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LETTERS TO THE EDITOR

Hepatocellular carcinoma treated by sorafenib with complete radiological response according to mRECIST criteria: Could we stop the treatment? About four cases

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To the Editor,

Hepatocellular carcinoma (HCC) is the fifth most common neoplasia worldwide, and represents the third most common cancer-related cause of death [1]. In patients not eligible for curative treatment or loco-regional therapy (i.e. patients with major vein invasion or extra-hepatic spread), systemic treatment by sorafenib is the standard of care according to two positive phase III trials [2,3].

Sorafenib increases overall survival and the time to progression in patients with advanced HCC and the treatment is maintained until disease progression. Currently, there is no evidence that this treatment should be used as adjuvant treatment, e.g. after resection or ablation. Complete response (CR) is uncommon, however, if a major or complete radiological response is obtained, the issue of a discontinuation of sorafenib is still unresolved. We report four cases of advanced HCC treated by sorafenib achieving a complete radiological response according to modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria (criteria developed to assess the response in patients with HCC, based on measurement of viable tumor with arterial enhancement on a dynamic imaging technique) [4], sustained after the discontinuation of the treatment, and we perform a review of the literature suggesting the safety of this attitude.

Case report

Patient 1

A 52-year-old man with viral C cirrhosis was admitted for constitutional symptoms (weight loss and fatigue) revealing an HCC, histologically proved, involving the whole right liver with right portal vein thrombosis. The Child-Pugh score was B7 and the patient remained in good clinical conditions (PS = 1). Initial α-fetoprotein (AFP) was 245 000 ng/ml. Sorafenib (400 mg twice daily) was started on August 2009. In February 2010, a dose reduction (200 mg twice daily) was necessary due to grade 3 hand-foot skin reaction. In November 2010, AFP decreased to 11 ng/ml and CT scan showed a CR according to mRECIST. At this time, a significant alteration of the liver function (Child-Pugh B9) led to an interruption of the sorafenib. During the follow-up, AFP level remained stable at 11 ng/ml without any evidence of recurrence on CT scan until November 2011 (one year). At this date, a recurrence was observed in the left lobe, the right liver remaining free of new lesions and sorafenib was restarted.

Patient 2

An HCC developed on alcoholic cirrhosis was discovered in June 2006 in a 65-year-old man. The

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HCC was in the left lobe, with a macroscopic invasion of the left bile duct. A complete resection of the left lobe of the liver was performed in December 2006.

In June 2008, MRI revealed a recurrence on the hepatectomy slice with metastatic hilar lymph nodes and peritoneal carcinomatosis. AFP level was 292 ng/ml. The Child score was A, and the performance status was 0. Sorafenib (400 mg twice daily) was started. In November 2008, AFP value decreased to 6.7 ng/ml with a significant shrinkage of the tumor on CT scan (50% according to RECIST criteria). In April 2009, sorafenib dose was reduced (200 mg twice daily) for side effects (diarrhea and alopecia). In June 2009, treatment was stopped after confirmation of a CR associating shrinkage of the HCC to 18 mm (40 mm before treatment) with a complete necrosis and disappearance of peritoneal carcinomatosis. AFP level was 2.1 ng/ml.

In December 2012, patient remained in good clinical conditions (PS 0) with normal liver function (Child-Pugh A5), AFP value was at 3.3 ng/ml and the complete radiological response was maintained.

Patient 3

An HCC, developed on non-fibrotic liver and located in segment VIII, was resected in October 2006, in a 73-year-old Caucasian man. In April 2007, the CT scan highlighted a peritoneal recurrence with one nodule (20 mm) near the liver. This lesion was treated by percutaneous radiofrequency in May 2007. In August 2007 CT scan evaluation showed recurrence in segment I of the liver and in the peritoneum (Figure 1A and B). Sorafenib treatment was started (400 mg twice daily). A complete radiological response (mRECIST criteria) was observed in November 2007 (Figure 1C and D). Sorafenib was maintained but had to be stopped in January 2008 because of serious adverse events including cerebellar stroke. Two months later, new peritoneal nodules were detected leading to resume sorafenib at 400 mg per day. In May 2008, treatment was stopped in front of the necrotic appearance of all the lesions. In October 2012, the patient was still alive without any lesion on the CT scan (Figure 1E and F).

Patient 4

A 68-year-old man was admitted in August 2011 for the management of an HCC involving the whole left lobe of the liver, with macrovascular venous invasion and multiples lung metastasis. HCC was developed on compensated cirrhosis related to alcohol consumption and metabolic syndrome. The PS status was 1. Sorafenib was introduced in September 2011 and a prompt and strong decrease of AFP was observed from 842 ng/ml before the treatment to 5.1 ng/ml in October 2011. The first radiological evaluation in October showed a complete necrosis of the liver tumor and a major shrinkage of lung metastasis. This response was confirmed by a new CT scan in December 2011 and sorafenib was stopped. In October 2012, the patient is still alive without any evidence of relapse on the CT scan and a normal AFP level.

Discussion

We report four CRs of HCC induced be sorafenib and sustained after the discontinuation of the treatment. CR under sorafenib is obviously uncommon although probably underestimated in initial studies by the use of conventional RECIST criteria. Indeed, we observed these four reported cases among the 250 patients treated by sorafenib over five years in our unit therefore accounting for 1.5% of cases. Therefore, this case report emphasizes the interest of mRECIST criteria for the evaluation of the response in HCC treated by sorafenib.

Up to now, 13 cases of CR induced by sorafenib have been previously published [5–14] to our knowledge. These reports are summarized in Supplementary Table I to be found at online http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.795286.

In three cases a secondary resection was possible with the confirmation of a complete pathological response [5,6] and sorafenib was stopped. In seven cases, sorafenib was maintained after the achievement of radiological response usually with a dose reduction required by side effects [7–11]. Finally, in three cases, sorafenib was discontinued after CR, without relapse after a follow-up of 6, 8 and 16 months [12–14].

These observations all together raise the question of sorafenib discontinuation in patients with radiological CR and not eligible for a secondary curative treatment.

There is no clear recommendation in this unusual situation, but the most common prevailing attitude is to indefinitely maintain sorafenib to avoid a potential reactivation of the tumor. This management was applied in most of case reports previously published. It should be stressed, however, that this attitude is not supported by strong biological or clinical evidences.

Nevertheless, this issue is especially crucial because: 1) side effects of sorafenib may strongly impact the quality of life; 2) there are currently no data on the long-term safety of this drug; and 3) the cost of the treatment has to be stressed.

Our case reports suggest that the discontinuation of sorafenib after radiological CR according to mRECIST criteria may be safe and does not expose the patient to a rapid and uncontrollable recurrence.

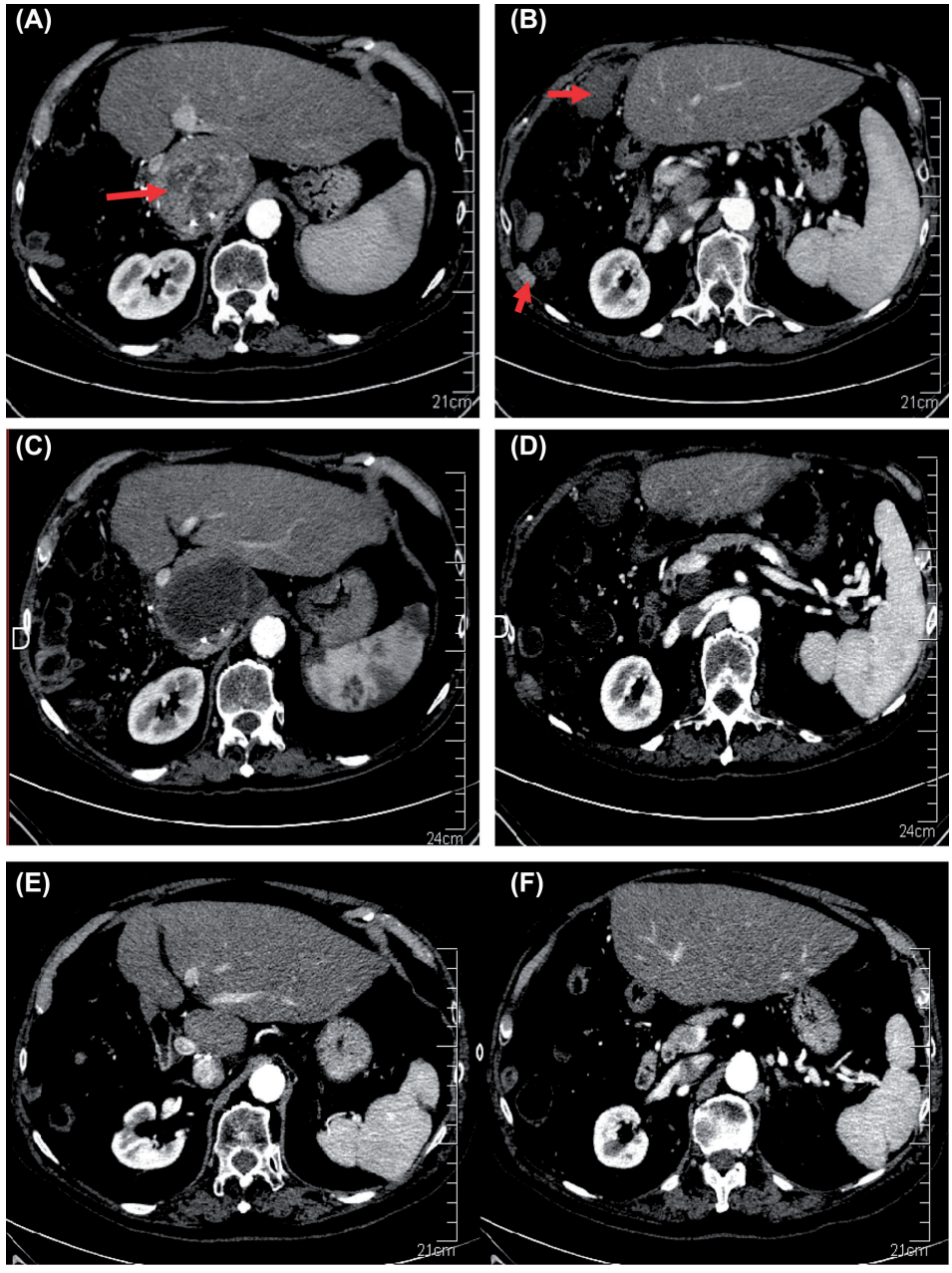

Figure 1. Patient 3. (A, B). In August 2007 CT scan evaluation showing a recurrence in the liver (A) and in the peritoneum (B). (C, D). A complete radiological response (mRECIST criteria) was observed in November 2007 after 3 months of sorafenib. (E, F). In October 2012, the patient was still alive without any lesion on the CT scan, 54 months after cessation of sorafenib.

A relapse was observed in only one of our patients, one year after the discontinuation of sorafenib. However, it should be pointed out that recurrence was observed in the left lobe of the liver while the initial tumor, in the right lobe remained necrotic without any arterial enhancement. We assume that this recurrence is likely related to de novo carcinogenesis, in this patient with cirrhosis and active viral hepatitis C, rather than a relapse of the initial tumoral disease. Nevertheless, the discontinuation of sorafenib has not been obviously deleterious for this patient. For patients 2, 3 and 4, no recurrence was observed after a strict and prolonged follow-up of, respectively, 36, 54 and 10 months.

In conclusion, few HCC achieve radiological and biological CR after sorafenib administration. Our experience and the review of the literature suggest that these patients are characterized by a very rapid response to sorafenib with an early dramatic drop of AFP and necrosis of HCC, usually in the first two or three months of therapy.

In these highly selected patients, the few clinical data available suggest that the discontinuation of sorafenib may be a safe and a reasonable alternative

to the maintenance of sorafenib at full or reduced dose. In case of disabling side effects this attitude seems clearly suitable.

Declaration of interest: The authors who have taken part in this case report declared that they have no relationship with the manufacturers of the drugs involved either in the past or present and did not receive funding from the manufacturers to carry out their research.

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Supplementary material available online

Supplementary Table I.