RESEARCH ARTICLE

Sorafenib Continuation after First Disease Progression Could Reduce Disease Flares and Provide Survival Benefits in Patients with Hepatocellular Carcinoma: a Pilot Retrospective Study

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Abstract

Background: Sorafenib is a promising drug for advanced hepatocellular carcinoma (HCC); however, treatment may be discontinued for multiple reasons, such as progressive disease, adverse events, or the cost of treatment. The consequences of sorafenib discontinuation and continuation are uncertain. Materials and Methods: We retrospectively analyzed 88 HCC patients treated with sorafenib from July 2007 to January 2013. Overall survival (OS), post-disease progression overall survival (pOS), and time to disease progression (TTP) were compared for survival analysis. Cox proportional hazard regression was performed to assess the effect of important factors on OS in the overall patient population and on pOS in patients who continued sorafenib treatment. Results: Sorafenib was discontinued and continued in 24 and 64 patients, respectively. The median OS (355 *vs* 517 days respectively; p=0.015) and median post-PD OS (260 *vs* 317 days, respectively; p=0.020) were statistically different between the discontinuation and continuation groups. Neither the median time to first PD nor the time to second PD were significantly different between the 2 groups. In the discontinuation group, 3 of the 24 patients (12.5%) suffered disease outbreaks. In Cox proportional hazard regression analysis after correction for confounding factors, BCLC stage (p=0.002) and PD site (p=0.024) were significantly correlated with pOS in patients who continued sorafenib treatment. Conclusions: Sorafenib discontinuation may cause HCC flares or outbreaks. It is advisable to continue sorafenib treatment after first PD, particularly in patients with Barcelona Clinic Liver Cancer stage B disease or only intrahepatic PD.

Keywords: Hepatocellular carcinoma - sorafenib - discontinuation - continuation - disease progression

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Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth and seventh most frequently diagnosed cancer and second and sixth most frequent cause of cancer death in men and women, respectively (El-Serag et al., 2007; Jemal et al., 2011). According to the Barcelona Clinic Liver Cancer (BCLC) system, hepatectomy and liver transplantation are only suitable for patients with stage A disease (Llovet et al., 1999). Sorafenib, an oral, multikinase inhibitor, provides both antiproliferative and antiangiogenic effects by inhibiting multiple signaling pathways, has been determined in the SHAPP and Asia-Pacific trials to prolong survival in HCC patients, and was recommended in the updated BCLC system for patients with stage C disease (Huynh et al., 2003; Avila et al., 2006; Carlomagno et al., 2006; Wilhelm et al., 2006; Stock et al., 2007; JM et al., 2008; Cheng et al., 2009; Bruix et al., 2011a). Several clinical studies have also demonstrated an improved survival benefit in patients with stage B disease receiving a combination of sorafenib and transcatheter arterial chemoembolization (TACE) (Chung et al., 2013; Park et al., 2012).

Severe adverse events (AEs, grades 3-4) and disease progression (PD) occurred in 37%-45.3% and 35.7%-42.6% of the patients in the previous trials, respectively, potentially leading to sorafenib discontinuation (JM et al., 2008; Cheng et al., 2009). Therefore, even under the ideal conditions of clinical trials with sorafenib alone or in combination with TACE, 19.5%-71.4% of patients discontinued treatment (JM et al., 2008; Pinter et al., 2009; Worns et al., 2009; Yau et al., 2009; Dufour et al., 2010). In clinical practice, where the cost of sorafenib treatment may influence patients' compliance, the discontinuation rate may be even higher. In lung cancer patients, discontinuation of multikinase inhibitors, such as tyrosine kinase inhibitors, affected overall survival (Chaft et al., 2011; Pop et al., 2012; Chen et al., 2013; Yang et

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al., 2013). In HCC, a study conducted on a small sample determined that continuation of sorafenib after first PD had survival benefits (Miyahara et al., 2013). Therefore, we believe that, unlike other therapies, compared with discontinuation, sorafenib continuation after PD may be more beneficial for HCC patients. To determine this association, we retrospectively analyzed a large sample of HCC patients who underwent sorafenib discontinuation/continuation after PD or severe AEs to determine the consequences of sorafenib discontinuation and identify patients who would benefit from sorafenib continuation in the hope of aiding both HCC treatments and the design of further clinical trials.

Materials and Methods

Approval for this study was obtained from the Guangdong General Hospital Ethics Committee. Exemption from informed consent was granted for this retrospective study.

The study population consisted of patients clinically or pathologically diagnosed with HCC (Bruix et al., 2011b) in the Department of Interventional Oncology at Guangdong General Hospital and the Department of Interventional Oncology at the First Affiliate Hospital, Sun Yat-Sen University, between July 2007 and January 2013. Each follow-up included clinical assessments, laboratory tests (international normalized ratio [INR], prothrombin time [PT], prothrombin activity [PTA], alanine aminotransferase [ALT], albumin [ALB], total bilirubin [TBIL], conjugated bilirubin [DBIL], and alpha-fetoprotein [AFP]), and radiological reviews (dynamic contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI]).

Inclusion criteria for this study included: (1) age ≥18 years, male or female; (2) an Eastern Cooperative Oncology Group (ECOG) performance status score 0-1; (3) a Child-Pugh Score ≤7; (4) a BCLC stage of B or C; (5) a life expectancy ≥12 weeks; (6) never having received systemic therapy prior to sorafenib; (7) at least 1 target lesion that could be measured in 1 dimension according to the Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009); (8) patients who had received previous surgery or local therapy (radiotherapy, TACE, or ablation) were eligible for the study, provided that the target lesion had PD according to RECIST and previous therapies were stopped at least 4 weeks before study entry; (9) after sorafenib administration, at least one PD or drug-discontinuation was confirmed; and (10) after discontinuation or first PD, the patients had been followed for at least 1 month before death occurred.

Exclusion criteria included: (1) BCLC staging of A or D; (2) a Child-Pugh score >7; (3) an ECOG performance status score ≥2; (4) severe co-morbidity, such as dysfunction of the heart, liver, kidney, brain, or other system; (5) irregular or non-cooperative follow-ups (average interval between follow-ups during the non-progressive period was ≥2-3 months); (6) allergy to a contrast agent; or (7) sorafenib administration for <1 month.

Treatment

Oral sorafenib was administered at 400 mg b.i.d. Patients were scheduled for laboratory tests and CT or MRI assessments. During treatment, TACE and ablation were scheduled if necessary. Sorafenib administration was suspended during the perioperative period and resumed 3-7 days after local therapies.

Outcomes and assessments

The primary and secondary outcomes of this study were overall survival (OS) and time to progression (TTP), respectively. TTP was measured before and after sorafenib discontinuation (in the discontinuation group) or before and after first PD (in the continuation group). PD was defined as radiologic progression according to RECIST (confirmed by dynamic contrast-enhanced CT or MRI) or death from HCC.

Statistical analysis

SPSS software (version 19.0) was used for the statistical analyses. Independent-samples t-tests (for quantitative data with normality, such as albumin at baseline), Mann-Whitney U tests (for ranked data or quantitative data without normality, such as age/BCLC stage/Child-Pugh class/TBIL/AFP at baseline and treatment duration, and TACE/ablation sessions and comparison between the first and second TTP), or Chi-square tests (for binomial distribution data, such as gender at baseline) were used as appropriate to compare the baseline of the patients. The survival rate was calculated by the Kaplan-Meier method. Survival curves were drawn, and log-rank tests were performed. Cox proportional hazard regression was performed to assess the effect of important factors on OS in the two groups and pOS in the continuation group. All reported P values are 2-sided, and P values of <0.05 were considered significant.

Results

Patient characteristics

Two hundred eight patients treated with sorafenib were screened, and 168 had regular follow-ups. Of these, 20 patients had no confirmed PD, 34 patients were followed for <1 month after drug discontinuation/first PD, and 26 patients had received sorafenib for <1 month. The remaining 88 patients met the inclusion criteria. Twenty-four patients discontinued sorafenib, and 64 continued treatment after first PD. All 88 patients were hepatitis B virus positive. Patient demographic and baseline characteristics are summarized in Table 1. There were no relevant differences between the 2 groups with regard to the cause or severity of liver disease, prognostic characteristics, Child-Pugh class, BCLC stage, or previous therapies.

Treatment

The median duration of sorafenib treatment was 338 days (range: 42-1770). Treatment lasted an average of 130 days (range: 42-169) in the discontinuation group and 512 days (range: 108-1770) in the continuation group, with a

Table 1. Demographic and Baseline Characteristics of the Patients

	Discontinuation N=24	Continuation N=64
Median age (Range)	57 (38- 59)	54 (28- 78)
Gender		
Male	20	57
Female	4	7
BCLC stage		
B	14	34
C	10	30
Macrovascular invasion	8	20
Extrahepatic spread	8	12
Child- Pugh class		
A	24	58
B	0	6
Biochemical analysis		
Median (Range)		
Albumin (g/L)	36.1 (27.7- 44.0)	35.0 (21.1- 48.1)
TBIL (μmol/L)	12.2 (4.6- 27.4)	16.5 (7.0- 45.2)
AFP (mg/L)	694.6 (3.2- 13, 454.0)	699.0 (2.0- 54, 000.0)

*BCLC: Barcelona Clinic Liver Center, TBIL: total bilirubin, AFP: alpha-fetoprotein

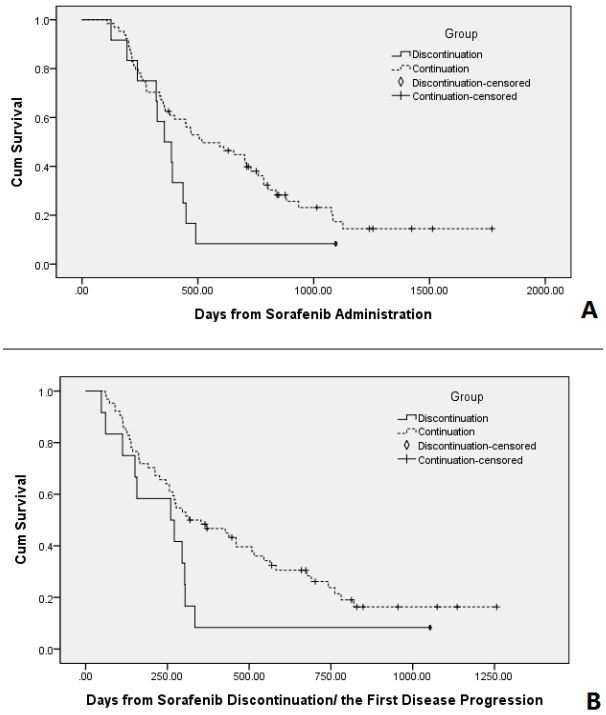

Figure 1. The mOS of the Overall Study Population was 436 days (95%CI: 362-510 days). The mOS in the discontinuation and continuation groups was statistically different (355 *vs* 517 days; 95%CI: 281-429 *vs* 292-742 days, respectively; χ^2=5.935; *p*=0.015). B: After first PD, the pmOS was 295 days (95%CI: 267-323 days). The pmOS in the discontinuation and continuation groups was statistically different (260 *vs* 317 days, 95%CI: 123-397 *vs* 151-483 days, respectively; χ^2=5.414; *p*=0.020)

significant difference between the 2 (*p*<0.001). Reasons for sorafenib discontinuation included PD (20 patients) and severe AEs (4 patients).

During the study, TACE was performed in 67 patients: 14 in the discontinuation group and 53 in the continuation group (median number of TACE sessions: 2, range: 0-10). There was no statistical difference between the discontinuation and continuation groups (2 *vs* 2; range: 0-9 *vs* 0-10, respectively; *p*=0.489). Ablation was performed in 22 patients, 6 in the discontinuation group and 16 in the continuation group (median number of ablation sessions: 0, range: 0-8). There was no statistical difference between the discontinuation and continuation groups (0 *vs* 0; range: 0-7 *vs* 0-8; *p*=0.824).

OS

Seventy-one deaths occurred (22 and 49 in the discontinuation and continuation groups, respectively) in the time interval between first sorafenib administration and the study cutoff date, with a median OS (mOS) of 436 days (95% confidence interval [CI]: 362-510 days). The mOS was significantly between the discontinuation and continuation groups (355 *vs* 517 days; 95%CI: 281-429 *vs* 292-742 days, respectively; χ^2=5.935; *p*=0.015) (Figure 1A).

In the time interval from first PD to the study cutoff date, the post-PD mOS (pmOS) was 295 days (95%CI: 267-323 days). The pmOS in the discontinuation and continuation groups were statistically different (260 *vs* 317 days, 95%CI: 123-397 *vs* 151-483 days, respectively; χ^2=5.414; *p*=0.020) (Figure 1B).

Time to progression

Before discontinuation in the discontinuation group and before the first PD in the continuation group, 84 patients showed PD (20 in the discontinuation group and

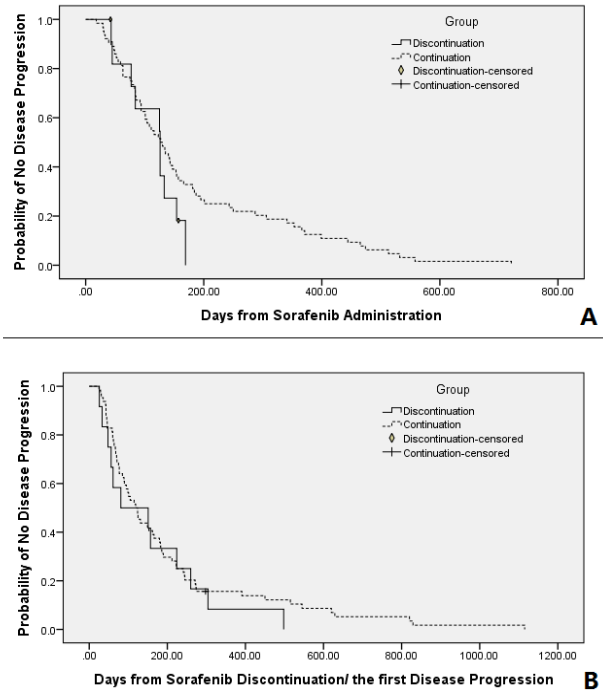

Figure 2. A) Before Discontinuation (in the Discontinuation group) or First PD (in the continuation group), the difference in the mTTP between the 2 groups was not statistically different (126 *vs* 127 days, 95%CI: 95-157 *vs* 96-158 days, respectively; χ^2=2.256; *p*=0.133). B) After drug discontinuation (in the discontinuation group) or first PD (in the continuation group), the difference in mTTP between the 2 groups was not statistically different (81 *vs* 119 days, 95%CI: 0-189 *vs* 88-150 days, respectively; χ^2=0.622; *p*=0.430).

64 in the continuation group). The remaining 4 patients in the discontinuation group had discontinued sorafenib because of AEs; these patients showed PD only after discontinuation. The difference in the median TTP (mTTP) between the 2 groups was not statistically different (126 *vs* 127 days, 95%CI: 95-157 *vs* 96-158 days, respectively; χ^2=2.256; *p*=0.133) (Figure 2A).

After sorafenib discontinuation (in the discontinuation group) or the first PD (in the continuation group), 87 PDs occurred (24 in the discontinuation group, and 63 in the continuation group). The difference in mTTP between the 2 groups was not statistically different (81 *vs* 119 days, 95%CI: 0-189 *vs* 88-150 days, respectively; χ^2=0.622; *p*=0.430) (Figure 2B).

There was no statistically significant difference between the first and second TTP in both the discontinuation (*p*=0.345) and continuation (*p*=0.973) groups.

Cox proportional hazard regression

Univariate analysis was used to screen potential prognostic factors for the 88 patients, including group (discontinuation/continuation, *p*=0.017), gender (*p*=0.047), age (*p*=0.068), BCLC stage (*p*<0.001), Child-Pugh class (CP, *p*=0.953), number of lesions (N, single or multiple, *p*=0.047), maximum lesion diameter (MD, mm, *p*=0.166), and AFP level (≤25 ng/mL, 25-400 ng/mL, or ≥400 ng/mL, *p*=0.003) at administration, as well as treatment with TACE (yes or no, *p*=0.024) or ablation (yes or no, *p*=0.370). Factors with a P<0.10 (group, gender, age, BCLC, N, AFP level, and TACE) were entered into the Cox proportional hazard regression model. Group (*p*<0.001, HR=2.844), gender (*p*=0.008, HR=3.213), and BCLC stage (*p*<0.001, HR=0.310) had a significant correlation with OS.

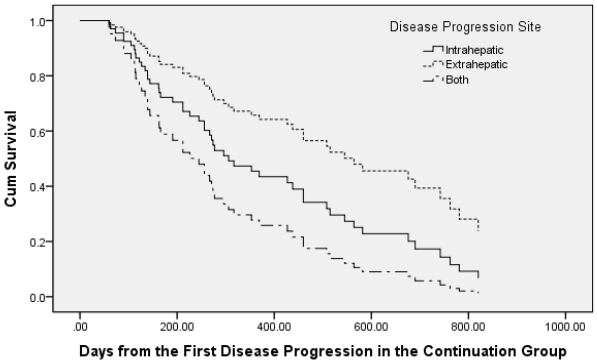

Figure 3. After Correction for Confounding Factors, the PD Site had a Significant Correlation with Post-First PD OS (*p*=0.024) in the Continuation Group. Compared with patients with both intrahepatic and extrahepatic PDs, the odds ratio for the patients with only extrahepatic PD was 0.008 (95%CI: 0.143-0.748), and the odds ratio for the patients with only intrahepatic PD was 0.283 (95%CI: 0.253-1.494)

With regard to the pOS in the continuation group, univariate analysis was used to screen potential prognostic factors, including gender (*p*=0.256), the situation at first PD (age, *p*=0.317;BCLC stage, *p*=0.002;CP, *p*=249;N, *p*=0.296; MD, *p*=0.182; AFP level, *p*=008), the first TTP (TTP1, *p*=0.032), the PD type (increase in diameter, new lesions, or both, *p*=0.340), the PD site (intrahepatic, extrahepatic, or both, *p*=004), the PD type of the intrahepatic lesions (increase in diameter, new lesions, both, or none, *p*=757), the PD type of the extrahepatic lesions and macroscopic vascular invasion (increase in diameter, new lesions/macroscopic vascular invasion, both, or none, *p*=0.202), and the treatment of TACE (yes or no, *p*=0.637). or ablation after administration (yes or no, *p*=0.210). Factors with a *p*<0.10 (BCLC, AFP level, TTP1, and the PD site) were entered into the Cox proportional hazard regression model. BCLC stage (*p*=0.002, HR=0.285) and the PD site [*p*=0.024, HR (intrahepatic/both)=0.008; HR (extrahepatic/both)=0.283] had a significant correlation with pOS (Figure 3).

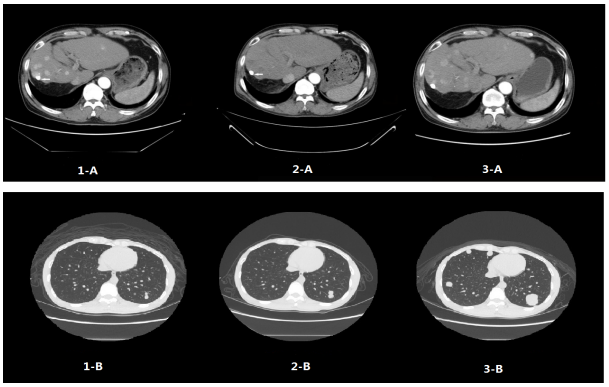

Figure 4. 4-A: Contrast-Enhanced CT Showed Multi-Focus, Abnormally Enhanced Lesions (largest in the S5 segment, 21×19 mm) in a 58-year-old Male before Sorafenib Administration (4-A-1). Before discontinuation (157 days), most of the previous lesions were only slightly enhanced, with shrinkage in the S5 lesion to 14×14 mm (4-A-2). After discontinuation due to cerebral hemorrhage (26 days), lesions were abnormally enhanced and accompanied by an obvious deterioration in both number and diameter (4-A-3). 4-B: Contrast-enhanced CT showed multiple metastases to the lungs, with a maximum diameter for the 2 lesions in the outer basal segment of the lower lobe in the left lung being 8 and 5 mm, respectively, in a 46-year-old male before sorafenib administration (4-B-1). Before discontinuation (42 days), the 2 lesions enlarged to 10 and 8 mm, respectively, with all other lesions being stable (4-B-2). After discontinuation (76 days), the 2 lesions merged into 1 lesion 30×25 mm in diameter, with new lesions in the medial segment of the middle lobe and basal segment of the lower lobe in the right lung and enlargement of the lesion in the lateral segment of the middle lobe (4-B-3)

Table 2. HCC Outbreak

	Discontinuation/First PD			Outbreak		
	Date	Intrahepatic	Extrahepatic	Date	Intrahepatic	Extrahepatic
1	7/14/10	M, Md 83 mm	None	8/16/10	M, N, Md 105 mm	None
2	2/24/11	S, Md 51 mm	ML, Md 10 mm	5/11/11	M, N, Md 78 mm	ML, N, Md 20 mm
3	11/4/11	M, Md 14 mm	None	11/30/11	M, N, Md 21 mm	None

S: Single lesion; M: multiple lesions; Md: maximum diameter, ML: multiple metastases in lung; N: multiple new lesions; Pt: tumor thrombus in portal vein; PD: disease progression

Disease outbreaks

From the first day of sorafenib discontinuation to the cutoff date of follow-up, 3 of the 88 patients (3.4%, all in the discontinuation group) had PD, meaning their lesions (intrahepatic, 3 cases; extrahepatic, 1 case) had significant progression within 3 months (Table 2, Figure 4).

Discussion

The objective for this study was to assess the consequences of sorafenib discontinuation and identify patients who would benefit from sorafenib continuation. Although there was no statistically significant change in mTTP, mOS and pmOS were both significantly different between the discontinuation and continuation groups. Three patients in the discontinuation group experienced disease outbreaks after a short period of sorafenib discontinuation, with the shortest discontinuation-to-outbreak period being 33 days.

Clinically, sorafenib is most commonly used in HCC patients with BCLC stage B or C disease. In previous reports, sorafenib was discontinued regardless of administration alone or in combination with TACE and under ideal situations (i.e. with rigorous follow-ups and no concern for expense) (JM et al., 2008; Cheng et al., 2009; Worns et al., 2009; Pinter et al., 2009; Dufour et al., 2010). And a meta-analysis also showed that sorafenib exerted significant curative effects in hepatocellular carcinoma (Wang et al., 2013). However, variation in the proportion of discontinuation might suggest a disagreement or different estimate of the consequences and risks for sorafenib discontinuation (Berk et al., 2013). A program supported by the China Charity Federation donates sorafenib treatment after administration for 3 months if patients are believed to benefit from continuation, regardless of the presence of PD. Without the additional financial burden for patients, most Chinese oncologists choose to continue sorafenib administration after first PD if it will provide further survival benefits. Based on these situations, this study focused on HCC patients treated with sorafenib, especially those who continue sorafenib after first PD to evaluate the survival benefit of sorafenib continuation. This study determined that, unlike other antineoplastic treatments for HCC, sorafenib discontinuation severely diminished prior efficacy, potentially causing harm to the patients. However, sorafenib continuation after first PD may provide further survival benefits. This study also determined that this benefit was correlated with BCLC stage and Child-Pugh class, but was not affected by gender, age, first TTP, number of lesions, maximum diameter of the lesions, change in AFP level the type of disease progression, or treatment with TACE or ablation after administration. Therefore, it is advisable to continue sorafenib treatment after first PD, particularly in patients with BCLC stage B disease or only intrahepatic PD.

There may be two reasons for this phenomenon. First, sorafenib controls tumor growth by inhibiting multiple signaling pathways. Thus, under continuous administration, some products of "upstream" pathways may accumulate. Once inhibition of the "downstream" target is removed, these accumulated products may act as strong stimuli on the receptors inhibited by sorafenib and subsequently boost cellular processes, such as angiogenesis, leading to growth of both the primary lesion and any metastases. Second, because signaling pathways are integrated, inhibition of one may potentially activate others. This has been proven by recent studies, where the inhibition of the Ras/Raf/MAPK pathway by sorafenib simultaneously increased the phosphorylation of mTOR and the activation of the PI3K/AKT/mTOR pathway, which is critical for the development and proliferation of HCC (Strumberg, 2005; Huynh et al., 2009; Gedaly et al., 2010). As a result, continuous sorafenib administration may upregulate pathways, such as the PI3K/AKT/mTOR pathway, as a compensatory mechanism. With sudden sorafenib discontinuation, cells may not have enough time to adjust and silence this "upregulation". The combination of these mechanisms may cooperatively induce a flare or outbreak of HCC. But both deductions need to be confirmed by further studies.

This retrospective study has some limitations. First, the sample size may be inadequate to comprehensively determine the consequences caused by sorafenib discontinuation and prognostic factors for sorafenib continuation. Second, a treatment plan for initial drug reduction to eventual discontinuation may be more advisable, but this could not been confirmed by our study. Prospective studies with strict follow-up are needed to fully determine the consequences of sorafenib discontinuation and delineate those patients that would benefit from treatment continuation.

In conclusion, this primary, retrospective study determined that sorafenib discontinuation may lead to disease flare and potential disease outbreak for HCC patients. It is advisable to continue sorafenib treatment after first PD, particularly in patients with BCLC stage B disease or only intrahepatic PD.

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