Long-lasting tumour response to sorafenib therapy in advanced hepatocellular carcinoma

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Abstract

The multi-kinase inhibitor sorafenib still remains the only approved agent for advanced HCC. Its benefits typically involve disease stabilisation, whereas an induction of response is rare.

We report a series of five cases with extraordinary response to sorafenib.

For two patients complete response to sorafenib was reported with a recurrence-free survival of 51 and 21 months. In another HCC patient pretreated with transarterial chemoembolisation (TACE) sorafenib treatment resulted in a complete response with no evidence of disease 18 months after first diagnosis. In patient 4 with unresectable HCC and sorafenib therapy secondary resectability and subsequent liver transplantation was achieved. Patient 5 had stabilised disease for 48 months after TACE and sorafenib treatment.

Sorafenib may be very potent in individual patients. Excellent interdisciplinary strategies are required to achieve best results. There is an urgent need of predictive biomarkers to identify HCC patients that will benefit the most. (Acta gastroenterol. belg., **2014**, 77, **386-388**).

Key words : HCC, response, sorafenib.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death. Therapeutic options for patients with advanced disease are still sobering (1). In 2007, the multi-kinase inhibitor sorafenib has shown survival benefits and remains the only approved agent (2). However, only 7 out of 1777 patients treated with sorafenib achieved a complete response and 98 patients achieved a partial response in recent phase III clinical trial (2-4). Herein, we report a series of five cases with advanced HCC including patients with complete response and long-term disease stabilisation following treatment with sorafenib.

Case histories

Patient 1

In 10/2004, a 60-year old female patient with alcoholic liver cirrhosis was first diagnosed with unifocal HCC in segment 3 (4 × 3 cm). Alpha-feto-protein (AFP) level was increased 86 fold above the upper limit of normal (ULN). After four percutanous alcohol instillations, the tumour progressed in number and size in 10/2009. Accordingly, AFP values massively increased. Transarterial chemoembolisation (TACE) was not possible due to portal vein thrombosis with cavernous transformation. Treatment with sorafenib was started with 600 mg/day (d). After 34 months of sorafenib, therapy was stopped with radiologic complete response and normalised AFP. 51 months after first diagnosis of advanced HCC, the patient was still recurrence-free.

Patient 2

A 71-year old man with alcoholic liver cirrhosis was diagnosed with unresectable HCC in segments 6 and 7 in 04/2012 (11 × 6.7 cm). AFP was 74467 fold above the ULN increased. TACE was not possible due to intrahepatic arterioportal shunts. In 08/2012, therapy with sorafenib was started with 800 mg/d. After 5 months of treatment, sorafenib was stopped with radiologic report of complete response and a rapidly normalised AFP. 21 months after first diagnosis the patient had no evidence of HCC.

Patient 3

In 08/2008, a 48-year old male patient with hepatitis-C-virus cirrhosis was diagnosed with unresectable HCC. AFP was 4333 fold the ULN elevated. TACE could not be performed due to portal vein thrombosis. Treatment with sorafenib was started in 09/2008 in full dosage. After 6 months of treatment a partial reponse was documented by CT scan accompanied by a massive decrease of AFP. Subsequently, a right hemihepatectomy was performed (pT2pNxM0R0G2). The resected liver lobe revealed wide-spread necrosis. Sorafenib was re-started in 05/2009. In 11/2009 liver transplantation (LT) was performed with no histologic evidence of malignancy in the explanted liver. This patient has been recurrence-free 65 months after first diagnosis.

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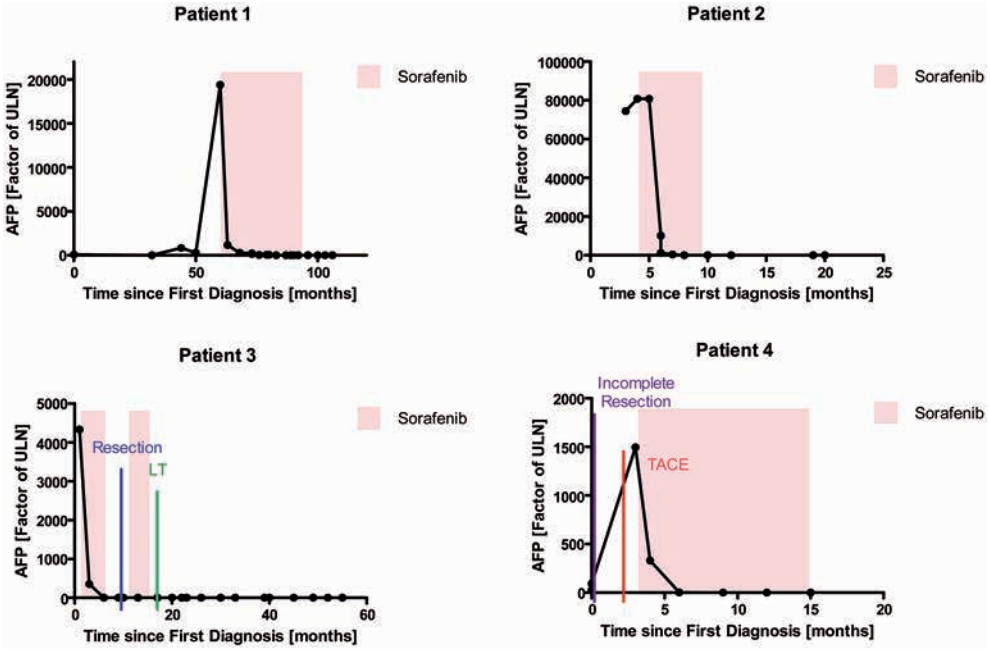

Fig. 1. — Response on sorafenib by terms of AFP [μg/L] decrease (fold change of ULN)

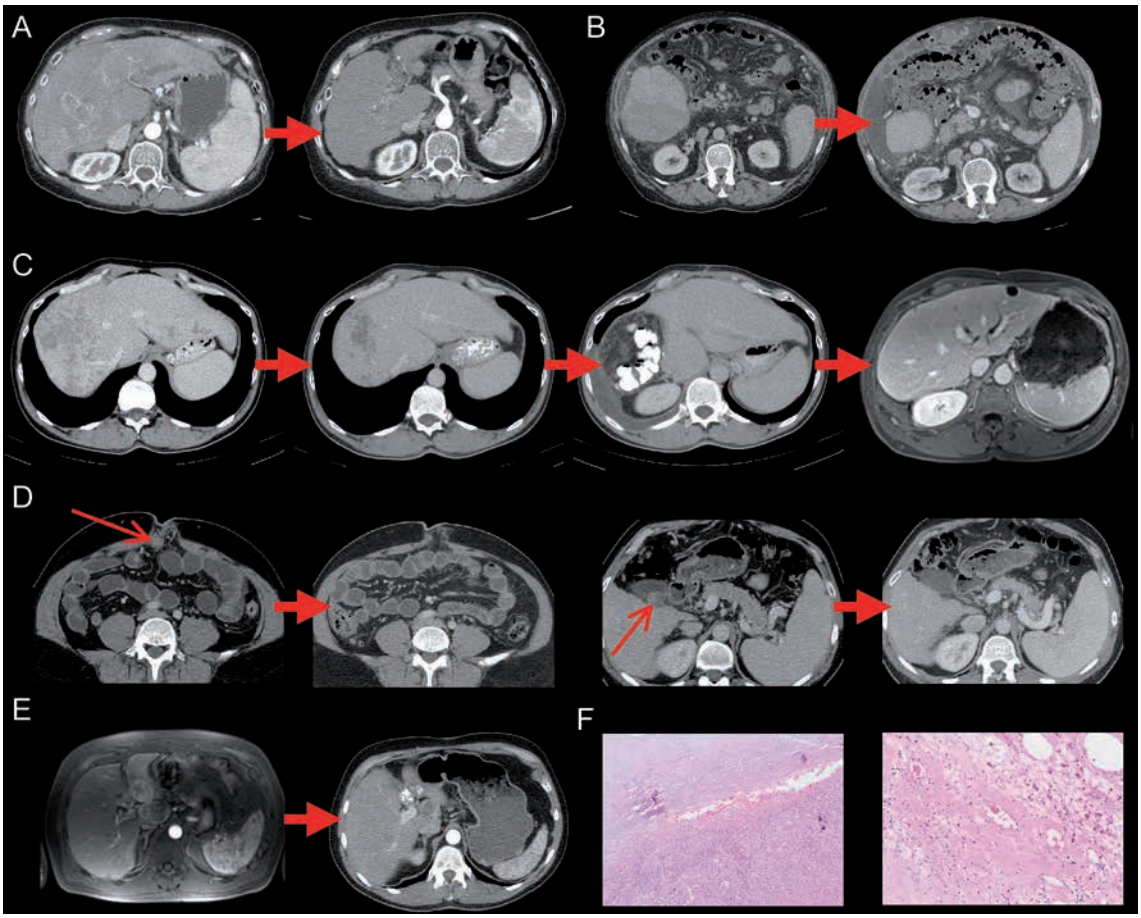

Fig. 2. — Contrastenhanced CT/MRI baseline and during/after sorafenib treatment and histologic regression. Patient 1 and 2 before sorafenib start and stop without any evidence of HCC (A, B). Patient 3 before sorafenib start, with partial response on sorafenib, after resection and after LT (C). Patient 4 before sorafenib start and with complete regression of the peritoneal lesions (slim arrows) (D). Patient 5 before and during sorafenib (E). Hematoxylin/eosin stained histologic sections of patient 3, 40× augmentation, showing regression zone with HCC (left) and regression zone with residuals of the tumoural bleeding (right) (F).

Patient 4

In 07/2012, a 48-year old male patient with a history of hepatitis-B-virus cirrhosis presented with an hemorrhagic shock due to tumour rupture. An emergency laparotomy was performed with incomplete HCC-resection (R2G2). AFP was 28 fold above the ULN increased. In 08/2012, one 2.1 cm HCC nodule was documented in segment 8a, which was treated with TACE. The follow-up CT scan revealed a progression of the hepatic lesion and peritoneal carcinomatosis in 11/ 2012, which was accompanied with an AFP increase. Subsequently, sorafenib was started with 800 mg/d. 18 months after first diagnosis no tumour lesions were detectable by CT.

Patient 5

A 54-year old male patient without any history of liver disease was incidentally diagnosed with unresectable HCC in 01/2010 by MRI imaging. AFP level was in normal range. After twice a TACE, sorafenib was started with 800 mg/d in 08/2010 and was continued until 07/2013 with stable disease on follow-up CTs. 48 months after first diagnosis this patient still had stable disease.

Discussion

Sorafenib is still the only approved agent for advanced HCC. In line with previous reports, we here provide evicence that despite the moderate benefit of 2.8 months in median overall survival, sorafenib may be particularly efficient in specific subpopulations (5-13).

Our results emphasise the need of predictive biomarkers to select patients that will benefit the most. Subgroup analyses from the previously performed phase III trials, Sharp and Sun1170, revealed a particular efficacy of sorafenib in non-asian patients with hepatits-C-virus infection with a median overall survival of 18.3 months (3). However, most of the reported patients did not suffer from hepatitis C infections. Based on a a nation-wide survey in Japan, female sex and early clinical stage were idenfied as predictive factor for sorafenib treatment (13). By contrast, the cases presented here had all advanced disease and 4 of 5 patients were male. In accordance with our observation, a rapid normalisation of AFP has been proposed as a surrogate and prognostic marker of sensitivity to sorafenib (5,14). *In vitro*, a mesenchymal profile and expression of the stem cell marker CD4 have been proposed as predictive factors for sorafenib resistance (15). Furthermore, in 26 HCC patients treated with sorafenib 522 microRNAs (miRNAs) were profiled and miR-425-3p was asscociated with a prolonged progression-free survival (16). Very recently, VEGF-A-amplified hepatocellular carcinomas were identified to be highly sensitive to sorafenib treatment (17). However, VEGF-A amplification were not detectable in the tumours of our patients. To the best of our knowledge, other predictive biomarkers for sorafenib in HCC have not yet been identified in any clinical, prospective trial. Future trials clearly need to include broad translational programs including tumor biopsies to validate these highly complex data.

In our patients local therapies were sequentely combined with sorafenib allowing long-term disease control in advanced HCC reiterating the need of multidisciplinary tumourboard evaluation to select the next best possible treatment option. Summarised, in selected patients with advanced HCC multidisciplinary treatment including sorafenib may alow long-lasting tumour control.

References

1. EL-SERAG H.B. Hepatocellular carcinoma. *N. Engl. J. Med.*, 2011, **365** (12) : 1118-1127.
2. LLOVET J.M., RICCI S., MAZZAFERRO V. *et al*. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.*, 2008, **359** (4) : 378-390.
3. CHENG A.L., KANG Y.K., LIN D.Y. *et al*. Sunitinib Versus Sorafenib in Advanced Hepatocellular Cancer : Results of a Randomized Phase III Trial. *J. Clin. Oncol.*, 2013, **31** (32) : 4067-4075.
4. JOHNSON P.J., QIN S., PARK J.W. *et al*. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma : results from the randomized phase III BRISK-FL study. *J. Clin. Oncol.*, 2013, **31** (28) : 3517-3524.
5. GERARDI A.M., STOPPINO L.P., LISO A., MACARINI L., LANDRISCINA M. Rapid long-lasting biochemical and radiological response to sorafenib in a case of advanced hepatocellular carcinoma. *Oncology letters*, 2013, **5** (3) : 975-977.
6. NAKAZAWA T., HIDAKA H., SHIBUYA A., KOIZUMI W. Rapid regression of advanced hepatocellular carcinoma associated with elevation of des-gamma-carboxy prothrombin after short-term treatment with sorafenib – a report of two cases. *Case reports in oncology*, 2010, **3** (2) : 298-303.
7. DI LORENZO G., IMBIMBO M., LEOPARDO D. *et al*. A long-lasting response to sorafenib treatment in an advanced hepatocellular carcinoma patient. *Int. J. Immunopathol. Pharmacol.*, 2010, **23** (3) : 951-954.
8. INUZUKA T., NISHIKAWA H., SEKIKAWA A. *et al*. Complete response of advanced hepatocellular carcinoma with multiple lung metastases treated with sorafenib : a case report. *Oncology*, 2011, **81** Suppl 1 : 152-157.
9. SACCO R., BARGELLINI I., GIANLUIGI G. *et al*. Complete response for advanced liver cancer during sorafenib therapy : case report. *BMC gastroenterology*, 2011, **11** : 4.
10. MONTELLA L., ADDEO R., CENNAMO G. *et al*. Sorafenib in elderly patients with advanced hepatocellular carcinoma : a case series. *Oncology*, 2013, **84** (5) : 265-272.
11. CURTIT E., THIERY-VUILLEMIN A., NGUYEN T. *et al*. Complete histologic response induced by sorafenib in advanced hepatocellular carcinoma : a case report. *J. Clin. Oncol.*, 2011, **29** (12) : e330-332.
12. IRTAN S., CHOPIN-LALY X., RONOT M., FAIVRE S., PARADIS V., BELGHITI J. Complete regression of locally advanced hepatocellular carcinoma induced by sorafenib allowing curative resection. *Liver Int.*, 2011, **31** (5) : 740-743.
13. SHIBA S., OKUSAKA T., IKEDA M., SAITO H., ICHIDA T. Characteristics of 18 patients with hepatocellular carcinoma who obtained a complete response after treatment with sorafenib. *Hepatol. Res.*, 2014.
14. PERSONENI N., BOZZARELLI S., PRESSIANI T. *et al*. Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. *J. Hepatol.*, 2012, **57** (1) : 101-107.
15. FERNANDO J., MALFETTONE A., CEPEDA E.B. *et al*. A mesenchymal-like phenotype and expression of CD44 predict lack of apoptotic response to sorafenib in liver tumor cells. *Int. J. Cancer*, 2014.
16. VAIRA V., RONCALLI M., CARNAGHI C. *et al*. MicroRNA-425-3p Predicts Response to Sorafenib Therapy in Patients with Hepatocellular Carcinoma. *Liver Int.*, 2014.
17. HORWITZ E., STEIN I., ANDREOZZI M. *et al*. Human and mouse VEGFA-amplified hepatocellular carcinomas are highly sensitive to sorafenib treatment. *Cancer Discov.*, 2014.