and normalize abnormal blood vessels. Normalized blood vessels can increase the sensitivity of tumor chemotherapy and radiotherapy, thus enhancing the killing effect on tumor cells. AFP is a specific tumor marker for hepatocellular carcinoma. 80% of patients with hepatocellular carcinoma have elevated serum AFP to varying degrees. ACE is a broad-spectrum tumor marker. In the study, the serum AFP and ACE levels in the observation group were significantly decreased after treatment, and the differences were statistically significant compared with control group. The results showed that bevacizumab in combination with TACE reduced AFP and ACE expression by inhibiting and killing tumor cells. The results also indirectly reflected that bevacizumab combined with TACE had better clinical efficacy than TACE alone [11]. The KPS score of the observation group was (76.86±6.75), significantly higher than that of the control group (72.79±5.83), and the difference was statistically significant. The survival rate of the observation group at 6 months after treatment was 91.67%, higher than 86.11% of the control group, but the difference was not statistically significant. The survival rate of the observation group at 12 months after treatment was 83.33%, significantly higher than 61.11% of the control group, and the difference between the two groups was statistically significant. The results showed that bevacizumab combined with TACE could significantly improve the quality of life and prolong the survival time of patients [12]. The results showed that the clinical control rate in the observation group was higher than that in the control group, and the level of serum alpha-fetoprotein and the incidence of adverse reactions were lower than that in the control group after treatment, indicating that bevacizumab assisted TACE treatment in patients with primary hepatocellular carcinoma and can effectively control the disease and reduce the incidence of adverse reactions [13]. Bevacizumab TACE can improve the quality of life of patients

with advanced primary hepatocellular carcinoma, prolong the survival time of patients, and reduce the levels of serum AFP and ACE, with definite curative effect [14]. Studies have shown that bevacizumab has definite effects on metastatic colorectal cancer, metastatic breast cancer and metastatic kidney cancer, as well as pancreatic cancer, hepatocellular carcinoma and gastric cancer [15]. At present, bevacizumab combined with TACE has been reported in the treatment of advanced hepatocellular carcinoma, and has achieved good efficacy [11]. The results showed that there was a statistically significant difference in CBR between the experimental group and the control group 3 and 6 months after surgery. There was no significant difference in card score 3 months after surgery. The level of alpha-fetoprotein 3 months after operation was significantly different from that before treatment. There was no significant difference in 6-month survival rate, but there was significant difference in 12-month survival rate. There was no significant difference in the incidence of adverse reactions. The results showed that the clinical efficacy of combination therapy was significantly better than that of TACE alone. Although it could not improve the quality of life of patients, it could effectively prolong the survival of patients without increasing the incidence of adverse reactions [16].

Lenvatinib is a highly selective chemotherapy drug that mainly targets VEGFR1-3, RET, FGFR1-4, cKIT, etc. By inhibiting the division and proliferation of tumor cells and inhibiting the growth of vascular endothelial cell growth factor receptor (VEGFR), it can reduce the generation of cancer cells and new blood vessels and prevent the development of the disease, as well as having the effect of prolonging patient survival. Lenvatinib has a good clinical effect in the treatment of primary hepatocellular carcinoma [17]. The number of patients with AFP, ACE and AST decreased in the observation group and was more than that in the control group. Lenvatinib can significantly reduce the levels of AFP, ACE and AST in serum and improve the overall therapeutic effect, suggesting that Lenvatinib can inhibit the proliferation and division of cancer cells, and then delay the damage of liver function. In the hepatocellular carcinoma study, sorafenib was used as the control group, and only Lenvatinib achieved positive results. Compared with sorafenib, Lenvatinib has a stronger affinity for VEGF-2 [18]. Related studies show that the main adverse reactions of Lenvatinib are hypertension, diarrhea, proteinuria, renal damage and renal failure. In the treatment of hepatocellular carcinoma, the incidence of high blood pressure reached 76%, and the mechanisms are still unclear, but with timely symptomatic treatment, the symptoms can be controlled and have good prospective on their own after the drug was stopped and symptomatic treatment can be improved. Therefore, close attention should be paid to vital signs in the process of medication. In case of arterial thromboembolism, Lenvatinib should be permanently discontinued [19]. Combined targeted therapy is an important method to prolong the survival of patients with TACE failure. Lenvatinib is a multi-target tyrosine kinase inhibitor. A Japanese study in 2017 reported that the objective response rate of Lenvatinib combined with TACE was 37%, the disease control rate was 78%, and the median overall survival was 18.7 months [20]. In 2018, Lenvatinib was not inferior to sorafenib in overall survival for patients with unresectable intermediate and advanced hepatocellular carcinoma A total of 36 patients were included in this study, with no complete response, and 7 patients (2 patients with partial response and 5 patients with stable response) had tumor control, with a disease control rate of 20.0% and an average overall survival of 11.5 months, lower than the 13.6 months reported by foreign scholars [21].

Conclusion

After hepatic arterial chemoembolization, Lenvatinib and bevacizumab can effectively improve the serum AFP, ACE, AST, albumin and platelet levels, improve liver pain, and improve the overall clinical treatment effect.

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Disclosure of conflict of interest

None.

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References

[1] Wallace MC, Preen D, Jeffrey GP and Adams LA. The evolving epidemiology of hepatocellular carcinoma: a global perspective. Expert Rev Gastroenterol Hepatol 2015; 9: 765-779.

[2] Anwanwan D, Singh SK, Singh S, Saikam V and Singh R. Challenges in liver cancer and possible treatment approaches. Biochim Biophys Acta Rev Cancer 2020; 1873: 188314.

[3] Bruix J, Han KH, Gores G, Llovet JM and Mazzaferro V. Liver cancer: approaching a personalized care. J Hepatol 2015; 62 Suppl: S144-156.

[4] Boysen AK, Jensen M, Nielsen DT, Mortensen FV, Sørensen BS, Jensen AR and Spindler KL. Cell-free DNA and chemoembolization in patients with liver metastases from colorectal cancer. Oncol Lett 2018; 16: 2654-2660.

[5] Zhang L, Ding J, Li HY, Wang ZH and Wu J. Immunotherapy for advanced hepatocellular carcinoma, where are we. Biochim Biophys Acta Rev Cancer 2020; 1874: 188441.

[6] Thandra KC, Barsouk A, Saginala K, Aluru JS, Rawla P and Barsouk A. Epidemiology of nonalcoholic fatty liver disease and risk of hepatocellular carcinoma progression. Clin Exp Hepatol 2020; 6: 289-294.

[7] Schultheiß M, Bettinger D, Neeff HP, Brunner TB and Thimme R. Hepatocellular carcinoma: therapeutic options 2015. Dtsch Med Wochenschr 2015; 140: 1063-1068.

[8] Schuppan D, Ashfaq-Khan M, Yang AT and Kim YO. Liver fibrosis: direct antifibrotic agents and targeted therapies. Matrix Biol 2018; 68-69: 435-451.

[9] Kudo M. Systemic therapy for hepatocellular carcinoma: latest advances. Cancers (Basel) 2018; 10: 412.

[10] Zhu AX, Duda DG, Sahani DV and Jain RK. Development of sunitinib in hepatocellular carcinoma: rationale, early clinical experience, and correlative studies. Cancer J 2009; 15: 263-268.

[11] Fiorentini G, Aliberti C, Mulazzani L, Coschiera P, Catalano V, Rossi D, Giordani P and Ricci S. Chemoembolization in colorectal liver metastases: the rebirth. Anticancer Res 2014; 34: 575-584.

[12] Bucalau AM, Tancredi I and Verset G. In the era of systemic therapy for hepatocellular carcinoma is transarterial chemoembolization still a card to play. Cancers (Basel) 2021; 13: 5129.

[13] Young C, Subramonian A and Argáez C. Yttrium-90 Microspheres for Intermediate- or Advanced-Stage Hepatocellular Carcinoma [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2021 Mar.

[14] Zhao Y, Yao Q, Tan H, Wu B, Hu P, Wu P, Gu Y, Zhang C, Cheng D and Shi H. Design and preliminary assessment of 99m Tc-labeled ultrasmall superparamagnetic iron oxide-conjugated bevacizumab for single photon emission computed tomography/magnetic resonance imaging of hepatocellular carcinoma. J Radioanal Nucl Chem 2014; 299.

[15] Umehara M, Umehara Y, Takahashi K, Murata A, Nishikawa S, Tokura T, Matsuzaka M, Tanaka R and Morita T. Preoperative chemotherapy with bevacizumab extends disease-free survival after resection of liver metastases from colorectal cancer. Anticancer Res 2016; 36: 1949-54.

[16] Vaeteewoottacharn K, Kariya R, Dana P, Fujikawa S, Matsuda K, Ohkuma K, Kudo E, Kraiklang R, Wongkham C, Wongkham S and Okada S. Inhibition of carbonic anhydrase potentiates bevacizumab treatment in cholangiocarcinoma. Tumour Biol 2016; 37: 9023-9035.

[17] Hatanaka T, Naganuma A and Kakizaki S. Lenvatinib for hepatocellular carcinoma: a literature review. Pharmaceuticals (Basel) 2021; 14: 36.

[18] Xia S, Pan Y, Liang Y, Xu J and Cai X. The microenvironmental and metabolic aspects of sorafenib resistance in hepatocellular carcinoma. EBioMedicine 2020; 51: 102610.

[19] Choi CS, Kim KH, Seo GS, Cho EY, Oh HJ, Choi SC, Kim TH, Kim HC and Roh BS. Cerebral and pulmonary embolisms after transcatheter arterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol 2008; 14: 4834-4837.

[20] Grenader T and Shavit L. Influence of vascular endothelial growth factor inhibition on simple renal cysts in patients receiving bevacizumab-based chemotherapy. Korean J Urol 2015; 56: 791-795.

[21] Kaseb AO, Morris JS, Iwasaki M, Al-Shamsi HO, Raghav KP, Girard L, Cheung S, Nguyen V, Elsayes KM, Xiao L, Abdel-Wahab R, Shalaby AS, Hassan M, Hassabo HM, Wolff RA and Yao JC. Phase II trial of bevacizumab and erlotinib as a second-line therapy for advanced hepatocellular carcinoma. Onco Targets Ther 2016; 9: 773-780.