Sudden cardiac death in a patient with advanced hepatocellular carcinoma with good response to sorafenib treatment: A case report with literature analysis

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Abstract. Hepatocellular carcinoma (HCC) is the principal primary liver tumor, representing the third largest cause of cancer-associated death worldwide. The actual reference standard systemic treatment for advanced HCC is represented by sorafenib, a multi-targeted orally active small-molecule tyrosine kinase inhibitor. Sorafenib has exhibited a good general safety profile in multiple clinical trials. However, adverse drug-associated events are common, occasionally severe, and special attention should be paid to cardiovascular adverse events, particularly in patients with risk factors or known heart disease. In the present study, the case of a patient with no known cardiovascular risk factors affected by highly enhancing advanced HCC in cirrhotic liver, who died during successful sorafenib monotherapy, is reported.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, with an incidence of approximately 780,000 new cases worldwide each year. It is also the third largest cause of cancer-associated death, with 745,000 deaths per year (1). Chronic liver disease, particularly cirrhosis, is the major risk factor for HCC development.

According to the Barcelona Clinic Liver Cancer (BCLC) staging system (2), advanced HCC is defined as follows: Unresectable HCC with extrahepatic spread (metastases or lymph nodes involvement) and/or vascular invasion (portal or segmental invasion) and/or systemic symptoms; Eastern Cooperative Oncology Group performance status 1 or 2; Child-Pugh score not higher than class B (3,4).

Sorafenib is a multi-targeted, orally active small-molecule tyrosine kinase inhibitor (TKI) that inhibits RAF kinase and the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathway (5). Sorafenib monotherapy is the actual reference standard systemic treatment for advanced HCC, as demonstrated in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial (6). Sorafenib has demonstrated a good safety profile in multiple clinical trials. However, adverse drug-associated events are common, sometimes severe, and particular attention should be paid to cardiovascular adverse events, particularly in patients with risk factors or known heart disease (6-8).

Provided with this evidence, our present study reports the case of a patient affected by highly enhancing advanced HCC in cirrhotic liver, who died during successful sorafenib monotherapy.

Case report

In March 2014, a 51-year-old man presented to the emergency department (ED) with intense and persistent pain in the upper right abdomen. A former history of drug addiction, no relevant disease and no cardiovascular risk factors were referred. In the ED, a chest X-ray, electrocardiogram (ECG) and measurement of troponin I was performed, all revealing no alterations. Abdominal ultrasound demonstrated a cirrhotic pattern of the right hepatic lobe, with multiple and variously sized confluent nodules; portal vein thrombosis was also present, and HCC in cirrhotic liver was suspected. Blood tests revealed signs of liver failure [international normalized ratio (INR) 1.7, albumin, 2.7 g/dl, total bilirubin, 3.1 mg/dl] with a Child-Pugh score of B8 and a Model for End stage Liver Disease (MELD) score of 17, hyper-transaminasemia (glutamic oxaloacetic transaminase, 94 U/l, glutamic pyruvic transaminase 41/l), serological evidence of past hepatitis B virus infection, anti-hepatitis C virus positivity, and a marked increase in α-fetoprotein

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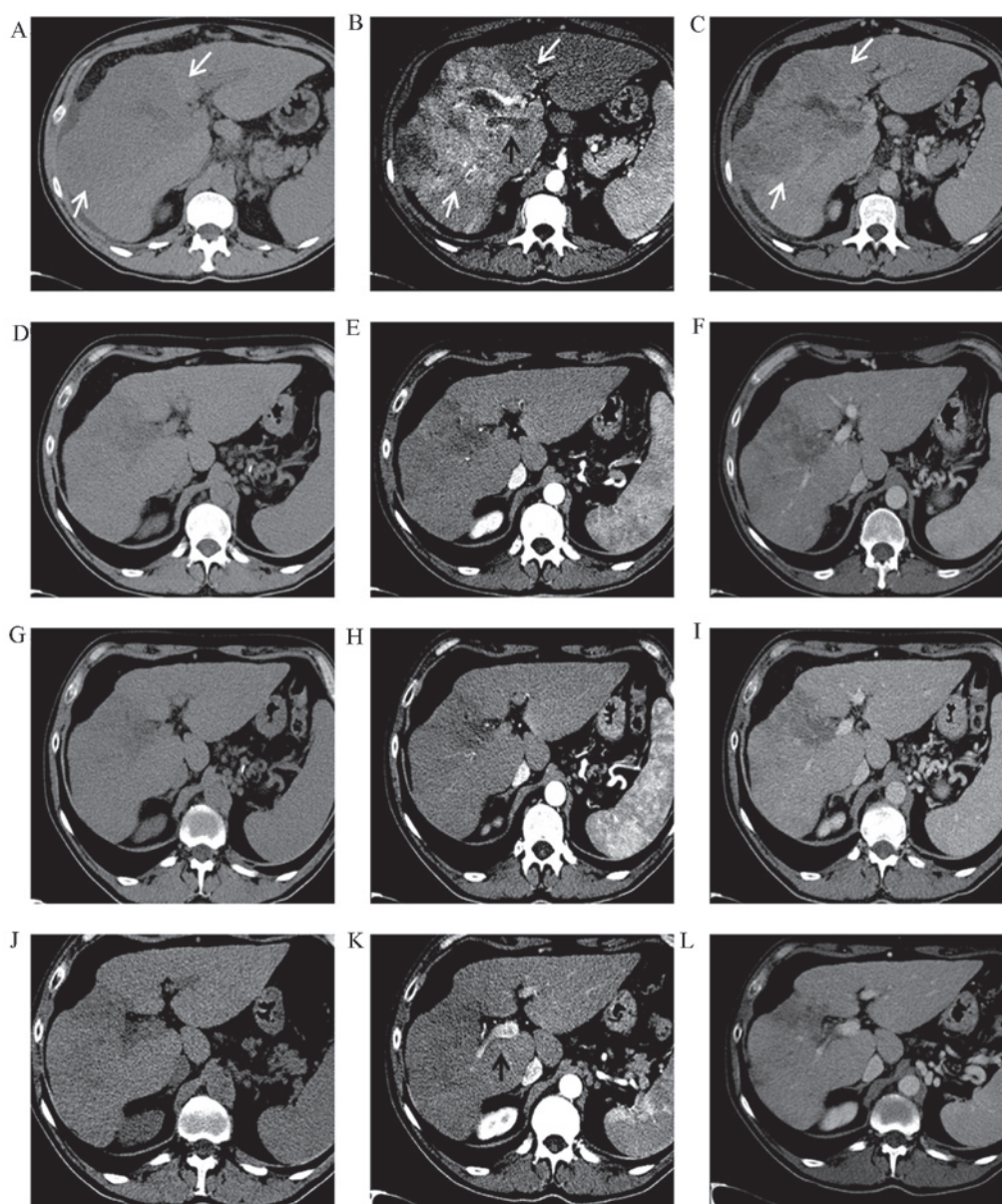E-mail: stefano.colagrande@unifi.it

Figure 1. Abdominal enhanced CT scans at the baseline, determined after 3, 4 and 7 months. (A) Abdominal unenhanced and enhanced CT baseline (March 2014) during the (B) arterial and (C) portal phases revealed multiple merging nodular lesions in the right hepatic lobe (illustrated by the white arrows). (B) The liver nodules present a marked enhancement in the arterial phase. Malignant thrombosis of the portal vein's right branches is present (denoted by the black arrow). (D-L) Unenhanced (D, G and J) and enhanced (E, H and K) CT during arterial and portal (F, I and L) phases after 3 (June 2014), 4 (July 2014) and 7 months demonstrated a progressive reduction in the size of the right hepatic lobe lesions, with significant devascularization. (K) Portal vein recanalization was also observed (denoted by the black arrow). CT, computed tomography.

(695,000 ng/ml). Esophagogastroduodenoscopy revealed the presence of F2-grade esophageal varices, with no red marks and hypertensive gastropathy, whereby treatment with a non-cardio-selective β-blocker (propranolol, 60 mg/day) was immediately started. An abdominal-enhanced Computed Tomography (CT) and a liver-specific gadolinium enhanced magnetic resonance imaging (MRI) examination confirmed the presence of multiple merging nodular lesions in the right hepatic lobe (12x8 cm overall diameter). The liver nodules also presented marked enhancement in the arterial phase (Fig. 1A-C; denoted by the white arrows). The CT enhancement rate ($D\%_{art}$) was calculated based on the mean density value from regions of interest (ROIs) drawn [expressed in Hounsfield Units (HU)] on an arterial phase (HU arterial) and on unen-

hanced acquisition (HU unenhanced) using the following equation: $D\%_{art}$ = (HU arterial-HU unenhanced) / HU unenhanced (9-12). It was estimated at 120%.

The MRI examination revealed low proton diffusivity, as a sign of high cellular density and architectural disorder [apparent diffusion coefficient (ADC) lesion, 0.74×10^{-3} mm^2/sec vs. ADC parenchyma, 0.92×10^{-3} mm^2/sec] (Fig. 2A and B). Portal vein thrombosis (particularly in the right branches) (Fig. 1B, black arrow), signs of portal hypertension with splenomegaly (14 cm), collateral spleno-renal circulation, recanalization of the umbilical vein and ascites were also present. The patient was subsequently diagnosed with class C HCC according to the BCLC classification system (2), and a full-dose oral sorafenib treatment (800 mg/day) was commenced in April 2014. The
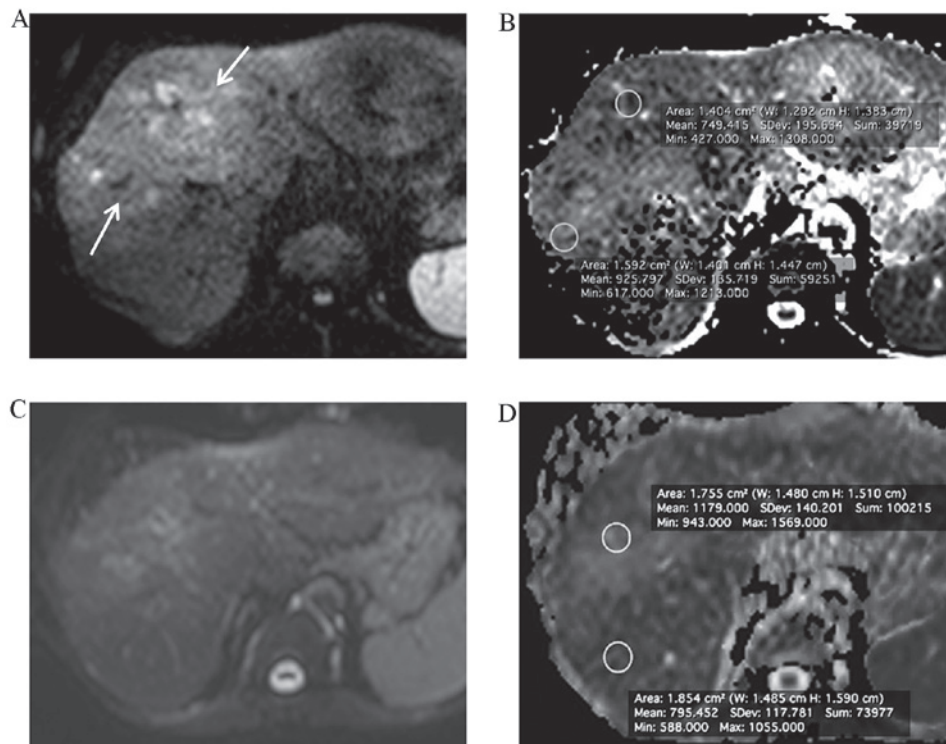
Figure 2. Abdominal enhanced MRI scans at the baseline and after 3 months. (A and B) MRI, heavily diffusion-weighted axial scan at the baseline (March 2014) revealed high signal intensity of the merging nodular lesions in the (A) right hepatic lobe illustrated by the white arrows. (B) The ADC map demonstrated a low ADC value of the lesion (0.74×10^{-3} mm²/sec; top circle) vs. ADC parenchyma (0.92×10^{-3} mm²/sec; bottom circle). (C and D) Following 3 months of therapy (June 2014), the MRI control revealed (C) no diffusion restriction with (D) ADC increase in the ADC map (ADC lesion, 1.17×10^{-3} mm²/sec; top circle, vs. ADC parenchyma, 0.79×0^{-3} mm²/sec, bottom circle).

administered dose was reduced to 400 mg/day after 3 weeks, as diarrhea and hand-foot syndrome had occurred. In May 2014, the patient was in a generally good medical condition.

The blood tests revealed an improvement of liver function (INR, 1.2, albumin, 3.2 g/dl, total bilirubin, 1.5 mg/dl) with a Child-Pugh rating of A6 and MELD score of 10, and a marked reduction in the level of α-fetoprotein (3,647 ng/ml). Enhanced CT imaging (Fig. 1D-F) demonstrated a reduction in size of the right hepatic lobe lesions (overall diameter, 10x7 cm) with signs of significant devascularization (D%$_{art}$ of 40%); portal vein thrombosis and ascites reduction were also observed. MRI diffusion-weighted acquisitions revealed an increase in the ADC lesion (ADC lesion, 1.17×10^{-3} mm²/sec vs. ADC parenchyma, 0.79×10^{-3} mm²/sec) (Fig. 2C and D). According to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (13), the patient was categorized as a partial responder, and treatment with sorafenib (400 mg/day) was therefore continued. After three (July 2014) and six (October 2014) months of therapy, enhanced CT revealed progressive reduction of both the liver lesion size (overall diameter, 8x5.5 and 7x5 cm, respectively) and contrast enhancement (30 and 25% D%$_{art}$, respectively), internal necrotic component increment, portal vein thrombosis reduction, recanalization of the right portal branch for the VI-VII segments and no ascites (Fig. 1G-L). The patient continued to be in a good general condition with stable liver function and a further reduction in α-fetoprotein levels (150 ng/ml), based on the blood tests.

In November 2014, while the possibility of radical surgical treatment was under evaluation, the patient's wife informed us that, after breakfast, the patient had complained of epigastric and retrosternal pain with general discomfort, and quickly succumbed to mortality within 10 min. The patient's personal physician determined that he most likely succumbed to sudden cardiac death.

Discussion

In our opinion, there are three elements of interest about this case: i) The rapid response to sorafenib monotherapy; ii) the progressive decrease in the lesion's CT enhancement rate during sorafenib monotherapy; and iii) the possible correlation between sudden cardiac death and sorafenib therapy.

The SHARP (6) and Asia-Pacific (7) studies revealed that overall survival, the primary endpoint, was significantly longer in sorafenib-treated patients (10.7 vs. 7.9 months and 6.5 vs. 4.2 months, respectively) compared with the placebo group. However, the incidence of an objective response to sorafenib monotherapy was low. The partial response (PR) rate in the sorafenib group was 2.0 vs. 1.0% (SHARP) and 3.3 vs. 1.3% (Asia-Pacific) compared with the placebo group (6,7). Only ten case reports of advanced HCC revealing a complete response (CR)/PR to sorafenib monotherapy are present in the literature, published between 2008 and 2011 (Table I) (14-19). In a multicenter study published in 2014 by Shiba et al, only 18 of 3,047 (0.6%) patients who were administered sorafenib monotherapy at institutions belonging to the Liver Cancer Study Group of Japan obtained a CR (20). The rapid response to therapy observed in the present study is unusual, and the reasons as to why this happens have yet to be fully elucidated. One possible explanation could be the oncogenic pathway

Table I. Patients receiving sorafenib monotherapy with complete response/partial response, based on an analysis of the literature.

Author/year	Gender/age	Etiology	Location/size of tumor	Extension	Treatment duration (months)	Dose (mg/day)	Time to CR/PR	Response evaluation criteria	AFP trend	Refs.
So *et al*, 2008	M, 78	Hemochromatosis	Right lobe/4,5x5 cm + satellites nodules	Lung metastases	6	800	CR to 5 months	Dimension, AFP, PET	13,599 →4,5 to 1 month	(14)
Curtit *et al*, 2011	M, 56	HCV	Not reported/15 cm + satellites nodules	Diaphragm Inferior vena cava	6	800 (1 month) →stop (15 days) →400	CR to 6 months	Histology after surgical resection	3,315 →20 to 40 days	(15)
Irtan *et al*, 2011	M, 59	Hemochromatosis	Left lobe/10 cm	Portal vein thrombosis Lymph nodes Lesser omentum	6	800	CR to 6 months	Histology after surgical resection	866 →<20 to 40 days	(16)
Irtan *et al*, 2010	M, 57	HBV	IV segment/8 cm	Portal vein thrombosis	12	800 (9 months) →400 (3 months)	CR to 12 months	Histology after surgical resection	17,000 →<20 to 6 months	(16)
Wang *et al*, 2010	M, 74	HCV	Right lobe/10x8 cm	Portal vein thrombosis	8	400	CR to 8 months	Imaging	3,300 →<20 to 8 months	(17)
Sacco *et al*, 2011	M, 84	HCV	III-IV segments/6 cm	Portal vein thrombosis	Not reported	800	CR to 6 months	RECIST	353 →<20 to 3 months	(18)
Abbadessa *et al*, 2011	M, 61	Not reported	Not reported/11x14 cm	Portal vein thrombosis Inferior vena cava thrombosis	12	Not reported 50% reduction dose after 11 months	PR to 12 months	WHO	10 →Not reported	(19)
Abbadessa *et al*, 2011	M, 63	HBV/HCV	IV segment/2x2,5 cm	Not reported	30	800 (7 months with periodical stop) → 400	PR to 16 months	Not reported	Not reported	(19)
Abbadessa *et al*, 2011	M, 70	HCV	Not reported/6x5 cm	Vascular	60	Not reported 50% reduction dose after 6 months	CR to 34 months	Not reported	15 → Not reported	(19)
Abbadessa *et al*, 2011	M, 69	HCV	Not reported/2x2.5 cm	Portal vein thrombosis	At least 62	Not reported 50% reduction dose after 10 days, with periodical stop	CR to 24 months	Histology	Not reported	(19)

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CR, complete response; PR, partial response; PET, positron emission tomography; RECIST, Response Evaluation Criteria In Solid Tumors; WHO, World Health Organization; M, male.

Table II. Cases of coronary heart disease associated with sorafenib, based on the literature analysis.

Author, year	Gender/Age	Tumor	Extension	Treatment duration	Dose (mg/day)	Response	Cardiovascular risk factors	Type of event	Coronorography	Refs.
Naib et al, 2011	M, 57	Hepatocellular carcinoma	Bone metastases	32 weeks	800→400	PD	Diabetes, hyperlipidemia, former smoker	Coronary vasospasm	Normal	(45)
Arima et al, 2009	M, 65	Renal cell carcinoma	Not reported	2 weeks	Not reported	Not reported	Hypertension arterial	Non ST-elevation myocardial infarction Coronary vasospasm	Normal	(43)
Porto et al, 2010	M, 63	Hepatocellular carcinoma	Multifocal	12 months	800	SD	Diabetes, Hypertension arterial, former minimal smoker	Variant angina with spontaneous coronary vasospasm	Absence of severe stenosis, minimal diffuse plaque disease	(44)
Pantaleo et al, 2012	M, 58	Clear cell renal carcinoma (right)	Hepatic and contralateral renal metastases	30 months	1,600 for 6 months →800 for 24 months	Initial PR and SD for 6 months → Resection hepatic and renal lesion (left)→CR in a few months	None	Chest pain, ischemia exercise-induced	Critical subocclusion common trunk, left and circumflex artery	(35)

PD, progression disease; SD, stable disease; PR, partial response; CR, complete response; M, male.

followed by HCC. According to certain authors (17,21), there are two principal pathways for HCC oncogenesis, with a smaller number of HCC cases arising from the dysregulation of only a few intracellular molecular pathways, such as the RAF or vascular endothelial growth factor receptor (VEGFR)-mediated cascades targeted by sorafenib, and the vast majority of HCC cases instead being generated by several genetic or biomolecular alterations (17,21). Since sorafenib specifically targets the RAF and VEGF pathways, multiple mutations could explain the resistance to molecular-targeted treatment in the majority of the patients. Despite previous attempts at doing so, it is not yet possible to identify reliable plasma, cancer and genetic biomarkers that enable the prediction of prognoses and the response to therapy with sorafenib in patients with advanced HCC (22-26). A previous study established that an early response of α-fetoprotein (defined as a reduction >20% from the baseline within the first 4 weeks of treatment) is an index of progression-free survival and overall survival in patients with HCC treated with anti-angiogenic drugs (27). Nevertheless, there are examples in the literature that highlight a delayed α-fetoprotein response, followed by disease remission (28). Our patient also presented with malignant portal vein thrombosis (a common feature), as shown in Table I. Sorafenib proved to be effective against portal neoplastic thrombosis through the inhibition of the VEGF cascade (29). The partial recanalization of the portal venous system corroborates the hypothesis that sorafenib has a direct action on tumor cells invading the portal system and a modulation effect on the production of pro-thrombotic cytokines by the neoplastic cells (18,30).

From the imaging point of view, as also described by other authors (31,32), in the present study a marked response to treatment in a highly enhancing lesion was observed. Such a response can be defined in terms of nodule devascularization (D%$_{art}$ reduction from 120 to 30/24% in our case), diameter stability, and, in a small number of cases, consistent volume decrease (maximum diameter reduction from 12 to 7 cm). By contrast, minor, or no, significant responses in low-enhancing nodules were noted. An increase in the ADC value was also observed: This could be interpreted as a reduction in the cellularity and a higher diffusivity (33). Pretreatment stratification of patients based on the enhancement rate of the lesions may yield more interesting insights in terms of the response to therapy (32). In fact, sorafenib's predominant mechanism of action is the inhibition of angiogenesis via actions on the VEGF and platelet-derived growth factor systems (34). As demonstrated in other conditions of anticancer therapy, a higher expression of the target system (in this case, tumor vascularization) increases the effects of the targeted treatment.

In our case, the patient probably experienced sudden cardiac death. It may be hypothesized that the devascularization induced by sorafenib and its cardiovascular adverse effects are associated. In the literature, three cases of severe cardiovascular complications in patients with a sorafenib monotherapy CR have been reported. With the exception of a case of renal cell carcinoma reported by Pantaleo *et al* (35), shown in Table II, Hagihara *et al* (36) and Shiozawa *et al* (37) reported CR of HCC treated with sorafenib following the failure of pretreatments (surgery, trans-arterial chemioembolization and percutaneous ethanol injection) and complicated by acute myocardial and cerebellar infarction, respectively.

The problems associated with the side-effects of sorafenib are indeed relevant. Certain of the most common adverse events (fatigue, diarrhea, hand-foot syndrome, bleeding, arterial hypertension, elevation of aminotransferase and/or bilirubin) appear to be more frequent and more severe than has generally been reported in the registration trials (6). Furthermore, the majority of these adverse effects, particularly the cardiovascular effects (hypertension, bleeding complications, arterial thromboembolic events and cardiac events), can be serious and potentially fatal (38). Previous studies reported that cardiotoxicity is a rare adverse event of sorafenib (8). The SHARP study identified no statistically significant differences in terms of severe adverse events, including myocardial infarction or ischemia, between the sorafenib and the placebo groups (3 vs. 1%) (6). Escudier *et al* (39) and Kane *et al* (40) reported an ischemia and/or myocardial infarction incidence in the sorafenib group of 4.9 and 2.7%, respectively. In a Phase I study that included patients with different types of cancer treated with sorafenib, Tolcher *et al* (41) reported that the effects of the drug on certain cardiovascular parameters (QT interval, ECG, left ventricular ejection fraction, blood pressure and heart rate) were modest, and therefore of limited clinical relevance. On the other hand, Schimidinger *et al* (42) reported that 33.8% of the patients treated with a TKI (sunitinib or sorafenib) experienced a cardiac event (42). An analysis of the literature reveals four cases of coronary heart disease associated with sorafenib: Three cases (43-45) were associated with the presence of known cardiovascular risk factors and were due to arterial vasospasm; in one case, there was evidence of coronary artery stenosis (Table II) (35). There are elements in common between the oncogenic pathways and those that regulate cardiomyocyte hypertrophy and survival, which could account for sorafenib's cardiovascular toxicity (46). For Ederhy *et al* (47) and Force *et al* (48), heart damage occurs as the direct consequence of the inhibition of cardiomyocyte survival through the interruption of the extracellular-signal-regulated kinase (ERK) kinase cascade mediated by the blockade of RAF kinase-1 and BRAF. However, studies on rat pups' myocytes have not supported this hypothesis (49).

The inhibition of RAF kinase and its downstream mediators, including mitogen-activated protein kinase kinase (MEK), may involve the stimulation of a small GTP-ase (RhoA) and its effector (Rho-associated protein kinase, or ROCK): This increases the Ca^{2+} sensitization of smooth muscle cells, leading to coronary hyper-contraction (43).

By inhibiting VEGF production, sorafenib also impairs nitric oxide (NO)- and prostacyclin (PG12)-mediated vasodilation, and, at the same time, promotes endothelin-1-induced vasoconstriction (50). Kawabata *et al* (51) have also observed that downregulation of stanniocalcin 1 (STC 1), a gene that serves a cardioprotective role, is responsible for the cardiotoxicity induced by sorafenib through the generation of reactive oxygen species.

In conclusion, sorafenib monotherapy is rarely able to induce a massive decrease in HCC nodule(s), and this appears to be even more likely as far as highly enhancing HCC nodules

are concerned. Since it is possible that those who show a good response to sorafenib treatment also experience a higher incidence of adverse cardiovascular events, improved cardiological surveillance would be advisable in these patients, even in the absence of known cardiovascular risk factors.

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