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ORIGINAL ARTICLE

Retrospective Study

Sorafenib after resection improves the outcome of BCLC stage C hepatocellular carcinoma

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Abstract

AIM: To evaluate whether sorafenib use after resection impacts tumor relapse and survival in Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC).

METHODS: This retrospective study enrolled 36 male BCLC stage C HCC patients with portal vein thrombus and Child-Pugh class A liver function. Twenty-four patients received only surgical resection (SR), and 12 patients received oral sorafenib within 30 d after surgery. The primary outcomes were time to progression (TTP) (the time from surgical resection until HCC recurrence or extrahepatic metastases) and overall survival (OS). The secondary outcome was the rate of postoperative recurrence or metastasis. TTP and OS were analyzed using Kaplan Meier curves.

RESULTS: There were no significant differences between the two groups in the serum levels of alpha-fetoprotein, copies of hepatitis B virus-DNA, preoperative laboratory results, degree of hepatic fibrosis, types of portal vein tumor thrombus, number of satellite lesions, tumor diameter, pathological results, volume of blood loss, volume of blood transfusion, or surgery time (all $P > 0.05$). Patients in the SR + sorafenib group had a significantly longer TTP (29 mo *vs* 22 mo, $P = 0.041$) and a significantly longer median

OS (37 mo *vs* 30 mo, *P* = 0.01) compared to patients in the SR group. The SR group had 18 cases (75%) of recurrence/metastasis while the SR + sorafenib group had six cases (50%) of recurrence/metastasis. A total of 19 patients died after surgery (five in the SR + sorafenib group and 14 in the SR group). The most common sorafenib-related adverse events were skin reactions, diarrhea, and hypertension, all of which were resolved with treatment.

CONCLUSION: Sorafenib after SR was well-tolerated. Patients who received sorafenib after SR had better outcomes compared to patients who received only SR.

Key words: Hepatocellular carcinoma; Survival; Hepatic resection; Sorafenib; Recurrence

Core tip: Barcelona Clinic Liver Cancer stage C patients with portal vein thrombus and Child-Pugh class A liver function who received sorafenib after surgical resection had significantly longer overall survival (37 mo *vs* 20 mo, *P* = 0.01) and significantly longer time to progression compared to patients who received only resection (29 mo *vs* 22 mo, *P* = 0.041). Our data suggested that better outcomes can be achieved with sorafenib after surgical resection, rather than sorafenib monotherapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related deaths worldwide[1]. The most important risk factors for HCC include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and the presence of liver cirrhosis[2-4]. The Barcelona Clinic Liver Cancer (BCLC) classification system recommended a standard classification system for the treatment of HCC that has been accepted by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver[5]. Based on these guidelines, patients diagnosed with HCC at an early stage (BCLC Stage 0, A) currently undergo surgical resection (SR), liver transplantation, or percutaneous ablation and have a survival rate of 60%-70%[3,6,7]. However, HCC recurrence after these therapies is still common. Patients at an intermediate stage (BCLC Stage B) undergo transarterial chemoembolization (TACE)[8,9], where abnormal neovascularization is identified and injected with an emulsion of chemotherapeutic drug and lipidol and then embolized with gelfoam to induce tumor necrosis[10]. Although repeated treatment with TACE was associated with improved survival in patients with intermediate HCC[9], its use is limited to patients with well-compensated cirrhosis[11]. SR was shown to result in high hepatic functional reserve in HCC patients with portal vein tumor thrombus (PVTT), while postoperative TACE delayed recurrence and prolonged overall survival (OS) in patients who could tolerate the treatment[12]. Interestingly, TACE has been shown to induce neoangiogenesis and upregulation of vascular endothelial growth factor (VEGF), which is an independent negative predictor of survival[13].

Patients with advanced HCC have a poor prognosis[14]. The multi-kinase inhibitor sorafenib, which is the only approved agent recommended by the AASLD for HCC BCLC Stage C, is currently recommended as the first-line therapy in these patients[14-16]. Two randomized controlled clinical trials recently showed that sorafenib prolonged OS and delayed the time to progression (TTP) in patients with advanced HCC[17,18], likely by inhibiting a number of growth factor pathways, including VEGFR-1,-2,-3, platelet derived growth factor receptor (PDGFR)-β, Raf, rearranged during transfection (RET), and FMS-like tyrosine kinase (FLT)-3[19]. However, certain BCLC stage C patients with Child-Pugh class A liver function have been shown to have better outcomes with SR than with sorafenib monotherapy[20,21]. Additionally, recent reports, which showed that (1) advanced HCC patients at BCLC stage C had favorable outcomes with SR, and (2) the presence of multinodular tumors, macrovascular invasion, and portal hypertension were not contraindications for SR, suggested that the guidelines for the use of sorafenib monotherapy for advanced HCC should be re-evaluated[22,23].

The main purpose of this retrospective study was to evaluate whether sorafenib use after liver resection had an impact on tumor relapse and OS in BCLC stage C HCC patients. We also evaluated the safety and tolerability of oral sorafenib after surgical resection in these patients.

MATERIALS AND METHODS

This retrospective study evaluated the medical records of 36 male HCC patients who underwent surgical resection and were treated at the First Affiliated Hospital of Kunming Medical University between January 2009 and December 2013. All patients were HBV positive and had cirrhosis.

Inclusion criteria were: (1) age 18-70 years old; (2) newly diagnosed liver cancer with no treatment received prior to surgical resection; (3) BCLC stage C [tumor thrombus in left/right branches or main portal vein; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ⩽ 2], Child-Pugh liver function class A; (4) tumor confined to left/right

lobe (single or multiple); maximum tumor diameter ⩾ 5 cm; all patients underwent anatomic left/right lobe resection + thrombus dissection, with negative surgery margin (R0). All operative procedures were classified according to the Brisbane terminology[24]. Anatomic left/right lobe resection was defined as resection of the tumor along with the related portal vein branches and corresponding hepatic artery territory; (5) patients treated with oral sorafenib received a dose of 200-800 mg/d within 30 d after surgery. The dose was reduced to 200 mg twice daily in the event of drug-related adverse effects; and (6) time of follow up ⩾ 6 mo (before June 2014); patients underwent at least once B-type ultrasound or computed tomography (CT)/magnetic resonance (MR) + chest X-ray every 2 mo during the follow-up period (if B-type ultrasound or X-ray found a new lesion, a confirmatory CT/MR scan was performed).

Exclusion criteria were: (1) presence of acute or chronic lesions in other organs outside the liver; (2) presence of metastases or suspected metastatic lesions outside the liver; (3) presence of other tumors at the time of diagnosis or during the follow-up period; (4) patient received any treatments (including TACE or RF) other than sorafenib after SR and before tumor recurrence or metastasis; and (5) tumor recurrence or metastasis within 3 mo after surgical resection or unnatural death during follow-up.

Outcome measures

The primary outcome was TTP (the time from SR until HCC recurrence or extrahepatic metastases discovered by CT/MR) and OS. The secondary outcome was the rate of postoperative recurrence or metastasis.

Statistical analysis

The demographic data and clinical characteristics of the patients were summaized as mean ± SD for continuous data, *n* (%) for categorical data, and median (range: min to max) for time-related data. Differences between groups were compared using two-sample *t*-test for continuous data, Pearson χ^2 test or Fisher exact test for categorical data, and log-rank test for time-related data. Additionally, a Mann-Whitney *U* test was considered for continuous data if data did not follow normal distribution. Time-related data (TTP and OS times) are represented using Kaplan-Meier curves, and differences between groups were analyzed by the log-rank test. The TTP and OS times were also summarized as median with 95%CI for both groups, separately. All statistical assessments were two-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences 17.0 for Windows (SPSS Inc., Chicago, IL, United States).

RESULTS

Of a total of 36 study patients, 12 patients received oral sorafenib after SR (SR + sorafenib group) and 24 received only SR (SR group). None of the patients exhibited any serious complications, including liver dysfunction, bleeding, or infection, within 30 d of surgical resection.

Demographics and baseline clinical characteristics

Table 1 summarizes the demographics and baseline clinical characteristics in the SR + sorafenib and the SR groups. All study patients were male. The average ages of patients in the SR + sorafenib and the SR groups were 49.8 ± 6.5 years and 52.8 ± 6.9 years, respectively ($P = 0.226$). There were no significant differences in the serum levels of alpha fetoprotein (AFP), copies of HBV-DNA, preoperative laboratory results, degree of hepatic fibrosis, types of PVTT, number of satellite lesions, tumor diameter, pathological results, volume of blood loss, volume of blood transfusion, or surgery time between the two groups (all $P > 0.05$).

Post-operative recurrence rate, TTP, and OS

The median follow-up time after SR for all patients was 23 mo (range of 9-54 mo). During the follow-up period, a total of 19 patients experienced residual liver relapse ($n = 5$ in the SR + sorafenib group, and $n = 14$ in the SR group), three patients developed lung metastasis ($n = 1$ in the SR + sorafenib group, and $n = 2$ in the SR group), one patient developed right adrenal gland metastasis ($n = 1$ in the SR group), and one patient developed thoracic vertebral metastasis ($n = 1$ in the SR group) (data not shown). The rate of patients with at least once recurrence (including relapse or metastasis) was, therefore, derived as 50% (6/12) for the SR + sorafenib group and 75% (18/24) for the SR group ($P = 0.157$) (Table 1).

Patients in the SR + sorafenib and SR groups had a median TTP of 29 mo (95%CI: 26.5-31.5 mo) and 22 mo (95%CI: 18.0-26.0 mo), respectively. The log-rank test showed that this difference was significant ($P = 0.041$), suggesting that sorafenib therapy after SR might prolong the time until recurrence compared to SR alone (Figure 1).

A total of 19 patients died after surgery (five in the SR + sorafenib group and 14 in the SR group) (Table 1). The SR + sorafenib and SR groups had median OS times of 37 mo (95%CI: 34.8-39.2 mo) and 30 mo (95%CI: 24.1-36.0 mo), respectively. The log-rank test showed that this difference was significant ($P = 0.010$), suggesting that patients who received sorafenib therapy after SR had longer survival times compared to patients who received only SR (Figure 2)

Adverse events

The most common sorafenib-related adverse events during the follow-up period included hand-foot-skin reaction (11 patients; 91.67%), diarrhea (10 patients; 83.3%), and hypertension (10 patients; 83.3%). All the sorafenib-related adverse events were resolved with treatment, and no treatment-related deaths

Table 1 Patients' demographics and clinical characteristics by group *n* (%)

Variables	SR + sorafenib (*n* = 12)	SR (*n* = 24)	*P* value
Age[1], yr	49.8 ± 6.5	52.8 ± 6.9	0.226
ECOG PS score[2]			1.000
0	10 (83.3)	19 (79.2)	
1	2 (16.7)	5 (20.8)	
Largest tumor diameters[1], cm	9.8 ± 2.1	11.2 ± 2.5	0.103
Pathologic results[3]			0.404
Well differentiated (grade 1)	3 (25.0)	2 (8.3)	
Moderately differentiated (grade 2)	7 (58.3)	18 (75)	
Poorly differentiated (grade 3)	2 (16.7)	4 (16.7)	
Satellite lesion[4], *n*	4 (33.3)	9 (37.5)	1.000
AFP			0.700
< 400 ng/mL	4 (33.3)	6 (25)	
⩾ 400 ng/mL	8 (66.7)	18 (75)	
HBV-DNA			0.664
< 1000 cps/mL	9 (75)	20 (83.3)	
⩾ 1000 cps/mL	3 (25)	4 (16.7)	
Degree of fibrosis[5]			1.000
0-2	2 (16.7)	3 (12.5)	
3-4	10 (83.3)	21 (87.5)	
Types of PVTT[6]			0.764
First-order branch (VP3)	10 (83.3)	19 (79.2)	
Main trunk (VP4)	2 (16.7)	5 (20.8)	
Preoperative laboratory results			
ALT[1], μmol/L	57.3 ± 19.9	50.8 ± 22.1	0.397
Albumin[1], g/L	39.5 ± 3.5	39.9 ± 4.5	0.781
Bilirubin[1], μmol/L	17.4 ± 4.5	19.8 ± 6.0	0.236
Hemoglobin[1], g/L	137.3 ± 10.9	132.0 ± 7.8	0.103
Platelet count[1], 10^9/L	185.4 ± 46.2	164.3 ± 48.6	0.220
Prothrombin time[1], s	12.1 ± 1.0	12.0 ± 1.0	0.785
INR[7]	1.4 ± 0.5	1.3 ± 0.4	0.436
Blood loss[7], mL	304.2 ± 151.4	343.8 ± 143.2	0.458
Blood transfusion[7], mL	37.5 ± 93.2	62.5 ± 124.5	0.679
Surgery time[7], min	218.3 ± 33.3	232.5 ± 47.8	0.265
TTP times[8], mo	26.5 (14-54)	21.5 (9-34)	0.041[9]
Patients with recurrence after SR[2]	6 (50)	18 (75)	0.157
Survival times[8], mo	32 (21-58)	25.5 (11-37)	0.010[9]
Patients died after SR[2]	5 (41.7)	14 (58.3)	0.483

[1]mean ± SD for continuous data, differences between groups were compared using two-sample *t*-test; [2]*n* (%) categorical data and differences between groups were compared using Pearson χ^2 test; [7]Mann-Whitney *U* test; [3]Median (range: min to max) for time-related data, and differences between groups were compared using Fisher exact test; [8]Log-rank test was used for time-related data; [4]Satellite lesions were defined as tumors ⩽ 2 cm in size that were located within a distance of 2 cm from the main tumor; [5]The degree of fibrosis of the hepatic parenchyma was graded according to the classification of Ishak *et al*[39] grade 0-2, no or minimal fibrosis; grade 3-4, incomplete bridging fibrosis; grade 5-6, complete fibrosis and nodules; [6]PVTT was typed according to the classification of primary liver cancer by the Liver Cancer Study Group of Japan[40]. Patients were defined as having a tumor thrombus in the first-order branch (VP3) and the main trunk (VP4) of the portal vein; [9]$P < 0.05$, indicates a significant difference between two groups. SR: Surgical resection; AFP: Alpha fetoprotein; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; PVTT: Portal vein tumor thrombus; TTP: Time to progression.

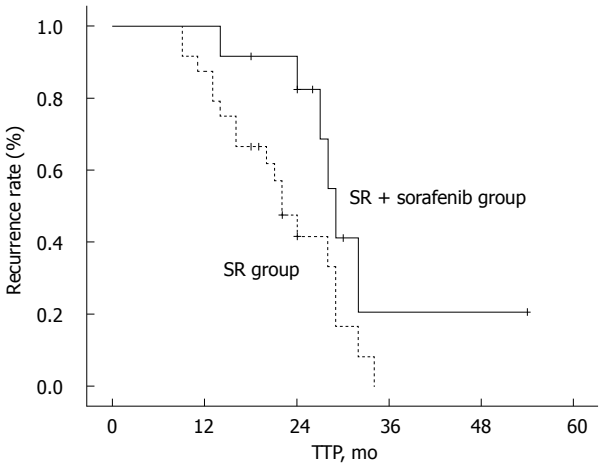

Figure 1 Kaplan-Meier curve of time-to-progression in the surgical resection + sorafenib and surgical resection groups. The median time to progression (TTP) was estimated from the patients with equivalent as 0.5 and derived as 29 mo (95%CI: 26.5-31.5 mo) and 22 mo (95%CI: 18.0-26.0 mo) for surgical resection (SR) + sorafenib and SR groups, respectively. + indicates censored patients. The log-rank test showed a significant difference in the TTP between groups ($P = 0.041$).

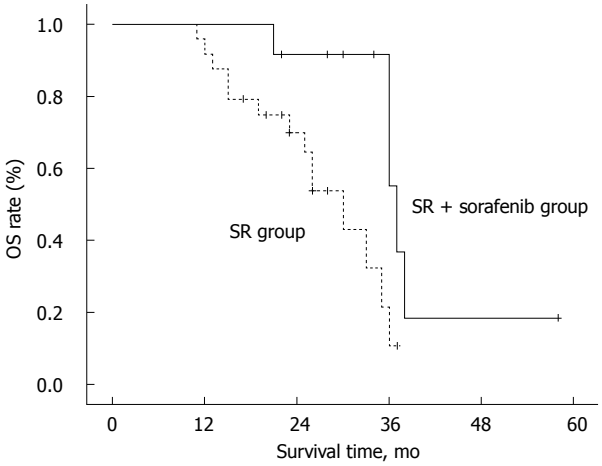

Figure 2 Kaplan-Meier curve of overall survival times in the surgical resection + sorafenib and surgical resection groups. The median overall survival (OS) time was estimated from the patients with equivalent as 0.5 and derived as 37 mo (95%CI: 34.8-39.2 mo) and 30 mo (95%CI: 24.1-36.0 mo) for the surgical resection (SR) + sorafenib and SR groups, respectively. + indicates censored patients. The log-rank test showed a significant difference in the OS times between groups ($P = 0.010$).

occurred (data not shown).

DISCUSSION

In this study, we showed that BCLC stage C patients who received sorafenib after SR had significantly longer OS and significantly longer TTP compared to patients who received only SR. There were fewer cases of recurrence/metastasis in the SR + sorafenib group

compared to the SR only group. Sorafenib after SR was generally safe and well-tolerated.

Based on the current standard of care, patients with advanced HCC (stage B or C) who cannot undergo radical resection, receive local palliative treatment, including TACE, hepatic arterial infusion chemotherapy, and systemic chemotherapy[10,25,26]. Patients with stage C (defined as portal vein aggressiveness, lymph node or distant metastasis, ECOG PS ⩽ 2, Child-Pugh liver function class A or B) are treated with sorafenib, which is an oral multi-kinase inhibitor with anti-tumor activity[27-29]. The multi-center European Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, which evaluated the efficacy of sorafenib monotherapy (400 mg twice daily) in 602 HCC BCLC stage C patients with Child-Pugh class A liver function, showed a significantly lower OS in the placebo group compared to the sorafenib group (7.9 mo *vs* 10.7 mo, HR = 0.69; 95%CI: 0.55-0.87)[18]. These data were similar to a study in the Asia-Pacific region that demonstrated an improvement in OS from 4.2 mo in the placebo group to 6.5 mo in the sorafenib group (HR = 0.68; 95% CI: 0.50-0.93)[17]. The shorter OS in the latter trial compared to the SHARP study could be because of the higher number of cases with extrahepatic metastases, larger tumor diameters, higher ECOG PS scores, and higher AFP levels compared to the SHARP trial. Data from both trials formed the basis for the widespread recommendation of sorafenib for the treatment of advanced liver cancer. It was recently suggested that the relatively low response rates in sorafenib-treated patients could be because sorafenib induces tumor dormancy and a prolonged duration of stable disease (SD). Interestingly, patients with a longer duration of SD had a better OS compared to patients with a shorter duration of SD[30].

In contrast, data from two HCC clinical institutes in Asia showed that selected HCC patients at BCLC stage C had better outcomes with SR compared to other treatment modalities[20,21]. Similarly, a recent study that used the same inclusion criteria as the SHARP trial (BCLC stage C, Child-Pugh class A, ECOG PS ⩽ 2) showed that patients who received SR (n = 68), locoregional ablation therapy (n = 8); transarterial embolization (n = 140); systemic chemotherapy or radiotherapy (CT/RT, n = 96) and sorafenib (n = 11) had a median OS of 33.4 mo, 9.5 mo, 9.2 mo, 6.6 mo, and 15.7 mo, respectively[31]. These data suggested that some advanced HCC patients who had tumors in a single lobe without extrahepatic spread had a better prognosis with SR compared to other methods.

There are currently no studies that have investigated the use of sorafenib after SR for advanced HCC. In our present study, we used the same inclusion criteria as the SHARP study. We included only newly diagnosed, naïve HCC patients in order to avoid the confounding effects of previous therapy. Additionally, all our study patients who underwent SR received no other treatment except for sorafenib prior to tumor recurrence. We used a follow-up time period of > 6 mo because of the difficulty in differentiating early recurrence from a residual tumor. A longer term follow-up is necessary to evaluate therapeutic efficacy. In this study, all the patients in the SR + sorafenib group received sorafenib within 30 d after surgery. This was because (1) comparisons between the two groups would be more reliable if all the patients were at a similar stage of recovery after SR, and (2) sorafenib would inhibit any VEGF-mediated promotion of tumor growth in patients who had a sub-optimal response to SR. It is important to note that sorafenib treatment is usually initiated 2 wk after SR, since sorafenib is known to delay healing.

Our data showed that BCLC stage C HCC patients who received oral sorafenib treatment after SR had a significantly longer TTP and a significantly longer median OS than patients who received only SR. Patients in the SR + sorafenib group also had a lower rate of tumor recurrence and extrahepatic metastasis than the SR only group. Interestingly, our data showed that patients in the SR + sorafenib as well as the SR groups had a longer TTP than the OS of patients in the sorafenib group from the SHARP study (29 mo and 22 mo *vs* 11 mo). These data suggested that it may be advantageous to use sorafenib after SR, rather than sorafenib monotherapy, in order to have better outcomes. Our data also showed that sorafenib was safe and well-tolerated. All sorafenib-related adverse events were resolved with dose reduction treatment, as previously reported[32]. Our data were consistent with a recent study that reported that adjuvant sorafenib therapy after hepatic resection in HCC patients resulted in reduced mortality and prolonged OS, possibly *via* inhibition of tumor growth after tumor recurrence[33].

Sorafenib has been shown to have anti-angiogenic as well as antitumor activities, possibly mediated *via* a number of tyrosine kinases, including VEGF, PDGFRs, Raf, and the phosphatidylinositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways[29,34-37]. Since vascular invasion was shown to be a critical predictor of HCC recurrence[38], it will be important to define further the mechanism of action of sorafenib in order to optimize the clinical management of patients with advanced HCC.

Since the cost of sorafenib therapy in China is almost three times the cost of SR, a few patients with advanced HCC are sometimes recommended SR by experienced physicians after a careful case-by-case assessment. The criteria for allowing SR in this group of patients are very restricted, making it a challenge to study large sample sizes. Although it is important to investigate whether the two groups were comparable for characteristics, such as presence of satellite tumors, and etiology of cirrhosis with HBV/HCV, the small sample size of our study precluded such an analysis. Indeed, the major limitation of this study was

the small sample size. Other limitations were (1) its retrospective nature; and (2) factors such as surgeon preference and the socio-economic heterogeneity of our study population. The decision to be treated with sorafenib was largely based on the condition of the patients, and this could result in an overestimation of the effect of sorafenib after SR. Additionally, our study patients received different HCC treatment modalities (TACE, RAF, Chinese traditional medicines, or experimental immunotherapy) after tumor recurrence or metastasis. OS comparison may be impacted by these confounding factors.

In conclusion, our data showed that BCLC stage C HCC patients with Child-Pugh class A liver function who received oral sorafenib after SR had better postoperative TTP. It is important to validate our data *via* large multicenter randomized controlled trials.

COMMENTS

Background

Patients with advanced hepatocellular carcinoma (HCC) have a poor prognosis. The multi-kinase inhibitor sorafenib is the currently recommended first-line therapy for patients with HCC Barcelona Clinic Liver Cancer (BCLC) Stage C based on data from two recent randomized controlled clinical trials that showed that sorafenib prolonged overall survival (OS) and delayed time to progression (TTP). However, certain BCLC stage C patients with Child-Pugh class A liver function had better outcomes with surgical resection than with sorafenib monotherapy, suggesting a need to re-evaluate the guidelines for the use of sorafenib monotherapy for advanced HCC. This retrospective study evaluated whether sorafenib use after liver resection had an impact on tumor relapse and OS in BCLC stage C HCC patients.

Research frontiers

Although sorafenib is currently the standard of care for advanced HCC, certain patients have better outcomes with surgical resection rather than with sorafenib monotherapy. This study investigated the use of sorafenib after surgical resection in specific groups of patients with advanced HCC and contributes to our ability to improve the clinical management of these patients.

Innovations and breakthroughs

There are currently no studies that have investigated the use of sorafenib after surgical resection (SR) for advanced HCC. The authors' data indicated that sorafenib after SR was safe and well-tolerated. BCLC stage C patients who received sorafenib after SR had significantly longer OS, significantly longer TTP, and a lower rate of recurrence/metastasis compared to patients who received only SR.

Applications

Sorafenib therapy after surgical resection may result in better postoperative TTP in certain populations of HCC BCLC stage C patients with Child-Pugh class A liver function who may not benefit from sorafenib monotherapy. This study calls for re-evaluation of current guidelines for treating advanced HCC.

Peer-review

The manuscript is an interesting study showing the benefit of using adjuvant sorafenib in patients in BCLC C after liver resection. The article is well-organized, and the study objectives are clearly stated in the introduction, pointing out the relevance of this study. The study is built stepwise, and the description of the results is well-written.

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15>