Original Article

Transarterial chemoembolization combined with apatinib versus transarterial chemoembolization alone for hepatocellular carcinoma with macroscopic vascular invasion: A propensity score matching analysis

Lujun Shen[1,2], Shuanggang Chen[1,2], Zhiyu Qiu[2,3], Han Qi[1,2], Hui Yuan[1,2], Fei Cao[1,2], Lin Xie[1,2], Qifeng Chen[1,2], Wang Li[1,2], Weijun Fan[1,2]

[1]Department of Minimally Invasive Interventional Therapy, Sun Yat-Sen University Cancer Center, [2]Collaborative Innovation Center of Cancer Medicine, State Key Laboratory of Oncology in South China, Sun Yat-Sen University, [3]Zhongshan School of Medical, Sun Yat-Sen University, Guangzhou, China

For correspondence: Prof. Weijun Fan, No. 1 Building, Level 10, No. 651 Dongfeng East Road, Sun Yat-Sen University, Guangzhou 510060, China.
E-mail: fanwj@sysucc.org.cn

ABSTRACT

Context: Macroscopic vascular invasion in hepatocellular carcinoma (HCC) remains challenging to treat.

Aims: The aim of this study was to compare the efficacy of transarterial chemoembolization (TACE)–apatinib therapy with TACE treatment alone in HCC patients with macrovascular invasion, using propensity score matching (PSM).

Settings and Design: Matched paired comparison between the TACE–apatinib and TACE alone group using 1:2 PSM was utilized.

Subjects and Methods: Between 2013 and 2019, 378 patients receiving TACE–apatinib or TACE alone were included based on specific selection criteria.

Statistical Analysis Used: Multivariate Cox regression models were used to determine the independent prognostic factors for overall survival (OS).

Results: Of the patients included, 40 (12.5%) received TACE–apatinib treatment and 280 (87.5%) received TACE alone. Tumor sizes of patients in the TACE–apatinib group were more frequently classified as small (<5 cm) compared to those in the TACE alone group ($P = 0.021$; mean: 8.6 cm vs. 10.2 cm). After 1:2 PSM, 40 pairs of HCC patients with well-matched covariates were selected from the two treatment groups. Patients in the TACE–apatinib group had higher OS rates than patients in the TACE alone group ($P = 0.018$). The median OS times were 18.2 and 8.5 months in the TACE–apatinib and TACE alone groups, respectively. The OS hazard ratio for the choice of TACE–apatinib treatment compared to TACE treatment alone was 0.50 (95% confidence interval: 0.28–0.90; $P = 0.021$).

Conclusions: TACE combined with apatinib may result in superior OS compared to TACE therapy alone for HCC patients with macrovascular invasion.

KEY WORDS: Apatinib, hepatocellular carcinoma, macrovascular invasion, transarterial chemoembolization

INTRODUCTION

Macroscopic vascular invasion in hepatocellular carcinoma (HCC) remains challenging to treat[1,2] and correlates with an increased risk of intrahepatic metastasis and portal hypertension, resulting in deteriorating liver function and hepatic encephalopathy.[3] The current Barcelona Clinic Liver Cancer (BCLC) guidelines for HCC recommend systemic treatment as the first-line treatment once macroscopic vascular invasion has occurred.[4]

Sorafenib is a first-line treatment option for HCC with macroscopic vascular invasion,[5] but it has only a mild response rate.[6] In China, transarterial chemoembolization (TACE) is widely performed as a palliative treatment for patients with macroscopic

Submitted: 27-Sep-2019
Revised: 01-Jan-2020
Accepted: 24-Mar-2020
Published: 29-Sep-2020

Access this article online
Website: www.cancerjournal.net
DOI: 10.4103/jcrt.JCRT_801_19
Quick Response Code:

Cite this article as: Shen L, Chen S, Qiu Z, Qi H, Yuan H, Cao F, *et al*. Transarterial chemoembolization combined with apatinib versus transarterial chemoembolization alone for hepatocellular carcinoma with macroscopic vascular invasion: A propensity score matching analysis. J Can Res Ther 2020;16:1063-8.

vascular invasion.[7] The combination of TACE and sorafenib has been reported to prolong the time to progression and overall survival (OS) compared to sorafenib monotherapy.[8-11] However, the survival rate of these HCC patients remains low, and a more effective combination is needed.

A recently developed tyrosine kinase inhibitor, apatinib, selectively targets vascular endothelial growth factor receptor 2 (VEGFR-2)[12] and can effectively target various malignancies.[13-16] Two previous studies have reported on the efficacy of TACE combined with apatinib treatment in HCC with macrovascular invasion.[17,18] However, there remains a lack of high-quality evidence supporting this strategy. A propensity score matching (PSM) analysis comparing this combination therapy with conventional TACE treatment is needed.

Therefore, this study aimed to compare the efficacy of TACE–apatinib treatment versus TACE monotherapy as the initial therapy in HCC patients with macroscopic vascular invasion, using a propensity matching analysis.

SUBJECTS AND METHODS

Study design

From January 2013 to June 2019, a consecutive series of 525 patients with HCC and macrovascular invasion were retrospectively reviewed. The Department of Clinical Research of Sun Yat-Sen University Cancer Center approved the study protocol (2018-FXY-247). This study was approved by the Hospital Ethics Committee of Sun Yat-Sen University Cancer Center, and the written informed consent was waived due to the retrospective design. The inclusion criteria included: (a) pathological or clinical diagnosis of HCC; (b) macroscopic vascular invasion demonstrated by contrast-enhanced computed tomography/magnetic resonance imaging (CT/MRI); (c) received TACE treatment alone or TACE–apatinib combination therapy as the initial treatment; (d) performance score of 0 or 1; (e) Child–Pugh class A/B; and (f) absence of hepatic artery-portal vein fistula or hepatic artery-hepatic vein (HV) fistula using digital subtraction angiography. The exclusion criteria were: (a) receiving another systemic treatment before disease progression; (b) recurrent disease after surgical resection; and (c) heart, lung, or kidney dysfunction. A total of 320 patients were enrolled, including 280 in the TACE alone group and 40 in the TACE–apatinib group [Figure 1].

All of the included patients were informed of the benefits and risks of the two treatment strategies, including treatment outcomes, costs, and adverse effects. The doctors and patients made the treatment decision jointly.

Transarterial chemoembolization

For the TACE procedure, based on the tumor size, location, number, and vascular supply, a superselective microcatheter was inserted into the supplying artery of the tumor. A combination of lipiodol (5–15 mL), lobaplatin (30–50 mg), and pirarubicin (30–50 mg) was then introduced into the tumor. Technical success was defined as full embolization of the tumor-feeding artery and no tumor staining observed by angiogram at the end of procedure. TACE was repeated every 4–5 weeks thereafter and was discontinued if the patients could not tolerate additional procedures due to adverse effects or if they refused further treatment.

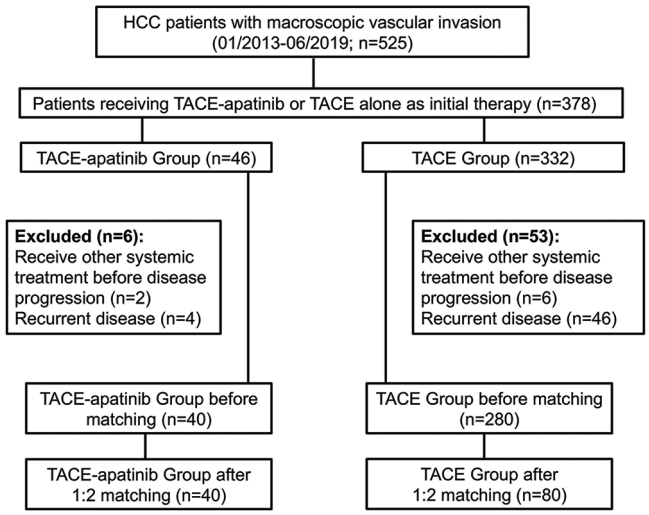

Figure 1: Flowchart of study design. A total of 525 hepatocellular carcinoma patients with macroscopic vascular invasion were reviewed and 120 were finally included. Forty pairs of patients in each arm were selected after 1:2 propensity score matching

Apatinib administration

In the TACE–apatinib group, apatinib was administered orally, starting within 1 week after the first TACE procedure, at a daily dosage of 500 mg. If a patient developed intolerable Grade 3 or 4 skin toxicity, hematologic toxicity, hepatic dysfunction, hypertension, or gastrointestinal toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0,[19] the daily dosage was reduced to 250 mg. If a dosage reduction did not alleviate or eliminate the adverse events, the administration of apatinib was halted.

Follow-up and endpoints

Patients in both the groups were followed up, and their response was evaluated by contrast-enhanced CT or MRI, every 4–5 weeks during sessions of repeated TACE treatment and then every 3 months, if complete remission of all lesions was achieved, until death.

The primary outcome was OS, which was defined as the time from the initial TACE procedure to death by any cause. The secondary outcome was the safety profile, as evaluated using NCI-CTCAE 4.0 in the TACE–apatinib group.

Statistical analysis

Pearson's Chi-square test was used to compare categorical variables, and Fisher's exact test was used when the expected

count of any cell in the contingency table was <5. Rates of OS between the TACE–apatinib and TACE alone groups were estimated using the Kaplan–Meier method and compared using a log-rank test. A multivariate Cox regression model was used to determine the independent prognostic factors for OS.

PSM analysis was performed at a ratio of 1:2, using the optimal matching method to minimize selection bias. The variables selected in the propensity model included gender, age, hepatitis B virus (HBV) infection, alpha-fetoprotein (AFP) level, tumor size, Child–Pugh class, number of tumors, type of portal vein tumor thrombus (PVTT), HV or inferior vena cava (IVC) invasion and distant metastasis. SPSS 21.0 (IBM, Armonk, NY, USA) or R 3.3.2 (The R Foundation for Statistical Computing, 2018) was used for all statistical analyses.

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2020001479.

RESULTS

Baseline characteristics of the study population

Of the 320 patients enrolled, 40 (12.5%) were in the TACE–apatinib group and 280 (87.5%) were in the TACE alone group. The baseline characteristics of the two groups are presented in Table 1. Before matching, patients in the TACE–apatinib group had a higher incidence of small tumor size (<5 cm), compared to those in the TACE alone group ($P = 0.021$; mean ± standard deviation: 8.6 ± 4.1 vs. 10.2 ± 3.8 cm). No significant differences in the distribution of gender, age, Child–Pugh class, HBV infection, AFP level, type of PVTT, HV/IVC invasion, or distant metastasis were observed between the two groups.

In the TACE–apatinib group, the median duration of apatinib administration was 3.7 months and the dosage of apatinib was reduced from 500 mg to 250 mg in 11 (27.5%) patients due to severe adverse effects. No patients discontinued apatinib treatment due to intolerable side effects [Table 2].

Overall survival in the whole population

The median OS times for the TACE–apatinib and TACE alone groups were 18.2 and 7.1 months, respectively. The 1- and 3-year OS rates were 63.6% and 45.5%, respectively, in the TACE–apatinib group and 40.6% and 20.3%, respectively, in the TACE alone group. Patients in the TACE alone group had lower OS rates than patients in the TACE–apatinib group [Figure 2a; $P = 0.002$]. In the whole population, a univariate analysis showed that tumor size (≥5 cm vs. <5 cm), Child–Pugh class (B vs. A), the number of tumors (multiple vs.

Table 1: Baseline characteristics of patients

Variable	Before PSM			After PSM		
	TACE only (*n*=280)	TACE-apatinib (*n*=40)	*P*	TACE only (*n*=80)	TACE-apatinib (*n*=40)	*P*
Gender						
Male	265 (94.6)	38 (95.0)	0.925*	74 (92.5)	38 (95.0)	0.605*
Female	15 (5.4)	2 (5.0)		6 (7.5)	2 (5.0)	
Age (years)						
<50	134 (47.9)	17 (42.5)	0.526	31 (38.8)	17 (42.5)	0.693
≥50	146 (52.1)	23 (57.5)		49 (61.3)	23 (57.5)	
Child-Pugh Class						
A	228 (81.4)	33 (82.5)	0.870	64 (80.0)	33 (82.5)	0.743
B	52 (18.6)	7 (17.5)		16 (20.0)	7 (17.5)	
HBV infection						
No	16 (5.7)	4 (10.0)	0.295*	5 (6.2)	4 (10.0)	0.462*
Yes	264 (94.3)	36 (90.0)		75 (93.8)	36 (90.0)	
Tumor size (cm)						
<5	28 (10.0)	9 (22.5)	0.021	14 (17.5)	9 (22.5)	0.512
≥5	252 (90.0)	31 (77.5)		66 (82.5)	31 (77.5)	
Number of tumors						
Single	130 (46.4)	14 (35.0)	0.174	19 (23.8)	14 (35.0)	0.193
Multiple	150 (53.6)	26 (65.0)		61 (76.2)	26 (65.0)	
AFP level (ng/ml)						
≤400	127 (45.4)	18 (45.0)	0.966	27 (33.8)	18 (45.0)	0.230
>400	153 (53.6)	22 (55.0)		53 (66.2)	22 (55.0)	
Type of PVTT						
Absent/Type I/Type II	208 (74.3)	27 (67.5)	0.363	52 (65.0)	27 (67.5)	0.785
Type III/Type IV	72 (25.7)	13 (32.5)		28 (35.0)	13 (32.5)	
HV or IVC invasion						
Absent	217 (77.5)	32 (80.0)	0.722	68 (85.0)	32 (80.0)	0.488
Present	63 (22.5)	8 (20.0)		12 (15.0)	8 (20.0)	
Distant metastasis						
Absent	218 (77.9)	27 (67.5)	0.148	56 (70.0)	27 (67.5)	0.780
Present	62 (22.1)	13 (32.5)		24 (30.0)	13 (32.5)	

*Fisher's exact test. PSM=Propensity score matching, TACE=Transarterial chemoembolization, HBV=Hepatitis B virus, AFP=Alpha-fetoprotein, PVTT=Portal vein tumor thrombus, HV=Hepatic vein, IVC=Inferior vena cava

single), distant metastasis (present vs. absent), and treatment method (TACE–apatinib vs. TACE alone) were significantly associated with OS. Multivariate analysis suggested that tumor size, the number of tumors, distant metastasis, and treatment method were independent predictors of OS [Table 3].

Propensity score matching analysis

Forty pairs of patients with well-matched covariates were selected from each group using 1:2 PSM [Table 1 and Figure 3]. The median OS times in the TACE–apatinib and TACE alone groups were 18.2 and 8.5 months, respectively. The 1- and 3-year OS rates were 63.6% and 45.5%, respectively, in the TACE–apatinib group and 46.8% and 15.1%, respectively, in the TACE alone group. The TACE–apatinib group had a significantly higher OS rate ($P = 0.018$) than the TACE alone group [Figure 2b]. The hazard ratio for the choice of TACE–apatinib treatment compared to TACE treatment alone was 0.50 (95% confidence interval: 0.28–0.90; $P = 0.021$).

Adverse events in the transarterial chemoembolization–apatinib group

The adverse events associated with apatinib in the TACE–apatinib group are presented in Table 4. No Grade 4 adverse events or treatment-related deaths were observed in either group. All of the Grade 3 adverse events were alleviated by a dose reduction or the treatment of associated symptoms.

DISCUSSION

Our study showed that TACE combined with apatinib was an effective combination strategy in HCC patients with macrovascular invasion and had superior therapeutic efficacy to TACE monotherapy.

Table 2: Characteristics of oral intake of apatinib in the transarterial chemoembolization-apatinib group

Category	*n* (%)
Length of intake (months)	
1-3	10 (25.0)
3-6	12 (30.0)
>6	18 (45.0)
Dose reduction	
No	29 (72.5)
Yes	11 (27.5)

The prognosis of HCC patients with macrovascular invasion remains poor, with an expected survival of 2–4 months after optimal supportive care.[20] In the BCLC guidelines, HCC with vascular invasion refers to Stage C disease and the recommended treatment is sorafenib, which has a modest efficacy. A recent survey showed that TACE is still prescribed by 52% of interventional oncologists for the management of HCC with macrovascular invasion. There is increasing evidence, suggesting that TACE, as a fast-evolving treatment, may be beneficial and justified for patients with vascular invasion.[7,21] Meanwhile, a series of combination strategies have also been proposed, including combined TACE–apatinib therapy. Chen *et al*. found that TACE combined with apatinib results in increased OS time, compared with TACE treatment alone (13.0 vs. 9.9 months), in patients with advanced-stage HCC. Currently, there is limited evidence comparing the efficacy of TACE–apatinib therapy with TACE treatment alone in HCC with macrovascular invasion. Our results suggested that TACE–apatinib combination therapy was more effective than TACE treatment alone in this subgroup of advanced-stage HCC patients, which is consistent with the findings of previous studies.[18,22-24] VEGFR-2 has been reported to be closely correlated with the development and growth of liver malignancies. Among all available multikinase inhibitors, apatinib has the highest selectivity for VEGFR-2, with more than ten times the binding affinity of sorafenib.[25] The reason for the improvement in OS may be that apatinib can potently target the vascular endothelial growth factor/VEGFR-2 pathway induced by hypoxia after vascular embolization, thus inhibiting the migration and tube formation of endothelial cells[26] and the proliferation, migration, and invasion of tumor cells.[27]

Although significantly higher 1- and 3-year OS rates were observed in the TACE–apatinib group, the median OS time of these two treatment groups remains short, indicating that just combining TACE and apatinib was not enough to achieve long-term survival for HCC patients with macrovascular

Table 3: Univariate and multivariate analysis of overall survival in the enrolled cohort

Variable	Number of cases	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (female vs. male)	17/303	0.66 (0.37-1.19)	0.168	-	-
Age (≥50 vs. <50)	169/151	0.89 (0.66-1.19)	0.438	-	-
Child-Pugh Class (B vs. A)	59/261	1.59 (1.10-2.28)	0.012	-	-
Liver tumor size (≥5 cm vs. <5 cm)	283/37	2.41 (1.40-4.17)	0.002	1.99 (1.15-3.44)	0.015
Number of tumors (multiple vs. single)	176/144	1.35 (1.01-1.81)	0.046	1.39 (1.03-1.87)	0.031
AFP level (>400 ng/ml vs. ≤400 ng/ml)	175/145	1.20 (0.89-1.60)	0.227	-	-
Type of PVTT (Type III/IV vs. Type I/II/Absent)	85/235	1.17 (0.84-1.62)	0.362	-	-
HV or IVC invasion (present vs. absent)	71/249	1.03 (0.72-1.47)	0.880	-	-
Distant metastasis (present vs. absent)	75/245	1.78 (1.29-2.47)	0.001	2.04 (1.46-2.86)	<0.001
Treatment (TACE-apatinib vs. TACE)	40/280	0.45 (0.26-0.76)	0.003	0.38 (0.22-0.66)	0.001

HR=Hazard ratio, CI=Confidence interval, AFP=Alpha-fetoprotein, PVTT=Portal vein tumor thrombus, HV=Hepatic vein, IVC=Inferior vena cava, TACE=Transarterial chemoembolization

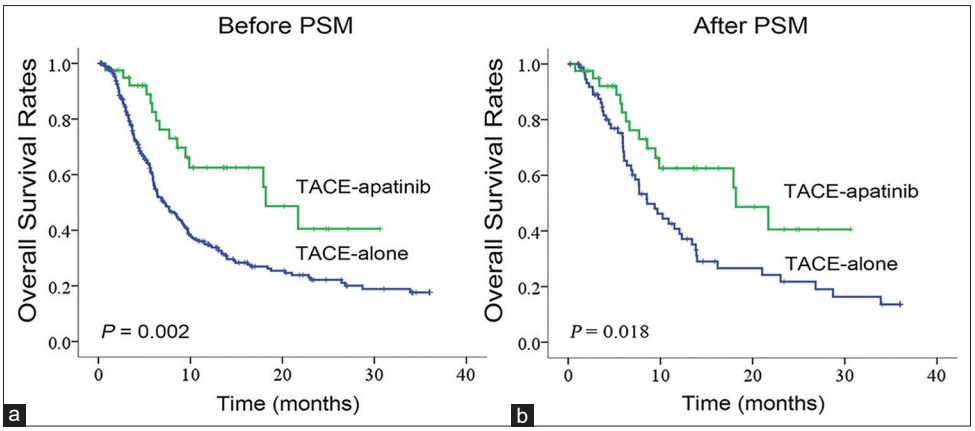

Figure 2: Kaplan–Meier curves showing the overall survival of hepatocellular carcinoma patients according to different combination therapies, before (a) and after (b) matching

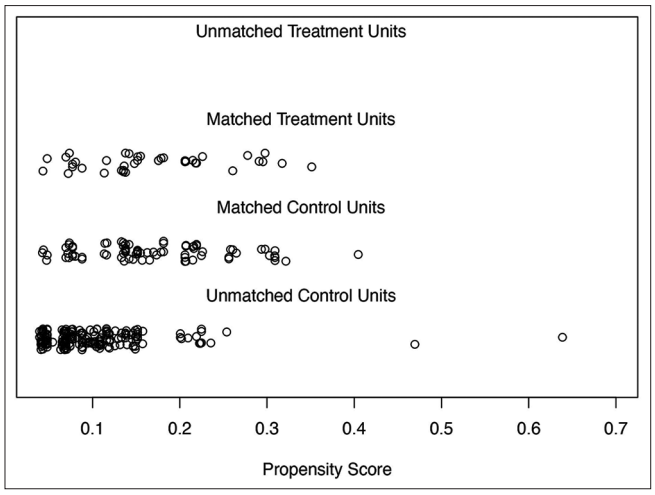

Figure 3: Distribution of propensity scores in the two groups before and after matching

invasion. Increasing the efficacy of the current treatment plan may require additional combination therapies, including ablative therapies, radiotherapy, and immunotherapies. Our previous study showed that TACE plus stereotactic body radiotherapy (SBRT) results in improved OS compared to TACE–sorafenib combination therapy, with higher 3- and 5-year OS rates.[28] Therefore, combining TACE, SBRT, and apatinib may bring additional survival benefits compared to TACE–apatinib treatment. Immunotherapy has recently emerged as a new direction in the management of patients with advanced-stage HCC. A recent study showed that SHR-1210 (Camrelizumab), a commercially available anti-PD-1 antibody, combined with apatinib, achieved a 50% partial response rate for advanced HCC,[29] which was higher than the response rate previously reported for monotherapy with the anti-PD-1 antibody, nivolumab.[30] Combining TACE, apatinib, and an anti-PD1 antibody may achieve a synergistic therapeutic effect.

Previous studies have shown that combining TACE with apatinib does not increase the number of adverse events

Table 4: Apatinib related adverse events in the transarterial chemoembolization-apatinib group

Adverse effects	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)
Diarrhea	2 (5.0)	5 (12.5)	2 (5.0)
Hypertension	2 (5.0)	6 (15.0)	5 (12.5)
Hand-foot syndrome	3 (7.5)	12 (30.0)	12 (30.0)
Hoarseness	3 (7.5)	2 (5.0)	0 (0.0)
Proteinuria	15 (37.5)	2 (5.0)	0 (0.0)
Oral ulcer	3 (7.5)	2 (5.0)	0 (0.0)
Fatigue	3 (10.3)	2 (10.3)	-

compared to apatinib alone in advanced-stage HCC,[31] suggesting that this combination strategy may also be safe for treating HCC patients with macrovascular invasion. In our cohort, more than half of patients in the TACE–apatinib group developed hand–foot syndrome and more than 30% of patients developed hypertension and proteinuria from the start of apatinib treatment. However, all of these adverse events were lower than Grade 4, and no treatment-related deaths occurred. Moreover, all Grade 3 adverse events were alleviated by a dose reduction or treatment of the associated symptoms. These results suggested that TACE–apatinib combination treatment is safe for HCC patients with macrovascular invasion.

Our study had several limitations. First, this was a single-center retrospective study. Second, although this study enrolled more cases with advanced-stage HCC than previous studies,[22,25,32] the sample size of our study was still relatively small, which may cause selection bias. A multi-institutional prospective clinical trial to confirm our findings is needed.

CONCLUSIONS

Our study found that TACE–apatinib combination therapy is safe and can significantly prolong the OS of HCC patients with macroscopic vascular invasion, compared to TACE monotherapy.

Financial support and sponsorship

This study was financially supported by the National Natural Science Foundation of China (No. 81801804).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, *et al*. Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. Hepatol 1999;29:62-7.
2. Peng Z, Chen S, Wei M, Lin M, Jiang C, Mei J, *et al*. Advanced recurrent hepatocellular carcinoma: Treatment with sorafenib alone or in combination with transarterial chemoembolization and radiofrequency ablation. Radiol 2018;287:705-14.
3. Costentin CE, Ferrone CR, Arellano RS, Ganguli S, Hong TS, Zhu AX. Hepatocellular carcinoma with macrovascular invasion: Defining the optimal treatment strategy. Liver Cancer 2017;6:360-74.
4. Yim HJ, Suh SJ, Um SH. Current management of hepatocellular carcinoma: An Eastern perspective. World J Gastroenterol 2015;21:3826-42.
5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
6. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A Phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
7. Silva JP, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, *et al*. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: A systematic review and meta-analysis. HPB (Oxford) 2017;19:659-66.
8. Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29:3960-7.
9. Abou-Alfa GK. TACE and sorafenib: A good marriage? J Clin Oncol 2011;29:3949-52.
10. Park JW, Koh YH, Kim HB, Kim HY, An S, Choi JI, *et al*. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. J Hepatol 2012;56:1336-42.
11. Choi GH, Shim JH, Kim MJ, Ryu MH, Ryoo BY, Kang YK, *et al*. Sorafenib alone versus sorafenib combined with transarterial Chemoembolization for advanced-stage hepatocellular carcinoma: Results of propensity score analyses. Radiol 2013;269:603-11.
12. Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (Stage III/IV) non-small cell lung cancer (NSCLC). Cancer Treat Rev 2013;39:252-60
13. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, *et al*. Randomized, double-blind, placebo-controlled Phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 2016;34:1448-54.
14. Scott AJ, Messersmith WA, Jimeno A. Apatinib: A promising oral antiangiogenic agent in the treatment of multiple solid tumors. Drugs Today (Barc) 2015;51:223-9.
15. Hamerlik P, Lathia JD, Rasmussen R, Wu Q, Bartkova J, Lee M, *et al*. Autocrine VEGF-VEGFR2-neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth. J Exp Med 2012;209:507-20.
16. Wu X, Wang H, Wu Y, Jin J, Zhan Y, Zhu G, *et al*. Efficacy of apatinib on multiple advanced-stage nongastric cancers. J Cancer Res Ther 2019;15:836-41.
17. Liu C, Xing W, Si T, Yu H, Guo Z. Efficacy and safety of apatinib combined with transarterial chemoembolization for hepatocellular carcinoma with portal venous tumor thrombus: A retrospective study. Oncotarget 2017;8:100734-45.
18. Fan W, Yuan G, Fan H, Li F, Wu Y, Zhao Y, *et al*. Apatinib combined with transarterial chemoembolization in patients with hepatocellular carcinoma and portal vein tumor thrombus: A multicenter retrospective study. Clin Ther 2019;41:1463-76.
19. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: Measuring symptomatic adverse events with the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book 2016;35:67-73.
20. Han K, Kim JH, Ko GY, Gwon DI, Sung KB. Treatment of hepatocellular carcinoma with portal venous tumor thrombosis: A comprehensive review. World J Gastroenterol 2016;22:407-16.
21. Xue TC, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: A meta-analysis. BMC Gastroenterol 2013;13:60.
22. Chen S, Yu W, Zhang K, Liu W. Comparison of the efficacy and safety of transarterial chemoembolization with and without apatinib for the treatment of BCLC Stage C hepatocellular carcinoma. BMC Cancer 2018;18:1131.
23. Qiu Z, Shen L, Chen S, Qi H, Cao F, Xie L, *et al*. Efficacy of apatinib in Transcatheter Arterial Chemoembolization (TACE) refractory intermediate and advanced-stage hepatocellular carcinoma: A propensity score matching analysis. Cancer Manag Res 2019;11:9321-30.
24. Liu J, Xu J, Zhang W, Chen J, Zhou X, Li Z, *et al*. Safety and efficacy of drug-eluting bead transarterial chemoembolization combined with apatinib in patients with advanced hepatocellular carcinoma. Acad Radiol 2019. DOI: https://doi.org/10.1016/j.acra.2019.07.003.
25. Lu W, Jin XL, Yang C, Du P, Jiang FQ, Ma JP, *et al*. 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;18:433-8.
26. Yang C, Qin S. Apatinib targets both tumor and endothelial cells in hepatocellular carcinoma. Cancer Med 2018;7:4570-83.
27. Huang M, Huang B, Li G, Zeng S. Apatinib affect VEGF-mediated cell proliferation, migration, invasion via blocking VEGFR2/RAF/MEK/ERK and PI3K/AKT pathways in cholangiocarcinoma cell. BMC Gastroenterol 2018;18:169.
28. Shen L, Xi M, Zhao L, Zhang X, Wang X, Huang Z, *et al*. Combination therapy after tace for hepatocellular carcinoma with macroscopic vascular invasion: Stereotactic body radiotherapy versus sorafenib. Cancers (Basel) 2018;10:12.
29. Xu J, Zhang Y, Jia R, Yue C, Chang L, Liu R, *et al*. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: An open-label, dose escalation and expansion study. Clin Cancer Res 2019;25:515-23.
30. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, *et al*. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
31. Wei Y, Liu J, Yan M, Zhao S, Long Y, Zhang W. Effectiveness and safety of combination therapy of transarterial chemoembolization and apatinib for unresectable hepatocellular carcinoma in the chinese population: A meta-analysis. Chemother 2019;64:94-104.
32. Yang Z, Chen G, Cui Y, Xiao G, Su T, Yu J, *et al*. The safety and efficacy of TACE combined with apatinib on patients with advanced hepatocellular carcinoma: A retrospective study. Cancer Biol Ther 2019;20:321-7.