Complete clinical response of a patient with lymph node and pulmonary metastatic hepatocellular carcinoma to very low-dose sorafenib (Nexavar®) therapy

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Abstract We present the case of a patient with metastatic hepatocellular carcinoma (HCC) who showed complete response (CR) to very low-dose sorafenib therapy. The patient was a 74-year-old woman who had previously undergone S7/8 hepatectomy for HCC in December 2002. Intrahepatic recurrence developed in August 2007, and transcatheter arterial chemoembolization was performed seven times. An increase in the level of the tumor marker alpha-fetoprotein (AFP) was observed, and thus positron emission tomography-computed tomography (PET-CT) was performed in June 2010. PET-CT showed an accumulation of metastatic cells resulted in a swollen periaortic lymph node. Based on the features of this lymph node metastasis, HCC was diagnosed. Oral sorafenib (Nexavar®) was started at an initial dose of 400 mg/day given three times a week. Sorafenib therapy was discontinued when adverse reactions such as bloody sputum and hand tremor were noted after 1 week of therapy. Following improvement of the adverse reactions, sorafenib therapy was resumed at 200 mg/day given three times a week. Two months after the reinitiation of sorafenib therapy, CT showed no change in the lymph node metastasis, and previously undetected pulmonary metastasis was diagnosed. At 5 months of therapy, CT showed no pulmonary and lymph node metastases. As the patient developed another adverse effect of sorafenib therapy, the frequency of sorafenib administration was reduced to two times a week at 200 mg/day. After 15 months of sorafenib therapy at

200 mg/day given two times a week, the patient showed CR and remains in CR at this writing.

Keywords Complete clinical response · Hepatocellular carcinoma · Sorafenib

Introduction

Recent advances in molecular biology have elucidated the mechanisms of cancer growth, invasion and metastasis. At present, molecular target drugs are being used as the standard therapy for different types of tumor. In Japan, the indication of sorafenib (Nexavar®) for hepatocellular carcinoma (HCC) that is not treatable by curative resection was approved in May 2009, and sorafenib is currently being used considerably in medical practice. Sorafenib has been demonstrated to prolong the overall survival of HCC patients in large-scale clinical studies conducted to validate its approval as standard therapy [1, 2]. In these previous studies, no complete clinical responders were identified. However, complete response (CR) cases have been reported occasionally, which has attracted increasing interest regarding the efficacy of sorafenib against HCC.

Case report

The patient was a 74-year-old woman who underwent complete examination for liver disorders in April 1988 and was given a diagnosis of chronic hepatitis B. In December 2002, the patient underwent S7/8 hepatectomy for HCC (35-mm moderately differentiated HCC vp1, vv0, b0, im2; stage III, The Liver Cancer Study Group of Japan). Immunotherapy was given as postoperative adjuvant

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Fig. 1 Clinical course of the patient. *AFP* alpha-fetoprotein, *PIVKA-2* protein induced by vitamin K abnormality, *TACE* transcatheter arterial chemoembolization

therapy. Frequent intrahepatic recurrences have been detected since August 2007, and transcatheter arterial chemoembolization (TACE) was performed seven times. Oral entecavir (Baraclude®) was given in April 2008, and negative conversion of the hepatitis B virus was maintained. In January 2009, the patient underwent partial resection of the right lung for primary lung cancer (18 × 13-mm well-differentiated adenocarcinoma, p0, pm0). In January 2010, CT showed a 10-mm viable lesion intensely stained in the arterial phase in S5. This lesion was treated by lipiodol-TACE with 50 mg of cisplatin in February 2010. Following these treatments, the level of the tumor marker alpha-fetoprotein (AFP) temporarily decreased, but later increased (AFP 822 ng/ml) (Fig. 1). In June 2010, ¹⁸F-fluorodeoxyglucose-positron emission tomography-computed tomography (PET-CT) was performed because the AFP level continued to increase despite the absence of an intrahepatic recurrent tumor on CT. There was also no abnormal contrast accumulation, indicating that the previous residual intrahepatic tumor had been effectively treated by TACE. However, an enlarged, wedge-shaped lymph node measuring 21 × 19 × 50 mm with abnormal contrast accumulation (SUV_{max} 2.93) was found on the right side of the aorta, inferior to the renal artery (Fig. 2a, b). This enlarged lymph node was found to have HCC metastasis. The metastatic lesion was solitary but it came in contact with the right half of the aortic wall. This prevented the radical resection of the lesion, and thus the oral administration of sorafenib (Nexavar®) was initiated (Fig. 3a).

With regard to sorafenib dosage, the patient's height (150 cm), weight (35 kg), and BMI (15.5) were considered. Further taken into account in addition to liver dysfunction was the presence of polycystic kidney-associated renal dysfunction (Table 1). Thus, the initial dose was reduced two steps to 400 mg/day given 3 times a week. After 1 week of oral administration of sorafenib, bloody sputum [Common Terminology Criteria for Adverse Events

(CTCAE) version 3.0: grade 1] and tremor of the fingers (CTCAE version 3.0: grade 2) were noted, and thus the therapy was discontinued. Following improvement of the adverse reactions, sorafenib administration was restarted at a reduced dose of 200 mg/day given three times a week. After 2 months of sorafenib therapy, CT showed no change in lymph node metastasis, but a new 8-mm pulmonary metastasis developed in the right upper lung field (Fig. 4a). The AFP level started to decrease at 4 months of sorafenib therapy, and both pulmonary and lymph node metastases disappeared on CT at 5 months of sorafenib therapy (Figs. 3b, 4b). Because facial flush as an adverse reaction (CTCAE version 3.0: grade 2) developed, the dose of sorafenib was further reduced to 200 mg/day given two times a week, and treatment was continued for several months. At 7 months of sorafenib therapy, PET-CT showed no peri-aortic lymph node enlargement or abnormal contrast accumulation (Fig. 2c, d). As of 15 months of sorafenib therapy at 200 mg/day given two times a week, the patient has continued to be in CR without tumor recurrence on imaging examinations. Moreover, the AFP level has remained low.

Discussion

The tumor growth-inhibitory effects of sorafenib have been demonstrated to prolong survival in large-scale clinical studies, namely, the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial and Asia-Pacific studies, both conducted before the approval of the indication of sorafenib for HCC in Japan [1, 2]. Although the survival-prolongation effect of sorafenib has been verified in these previous studies, its tumor size-reducing effect is not very pronounced. Also, no CR cases were noted in these previous large-scale clinical studies. However, several CR cases have recently been reported. In Japan, 15 CR cases were reported from multiple centers, as stated in the report of the Japan Association of

Fig. 2 18F-fluorodeoxyglucose-positron emission tomography-computed tomography. **a, b** Before treatment with sorafenib. **c, d** At 7 months of sorafenib administration

Fig. 3 Abdominal enhanced computed tomography. **a** Before treatment with sorafenib. **b** At 5 months of sorafenib administration

Molecular Targeted Therapy [3]. This suggests that some Japanese HCC cases are highly sensitive to sorafenib.

In the present patient, the absence of intrahepatic lesions has been maintained for more than 4 months after the disappearance of all tumors, including the lymph node and pulmonary metastases. The patient is thus considered to be in CR, as indicated by the absence of intense staining, shrinking, and disappearance of the tumors.

For the evaluation of the effects of anticancer drugs on solid cancers, the Response Evaluation Criteria in Solid Tumors (RECIST) are widely used. RECIST indicates the tumor size-reducing effect of a given therapy, but are considered by others as not applicable for the evaluation of a given therapy for HCC. For example, the sorafenib-induced disappearance of intense tumor staining is not considered to indicate effective therapy. In Japan, the effect

of TACE is comprehensively assessed using the Response Evaluation Criteria in Cancer of the Liver (RECICL) [4] based on the disappearance of intense staining and size reduction rate of a tumor. In Western countries, the modified RECIST (mRECIST) for HCC, which consider regions showing the disappearance of intense tumor staining as indicative of tumor necrosis, have been proposed [5] and used for evaluating treatment effect on HCC. On the other hand, some researchers doubt the merit of evaluating treatment effect based on the disappearance of intense tumor staining. Schor-Bardach et al. [6] reported that tumor size was not changed despite the sorafenib-induced reduction of blood flow in the tumor region in a mouse human renal cell carcinoma-transplanted model. Moreover, blood flow in the tumor region and tumor size increased despite the continuation of sorafenib therapy. This suggests that sorafenib-induced

reduction of blood flow in the tumor region does not immediately lead to tumor size reduction or necrosis. Specifically, the primary mechanisms of action of sorafenib are the induction of necrosis by inhibition of vascularization and the induction of apoptosis [7]. This leaves a question of whether the evaluation criteria for the therapeutic efficacy of sorafenib are simply based on the induction and development of tumor necrosis. Further investigation to clarify the basis of therapeutic efficacy using these criteria is necessary.

A high frequency of adverse reactions, such as hand-foot syndrome, and relatively high frequencies of skin eruption and diarrhea are also characteristics of sorafenib therapy. In our experience at our hospital, sorafenib was initially given to more than 50 patients with unresectable HCC at the standard dose of 800 mg/day; however, this initial dose was reduced to a one-step lower dose at 400 mg/day because of the high frequency of adverse reactions. It has been reported that when the rates of adverse events were compared between phase I clinical studies performed in Japan and other countries, there were no marked differences in the type, symptoms, findings, severity, or incidence between Japanese and non-Japanese patients. Based on this finding, the main trend in sorafenib therapy is to set the initial dose as close as possible to 800 mg/day. However, the use of a lower dose of sorafenib at 400 mg/day has been reported in Japan in cases of increased frequency of treatment or continuous therapy because of the use of an initial reduced dose [8]. This does not mean that Japanese patients offer an effective treatment group for sorafenib. Further studies regarding the optimal dose of sorafenib for HCC are needed.

Table 1 Laboratory data before sorafenib treatment

WBC $4,010/\text{mm}^3$	Alb 3.3 g/dl
RBC $296 \times 10^4/\text{mm}^3$	AST 33 IU/l
Hb 8.6 g/dl	ALT 16 IU/l
Plt $22.7 \times 10^4/\text{mm}^3$	ALP 436 IU/l
PT 89.1 %	T-bil 0.5 mg/dl
PT-INR 1.00	BUN 33.2 mg/dl
AFP 2,786 ng/ml	Cr 1.64 mg/dl
AFP-L3 1.3 %	CRP 0.58 mg/dl
PIVKA-2 171 mAU/ml	HBsAg(+) > 2,000
	HB DNA real-time < 2.1 log IU/ml
	HCVAb(-)

Fig. 4 Chest enhanced computed tomography. **a** A new 8-mm pulmonary metastasis developed in the right upper lung field after 2 months. **b** Pulmonary metastasis disappeared at 5 months

Table 2 Recent reports describing CR cases

	Case	Sex	Age	Dose ^a	Location ^b	Published ^c
	1	M	74	400	Liver	2010/USA/[10]
	2	M	68	400	Liver, lung	2010/Japan/[9]
	3	M	68	800	Liver, lung, lymph node, adrenal	
	4	M	69	800	Liver, lymph node	2010/Greece/[11]
^a Dose administered (mg/day)	5	M	84	800	Liver (PVTT)	2011/Italy/[12]
^b Tumor location of HCC (and the site of metastasis)	6	M	56	800	Liver	2011/France/[13]
	7	M	59	800	Liver (PVTT), lymph node, dissemination,	2011/France/[14]
^c Published year/country/reference number	8	M	76	400	Liver, lung	2011/Japan/[15]

Sorafenib requires a specific period to exhibit its dose-dependent effect, although its effect is directly related to the dose. Kudo et al. [9] reported that 2 of 90 patients treated with sorafenib achieved CR. In these two patients, the tumor disappeared after 2 months of oral sorafenib administration at 400 mg/day in one patient, whereas an intrahepatic tumor and pulmonary and lymph node metastases disappeared after 1 month and an adrenal metastatic lesion shrank after 6 months in the other patient treated with sorafenib at 800 mg/day. Complete necrosis was pathologically confirmed in the excised specimens. We searched recent reports describing CR cases [9, 10] (Table 2). However, there were no reports of effective cases of very low-dose sorafenib therapy.

So et al. [16] reported that intrahepatic lesions disappeared after 5 months of oral sorafenib administration at 400 mg/day. Lassau et al. [17, 18] reported marked tumor size reduction after 6 months in HCC patients treated with the molecular target drug bevacizumab; in these patients reduced tumor blood flow early after treatment initiation was confirmed by contrast echography. In the present patient, sorafenib administration was initiated at about 21 % of the standard dose per week (i.e., 400 mg/day given 3 times a week), and the dose was further reduced twice because of adverse reactions. The dose has been maintained at about 7 % of the standard dose (200 mg/day, given 2 times a week), and CR was achieved after 5 months and maintained for more than 4 months. It is suggested that sorafenib administration must be continued when its dose is reduced in individual cases as CR may be achieved by continuous low-dose therapy. Taken together, this is an important case that showed that long-term low-dose sorafenib therapy achieved CR in terms of lymph node and pulmonary metastases in a patient following surgery for HCC.

Conflict of interest No author has any conflict of interest.

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