Transarterial Chemoembolization Plus Sorafenib: A Sequential Therapeutic Scheme for HCV-Related Intermediate-Stage Hepatocellular Carcinoma: A Randomized Clinical Trial

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Key Words. Hepatitis C virus • Hepatocellular carcinoma • Liver cirrhosis • Sorafenib • Time to progression

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ABSTRACT

Background. Recurrence of hepatocellular carcinoma (HCC) is a major problem after surgical or ablative treatments. The aim of this prospective, single-center, placebo-controlled, randomized, double-blind clinical study was to evaluate the effectiveness of transarterial chemoembolization (TACE) combined with sorafenib as a sequential treatment regimen in delaying time to progression (TTP) of intermediate-stage HCC in patients with chronic hepatitis C virus (HCV) infection.

Material and Methods. Between October, 2007 and January, 2011, 80 HCV-infected patients with Barcelona Clinic Liver Cancer stage B HCC underwent the TACE procedure. All had Child-Pugh class A disease. They were randomized 1:1 to receive sorafenib at a dose of 400 mg

twice daily or placebo. Endpoints were the TTP and the rates of adverse events and toxicity.

Results. Sixty-two of 80 patients (77%), 31 in the sorafenib group and 31 in the control group, completed the study. The median TTP was 9.2 months in the sorafenib group and 4.9 months in the placebo group (hazard ratio, 2.5; 95% confidence interval, 1.66–7.56; $p < .001$). Metachronous, multicentric HCC progression occurred less frequently in sorafenib-treated patients ($p < .05$). Adverse reactions to sorafenib caused withdrawal from the study of 9 (22%) patients.

Conclusion. A conventional TACE procedure followed by sorafenib treatment resulted in a significantly longer TTP in patients with intermediate-stage HCV-related HCC, with no unexpected side effects. *The Oncologist* 2012;17:359–366

INTRODUCTION

Based on available treatments, prevention of hepatocellular (HCC) progression remains the most important challenge to improve prognosis. Although a radical approach seems to ameliorate HCC outcome, recurrence rates are not affected [1]. In hepatitis C virus (HCV)-infected people, HCC is stringently dependent on cirrhosis development. Cirrhosis that follows chronic hepatitis is indeed a well-established precancerous state [2]. Hepatocytes undergo intense mitogenic stimulation,

induced by elevated levels of growth factors and inflammatory cytokines [3]. Mutations and promotion lead to a higher risk for developing HCC [4].

No benefit has been demonstrated with the administration of systemic or regional chemotherapy, including oral acyclovir [5], adoptive immunotherapy [6], and intra-arterial radioiodine injection [7]. Also, no effect has been reported using cytokine-induced killer cell immunotherapy [8]. Carmofur, a pyridine analog, was found to lead to a longer disease-

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free survival (DFS) interval, but it had no effect on overall survival (OS) [9]. No significant effect on DFS or OS outcomes was recorded with i.v. epirubicin and oral capecitabine [10]. Similar results were achieved with oral tegafur, a 5-fluorouracil prodrug [11], whereas the OS duration appeared to be shorter in the group receiving uracil and tegafur [12]. Thus, the development of new and effective therapies for HCC is urgently needed.

Sorafenib, a multikinase inhibitor acting on vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and Raf signaling, is able to inhibit tumor growth and neoangiogenesis [13]. The successful clinical application of sorafenib stems from the demonstration of a survival advantage following its systemic administration to patients with advanced HCC. In a multicenter, phase III, double-blind, placebo-controlled trial carried out on 602 patients with advanced HCC, the median survival time and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo [14]. A further phase III trial confirmed these results in patients from the Asia-Pacific region [15]. Overall, the survival benefit of sorafenib was also seen in some patients who experienced failure with previous local HCC treatment.

Transarterial chemoembolization (TACE) has become the standard of care for patients with HCC not suitable for surgical or ablative treatments when metastases and advanced liver disease are lacking [16]. This procedure, however, is a potent stimulator of local angiogenic factors capable of promoting tumor regrowth, thus increasing the risk for metastasis and worsening outcome [17, 18]. Whether or not sorafenib might be used to target upregulation of TACE-induced angiogenic factors and hence potentially enhance its efficacy remains a reasonable hypothesis [19].

Here, we describe the results of a prospective, placebo-controlled, randomized, double-blind clinical study that we conducted to evaluate whether or not TACE combined with sorafenib could significantly extend the TTP of HCV-infected patients with intermediate-stage HCC.

MATERIALS AND METHODS

Patient Recruitment

The final protocol was approved by the Italian Medicines Agency (AIFA) on behalf of the National Health Service to support independent research contributing to the knowledge of drug efficacy, effectiveness, and safety and improving the appropriateness of drug use. The study (AIFA Register, FARM7SJ7X9) [20] was also approved by the local ethics committee of the Azienda Ospedaliero-Universitaria Policlinico of Bari (ID 1444/CE). Written informed consent was obtained from 80 adult patients with HCC without neoplastic occlusion of the portal vein or extrahepatic spread and potentially eligible for therapeutic procedures. Recruitment started in October, 2007 and was closed in January, 2011.

Patient eligibility was established on the basis of the following inclusion criteria: Barcelona Clinic Liver Cancer (BCLC) stage B HCC [1], anti-HCV and HCV RNA positivity, Child-Pugh class A cirrhosis; and Eastern Cooperative Oncol-

ogy Group (ECOG) performance status score of 0–1, no prior targeted antiangiogenic therapy or at least 4 weeks since prior systemic chemotherapy, at least 4 weeks since prior antiviral therapy, no major renal impairment, no current infections requiring antibiotic therapy, not on anticoagulation or suffering from bleeding disorders, no unstable coronary artery disease or recent myocardial infarction, a platelet count $\geq 40,000/\mu\text{L}$, a hemoglobin level $\geq 8 \text{ g/dL}$, total bilirubin $\leq 3 \text{ mg/dL}$; alanine aminotransferase $\leq 5 \times$ the upper limit of normal, a prothrombin time (PT) international normalized ratio ≤ 2.3 , an absolute neutrophil count $> 1,500/\text{mm}^3$, the ability to understand the protocol and to agree with it and sign a written informed consent, and the absence of pregnancy.

Exclusion criteria included any concomitant cancer distinct from HCC, renal failure requiring hemo- or peritoneal dialysis, congestive heart failure, hepatitis B virus or HIV infection, drug or alcohol abuse ($\geq 25 \text{ g/day}$), cardiac ventricular arrhythmia, thromboembolic event, hemorrhage or bleeding in the previous 4 weeks, and major surgery within 8 weeks prior to enrollment.

Study Coordination

The study was coordinated by the Liver Unit of the Department of Internal Medicine and Clinical Oncology, University of Bari Medical School, including the overall management, registration, database analysis, and quality assurance.

Data Safety Monitoring Board

An independent data safety monitoring board closely monitored the proper conduct of the study. The committee consisted of three independent physicians (one internist, one surgeon, and one oncologist) who decided on the final diagnostic classification of critical clinical events. Drug toxicities were assessed using National Cancer Institute (NCI) common toxicity criteria [21]. Toxicity was evaluated biweekly during the first month and monthly during the remaining treatment time. Drug-related adverse events of grade 3 or 4 were considered unacceptable and patients experiencing such events were withdrawn from the study.

The study was performed according to the principles for guidance of good clinical practice [22] and the current revision of the Declaration of Helsinki [23].

Study Design

AIFA FARM7SJ7X9 is a prospective, single-center, placebo-controlled, randomized, double-blind clinical study with two parallel groups receiving conventional TACE treatment plus sorafenib (Bayer HealthCare, Leverkusen, Germany) or TACE plus placebo. Patients were allocated as having intermediate-stage HCC (BCLC stage B) if they were found to have a single nodule $\geq 5 \text{ cm}$ or a multifocal tumor with more than three HCC nodules. Eligible patients were assigned to receive oral treatment with sorafenib starting 30 days after TACE treatment. TACE was performed through the transfemoral route. A 5-Fr catheter was advanced to the superior mesenteric artery to confirm the patency of the portal vein trunk on post-mesenteric portography. Common hepatic or celiac arteriogra-

phy was performed to assess the number and location of lesions, tumor size, feeding artery, and presence of anatomic variations. A coaxial microcatheter (2.7 Fr or 3.0 Fr) was selectively inserted through a 5-Fr catheter into the feeding artery as close to the lesion as possible. In cases of multiple foci occupying the hepatic lobe, the right or left or both hepatic arteries were treated. Doxorubicin (30 mg) and mitomycin C (10 mg) with 10 mL of iodinated nonionic contrast media and 20 mL of iodinated oil (Lipiodol®, Guerbet, Villepinte, France) were delivered to the cannulated feeding artery. Subsequently, the feeding artery was embolized using gelatin sponge pledgets in order to temporarily occlude the arterial supply and consequently ensure prolonged permanence of the injected drug mixture in the tumor-hosting region, thus enhancing tumor necrosis. This procedure also prevented the drugs from gaining access to the systemic circulation. Patients were given intra-arterial lidocaine (10 mg) between 10-mL aliquots of chemoembolization material to reduce pain.

All patients had a biopsy-proven histological diagnosis of cirrhosis. HCC was diagnosed using imaging techniques such as dynamic multiphasic spiral computed tomography (CT) scan and dynamic contrast-enhanced magnetic resonance imaging (MRI). In typical HCC, the signal intensity appears highly attenuated in the arterial phase and poorly attenuated or washed out in the delayed phase (~3 minutes after initiation of contrast injection) [24]. Extrahepatic metastatic lesions were looked for and vascular invasion of the portal vein was excluded.

Short- and long-term outcome measures included the post-TACE complication rate, treatment-related mortality rate, complete ablation rate, and tumor progression pattern. A complication was defined as any adverse event after TACE, excluding pain or a transient febrile reaction. Treatment-related mortality was defined as any death occurring within 30 days following a TACE procedure.

Tumor response was assessed by CT scan 30 days after TACE. Complete response (CR) was defined as the absence of contrast enhancement within the original tumor. Any contrast-enhancing areas within the targeted tumor on a post-TACE CT scan indicated incomplete tumor ablation. These criteria were implemented and evaluated in terms of patterns of Lipiodol® retention in the target lesions reflecting tumor necrosis [25]. Lipiodol® uptake was considered compact if the oily contrast medium was distinctly visible and well scattered throughout the viable tumor [26].

Local progression was defined as tumor recurrence within or at the periphery of the original ablated lesion. Metachronous, multicentric intrahepatic recurrence was defined as any new tumor that occurred in Couinaud's segments different from the original tumor site. The term extrahepatic recurrence was applied to any recurrence outside the liver. All images from CT and MRI scans were independently assessed by two expert radiologists.

Sorafenib was administered in step with the diagnosis of a tumor CR on CT scan evaluation 30 days after TACE treatment. As recently emphasized [27], in this sequential therapeutic scheme, sorafenib is used as an adjuvant therapy to prevent

new HCC lesions after visible areas have been eradicated by the TACE procedure and to target tumor cells that escape local treatment. Patients were given sorafenib at a dosage of 400 mg twice daily and were monitored for the occurrence of adverse events. In cases of NCI grade 3 or 4 toxicity, treatment was discontinued and patients were withdrawn from the study. Dropout patients were permitted to receive reduced doses of sorafenib.

The TACE procedure was repeated at intervals of 4–6 weeks until complete necrosis of the tumor was detected. To avoid hepatic failure, patients who did not achieve a CR after four TACE procedures were excluded from the study. In no case did the HCC occlude the portal vein vessels or spread extrahepatically. Sorafenib administration was stopped following evidence of tumor progression.

Study Objectives

This study was designed to reveal the potential superiority of the TACE procedure plus sorafenib over TACE alone in patients with intermediate-stage HCC. The primary endpoint was the TTP, defined as the time from the date of randomization to the date of disease progression. In the absence of progression, TTP was censored at the date of the last clinical assessment. Further endpoints were the rate of adverse events and grade of toxicity.

Randomization

Patients were randomly assigned, on 1:1 basis and in a blinded fashion, to the sorafenib (400 mg twice daily) arm or placebo arm. The investigator received a set of sealed envelopes via the distributing local pharmacy. Envelopes containing information on the patient's trial medication were not opened throughout the study.

Schedule and Follow-Up

Pretreatment evaluation included demographic data, a medical history, a physical examination, an evaluation of comorbidities, and the use of concomitant medications. In addition to routine laboratory parameters, measurement of α -fetoprotein (α -FP), the HCV RNA level and HCV genotype, as well as a complete radiological study were carried out to meet the inclusion criteria. During treatment, patients were visited biweekly during the first month and monthly thereafter. A contrast-enhanced ultrasonography (CEUS) was adopted to detect intrahepatic HCC progression. In addition, each visit included a chest radiograph, laboratory measurements, physical examination, and performance status assessment. Sorafenib-related toxicities were monitored until tumor progression. CT- and MRI-based characterization was carried out when tumor progression was suspected using CEUS.

Statistical Analysis

All data are presented as the percentage of patients or mean with standard deviation. Categorical variables were compared using Fisher's exact test where appropriate, and continuous variables were compared using the *U*-test. TTP curves were obtained using the Kaplan–Meier method and differences be-

Figure 1. Flow diagram of the randomized controlled trial design.

Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma.

tween the groups were compared using the log-rank test. Prognostic factors after recurrence were assessed using Cox regression analysis.

RESULTS

In total, 80 patients with HCC who met the inclusion criteria underwent the TACE procedure between October 2007 and January 2011. They were randomly assigned to either the sorafenib arm ($n = 40$) or the placebo group ($n = 40$) (Fig. 1). As summarized in Table 1, there were no significant differences in the baseline characteristics of the patients included in the two arms. The median patient age was >70 years in both arms and there was a male predominance. Liver cirrhosis was present in all patients, as shown using histological diagnosis. All patients had chronic HCV infection and were viremic. HCV genotype 1 was largely prevalent. Well-preserved liver function was found in all patients. The mean serum levels of α -FP, the number (either solitary or multiple) of HCC nodules, and the mean tumor size were fairly comparable between the two groups. Overall, further TACE treatments were required to achieve complete tumor ablation in nine and eight patients belonging to the sorafenib and control groups, respectively.

Dropout Patients

During the study period, 18 patients (nine in the sorafenib group and nine in the control group) were prematurely withdrawn from the trial. Moreover, NCI grade 3 and 4 toxicities led to drug interruption in the sorafenib group. Four patients experienced hand-foot skin reaction, three had adverse hematological events including severe anemia, neutropenia, and thrombocytopenia, and one had uncontrollable diarrhea. The remaining patient withdrew consent (Table 2). In the control group, nine patients dropped out for the following reasons: three patients denied their approval to proceed with the study, two complained of logistical problems, and the other four missed the appointments for the study. The main adverse event was post-TACE syndrome, which occurred in nine (22.5%) and 10 (25%) sorafenib-treated and control patients, respectively. None of them required specific treatment, other than

surveillance. No additional dropouts were recorded among the remaining 62 patients.

Tumor Progression

Intrahepatic tumor progression occurred in 21 (68%) patients in the sorafenib group and in all 31 patients (100%) in the placebo group. No extrahepatic spread was detected. The median TTP was significantly longer in the sorafenib group than in the control group ($9.2 \text{ months} \pm 5.8 \text{ months}$ versus $4.9 \text{ months} \pm 3.2 \text{ months}$; $p < .001$; hazard ratio, 2.5; 95% confidence interval, 1.66–7.56) (Fig. 2).

The proportion of patients who experienced intrahepatic tumor recurrence within 6 months of the TACE procedure was significantly higher in the control group than in the group of sorafenib-treated patients. Such early progression occurred in 22 (71%) control patients and in only seven (22%) patients in the study arm ($p = .005$). However, the proportion of HCC patients with local progression was not significantly different between the two groups in that it occurred in 14 (45%) and 16 (52%) sorafenib-treated patients and control patients ($p = .3$), respectively. Metachronous, multicentric tumor progression occurred in seven (22%) and 15 (48%) patients belonging to the sorafenib and control groups ($p < .05$), respectively.

Cox regression analysis stratified by disease-free patients and relapsers in the sorafenib-treated group indicated that age, HCV RNA serum level, HCV genotype, α -FP level, number of tumor nodules, mean tumor dimensions, and liver function parameters (including serum bilirubin, PT, and serum albumin) were not prognostic predictors of HCC recurrence (Table 3).

DISCUSSION

Our data indicate that, compared with placebo, conventional TACE followed by sorafenib administration led to a significantly longer median TTP in HCC patients. To substantiate the beneficial effect of sorafenib, given the confounding role of underlying cirrhosis, it was critical to select patients with well-preserved liver function (Child-Pugh class A), with an ECOG performance status score of 0–1, and without neoplastic invasion of intrahepatic vascular structures or extrahepatic spread.

The design of the present study included a double-blind randomization phase to minimize the likelihood of erroneous conclusions regarding the efficacy of sorafenib, and results were compared with the outcome in a homogeneous control group that met the same inclusion criteria. Early evidence of HCC progression is a critical point in the assessment of sorafenib efficacy. Indeed, short surveillance intervals and CEUS provided unequivocal advantages in that HCC nodules were detected when they were $<20 \text{ mm}$ in diameter ($15.3 \text{ mm} \pm 2.1 \text{ mm}$).

Sorafenib is likely to delay disease progression in patients with resected or ablated HCC by inhibiting both tumor growth and neoangiogenesis as a result of blocking the molecular components of Raf–mitogen-activated protein kinase/extracellular signal–related kinase (ERK) kinase–ERK signaling, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR- β [14, 28], which are the key pathways in the pathogenesis of HCC [29]. We found that the rate of metachronous, multicentric progres-

Table 1. Baseline clinical characteristics of patients treated with sorafenib and those of the control group

	Sorafenib	Placebo	<i>p</i>
<i>n</i> of patients	31	31	
Epidemiology			
Age (mean ± SD), yrs	73 ± 4	72.8 ± 6.4	.81
Gender (male/female)	18/13	19/12	
Virology			
HCV antibody, <i>n</i> (%)	31 (100)	31 (100)	
HCV RNA (mean ± SD), IU/mL	254,735 ± 220,714	325,700 ± 259,545	.68
HCV genotype, <i>n</i> (%)			
1	22 (71)	20 (64)	.30
2	9 (29)	11 (36)	.36
Liver function			
Child-Pugh class A, <i>n</i> (%)	31 (100)	31 (100)	
Presence of cirrhosis, <i>n</i> (%)	31 (100)	31 (100)	
Total bilirubin (mean ± SD), mg/d	1 ± 0.4	0.96 ± 0.6	.18
Prothrombin INR (mean ± SD)	1.3 ± 0.17	1.23 ± 0.2	.15
Serum albumin (mean ± SD), g/dL	3.4 ± 0.4	3.5 ± 0.5	.28
Platelet count (mean ± SD), ×10 ⁴ /μL	12.9 ± 5.9	11.6 ± 7.8	.24
ECOG performance status score			
0 (normal activity)	26 (86)	24 (77)	.31
1 (symptoms)	5 (24)	7 (23)	.27
Neoplasia			
<i>n</i> of HCC nodules (single/multiple)	16/15	18/13	1.0
Tumor size (mean ± SD), mm	73.6 ± 22.2	69.4 ± 33.4	1.0
α-FP (mean ± SD), n.v. <14 ng/mL	87 ± 108	101 ± 145	.69

Abbreviations: α-FP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; n.v., normal value; SD, standard deviation.

Table 2. Drug-related adverse effects

	Sorafenib (<i>n</i> = 40)		Placebo (<i>n</i> = 40)	
	All (%)	Grade 3 or 4	All (%)	Grade 3 or 4
Alopecia	0	0	0	0
Anorexia	3 (7.5)	1 (2.5)	4 (10)	2 (2.5)
Diarrhea	4 (10)	1 (2.5)	3 (7.5)	0
Fatigue	9 (22.5)	3 (7.5)	3 (7.5)	2 (2.5)
Hand-foot skin reaction	4 (10)	4 (10)	0	0
Hematological event	5 (13)	3 (7.5)	0	0
Hypertension	6 (15.3)	0	4 (10)	0
Nausea	7 (17.5)	1 (2.5)	3 (7.5)	0
Rash/desquamation	8 (20)	4 (10)	1 (2.5)	0

Figure 2. Kaplan-Meier analysis of time to progression (TTP). Among 62 patients, 31 received sorafenib and 31 received placebo. The median TTP was 9.2 months in the sorafenib group and 4.9 months in the placebo group.

Table 3. Comparison of clinical parameters in disease-free and relapsed in sorafenib-treated patients

	Relapsed	Disease free	<i>p</i>
<i>n</i> of patients	21	10	
Epidemiology			
Age (mean ± SD), yrs	73 ± 4	72.8 ± 6.4	.21
Virology			
HCV RNA (mean ± SD), IU/mL	227,800 ± 116,821	293,827 ± 240,622	.87
HCV genotype, <i>n</i> (%)			
1	15 (71)	6 (60)	.30
2	6 (29)	4 (40)	.36
Liver function			
Total bilirubin (mean ± SD), mg/dL	1.4 ± 0.9	0.8 ± 0.3	.1
Prothrombin INR (mean ± SD)	1.28 ± 0.18	1.23 ± 0.1	.63
Serum albumin (mean ± SD), g/dL	3.2 ± 0.26	3.3 ± 0.3	.47
Platelet count (mean ± SD), ×10 ⁴ /μL	11.7 ± 6.3	11.5 ± 10.7	.31
Neoplasia			
<i>n</i> of HCC nodules (single/multiple)	12/9	4/6	1.0
Tumor size (mean ± SD), mm	67.4 ± 26	66 ± 8.6	.45
α-FP <50 ng/mL, <i>n</i> (%)	13 (62)	5 (50)	.2

Abbreviations: α-fetoprotein, α-FP; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; SD, standard deviation.

sion of HCC was substantially lower in sorafenib-treated patients, whereas the proportion of local progression was comparable with that found in the control group. The clinical importance of these findings is further emphasized by the knowledge that HCC progression distant from the primary site appeared late in time. It is likely that metachronous, multicentric HCC nodules originate from de novo hepatocarcinogenesis and are effectively influenced by sorafenib treatment, which has a smaller effect on local HCC progression. Indeed, long-term follow-up studies in patients with HCV-related HCC showed a higher frequency of metachronous, multicentric progression than in patients with HCC arising from different etiologies [30].

This likely reflects the high carcinogenic risk of nontumoral areas in HCV-related HCC. It is known that the pathophysiology of hepatocarcinogenesis is tightly linked to the evolution of underlying cirrhosis, which accelerates cancer formation through different pathways, such as chromosomal instability and alterations in the microenvironment that stimulate cell proliferation in HCV-related damage [31]. In addition, HCV-related hepatocyte necrosis and chronic inflammation may be closely involved in the pathophysiology of HCC progression in chronically HCV-infected patients who have had complete HCC resection or ablation [32]. Hence, it was postulated that HCV elimination would help prevent HCC progression by clearing the carcinogenic field and eliminating the chances of novel tumorigenesis [33].

The question of why certain molecularly defined HCC subgroups show a poor or no response to sorafenib is difficult to answer. No predominant or pathognomonic molecular mech-

anisms have been described to explain why a single targeted agent does not achieve clinical CR in HCC patients. Molecular alterations may differ depending on the etiology, activity, and duration of the underlying liver injury, thus influencing the response to therapy [34]. No independent predictor of HCC progression was detected among several clinical and laboratory parameters, including tumor burden, number of HCC nodules, and α-FP level. Indeed, these conventional indicators of HCC progression do not seem to be appropriate. Promising innovations, which delineate gene signatures pertaining to premalignant conditions [35], are coming from molecular biology. Serum or tissue-based molecular biomarkers are eagerly awaited to predict HCC progression.

Common side effects, including hand-foot syndrome, erythema, hyperbilirubinemia, hematological toxicity, and diarrhea, were noted in 22% of sorafenib-treated patients. Though recognized as common side effects of antikinases molecules, they are a leading problem in the clinical management of these patients. Dose reductions and pauses in the administration of sorafenib may prevent the attainment of therapeutic benefit in the adjuvant setting. Different treatment strategies should be recommended for this subgroup of patients, who deserve further consideration in terms of tailored dose and treatment schedules.

In conclusion, our data indicate that sorafenib administered as a sequential modality holds promise to become a useful adjuvant treatment to support the current TACE procedure for patients with HCV-related, intermediate-stage HCC. Obviously, our results need confirmation in a larger, well-designed,

phase III clinical trial, which should include a follow-up period long enough to demonstrate an overall survival advantage.

Additional administration modalities can also be envisaged and should be thoroughly examined. Recent reports indicate that improvements in the control of HCC growth and in the prevention of HCC progression can be achieved using concurrent sorafenib and transarterial therapy in patients receiving sorafenib 2–4 weeks before transarterial therapy [19], using continuous administration of sorafenib starting 7 days prior to TACE with doxorubicin [36], and using sorafenib combined with concurrent TACE with doxorubicin-eluting beads [37].

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