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Case Report Open Access

Complete Response of Hepatocellular Carcinoma to Sorafenib: A Case Report and Review of Literatures

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Abstract

Background: Sorafenib is the current standard treatment for advanced and unresectable hepatocellular carcinoma (HCC). Although the efficacy of sorafenib on the overall survival and time to progression has been repeatedly proven, clinically evident and sustainable response especially Complete Response (CR) is rarely observed after its treatment.

Case Report: We report a case of a 64-year old female patient with unresectable HCC who received sorafenib treatment of more than 8 months following a Transarterial Chemoembolization (TACE) treatment. The patient had a rapid and complete response within 1 month of sorafenib treatment, which sustained for more than 7 months after the initiation of the therapy.

Conclusions: This result suggests that sorafenib alone or its use with TACE may be useful in the treatment of unresectable HCC. Translational clinical trials are needed to identify and exploit the underlying mechanism for this superb but rare observation.

Keywords: Hepatocellular Carcinoma (HCC); Sorafenib; Molecular target therapy

Background

Hepatocellular Carcinoma (HCC) is the fifth most commonly diagnosed cancer and the third leading cause of cancer death worldwide [1]. The majority of patients diagnosed with HCC present with advanced disease, and radical treatment is usually not a valid treatment option. Before the launch of sorafenib (BAY 43-9006), there was no standard therapy for advanced HCC, and liver transplantation and chemoembolization were treatments only applicable for selected groups of patients with locally advanced disease [2]. Currently, sorafenib is the only systemic treatment modality approved for unresectable or metastatic HCC, which has demonstrated efficacy in improving Progression-Free Survival (PFS). However, radiologically evident partial or complete response is rare after sorafenib treatment. Here, we report a case of a 64-year-old female with advanced non-metastatic HCC who achieved a CR within 1 month of sorafenib treatment, which sustained for more than 7 months after the initiation of the therapy. So far, the patient is still alive.

Case Report

A 64-year-old female patient with a significant past medical history of hypertension, diabetes mellitus, and hepatitis B for more than 30 years, was admitted to the Shanghai Cancer Hospital, Fudan University in May 2009, for a 10-day history of fever and multiple masses in liver detected by ultrasound. The initial MRI-scan of the abdomen preformed on May14, 2009 (Figures 1 and 2) demonstrated multiple intrahepatic masses and a portal mass. The Alpha-Feto Protein (AFP) levels were 3.6 ug/L (May 08, 2009) and 2.22 ug/L (May 20, 2009). A fine needle aspiration of the intrahepatic masses was performed and pathology study confirmed a diagnosis of primary HCC. According to the clinical presentation and imaging studies, a diagnosis of BCLC stage C, Child-Pugh A HCC was made. The patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1 at the time of diagnosis.

The patient received a TACE (Arteria hepatica propria proper hepatic artery: L-OHP 200mg, right branch of proper hepatic artery: THP 60 mg plus lipiodol 3 ml) on June 4, 2009. The patient tolerated the treatment very well except for mild nausea and vomiting after TACE and the symptoms subsided on Day 5 after the treatment on June 6, 2009. Oral sorafenib was initiated then at 400 mg, twice daily. There was a transient elevation of blood pressure (grade 1) after the first dose which subsided by one dose of extended release nifedipine (25 mg). No other adverse-reactions appeared except for mild hand-foot skin reaction (grade 1). The condition was well controlled by Mucopolysaccharide Polysulfate Cream without dose reduction of sorafenib. During that time, there were no other anticancer treatments given to her.

Two lesions measured 3.0×2.5 cm and 2.0×2.0 cm were observed in the initial MRI of the abdomen on May 14, 2009 (Figure 1 and 2). A CT scan of the abdomen obtained on July 10, 2009, i.e., one month after sorafenib treatment demonstrated CR for both lesions. The patient's ECOG status was 0. Subsequent CT scans preformed after 2 months and 4.months (Aug 22, 2009 and Oct 17, 2009) revealed no significant findings in the liver. In addition, MRI of the abdomen performed on Dec 18, 2009 and Feb 28, 2010 (i.e., about 6 and 8months after initiation of sorafenib) confirmed a sustained radiological CR. Patient's AFP level was negative during the treatment (From 2.02 to 3.6 ug/L).

Discussion

In the current case study, we report a female patient with advanced nonmetastatic HCC who achieved a radiologically evident CR that

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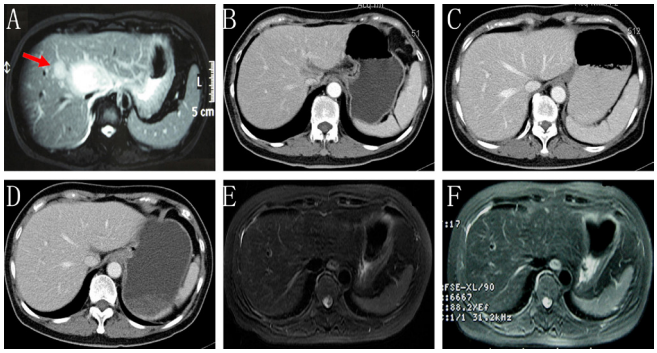

Figure 1: The bigger lesion
A: May 14, 2009 MRI; B: July 10, 2009 CT; C: Aug 22, 2009 CT; D: Oct 17, 2009 CT; E: Dec 18, 2009 MRI; F: Feb 28, 2010 MRI.
Comparison of MRI and CT scans taken from various point before and after the initiation of sorafenib demonstrated a sustainable radiological complete response.

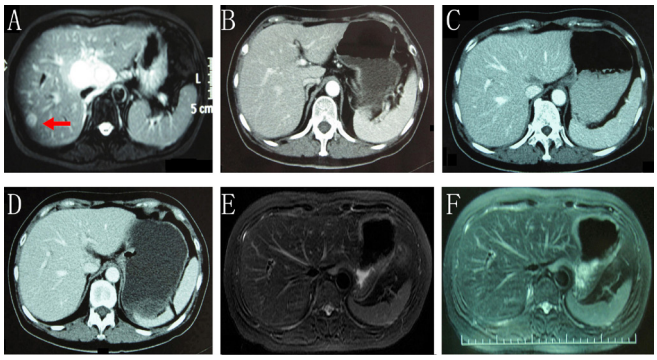

Figure 2: The smaller lesion
A: May 14, 2009 MRI; B: July 10, 2009 CT; C: Aug 22, 2009 CT; D: Oct 17, 2009 CT; E: Dec 18, 2009 MRI; F: Feb 28, 2010 MRI.
Comparison of MRI and CT scans taken from various point before and after the initiation of sorafenib demonstrated a sustainable radiological complete response.

has last for more than 7 months after TACE followed-by sorafenib treatment. She is clinically without evidence of disease at the time of this report. Furthermore, the patient tolerated both treatments well, and has not experienced substantial side-effects associated with either treatment. The only adverse-reactions to sorafenib observed were grade 1 transient hypertension and grade 1 hand-foot skin reaction.

HCC is one of the most malignant neoplasms of gastrointestinal tract. Surgical resection is the only curative treatment modality for HCC; however, prognosis of patients with unresectable disease is usually dismal. Selected patients with advanced HCC can be palliated with local treatment options including TACE, cryotherapy, radiation therapy, or radiofrequency ablation. Unfortunately, clinically evident and sustainable response especially CR observed after local palliation such as TACE is exceedingly rare [3]. Furthermore, effective systemic cytotoxic chemotherapy is still lacking.

Sorafenib, an oral multikinase inhibitor, was approved for the treatment of advanced HCC by Food and Drug Administration of the United States, the European Medicines Agency, as well as the State Food and Drug Administration of China. It is the current standard treatment modality for advanced HCC (Child-Pugh A or B) [4]. With a recommended oral dose of 400mg twice a day (b.i.d.), sorafenib has been shown to improve the progression free survival in patients with Child-Pugh A or B HCC [5]. In a prospective phase II clinical trial, 137 patients with advanced inoperable HCC (Child-Pugh A or B) without prior systemic treatment were treated with sorafenib (400 mg b.i.d.) in 4-week cycles. The results revealed a median TTP of 4.2 months, and a median overall survival (OS) time of 9.2 months [6]. These preliminary results were further confirmed by randomized phase III trials. Llovet et al. [7] first reported the results of an international phase III randomized placebo-controlled trial (i.e., the SHARP trial), and demonstrated that sorafenib improved survival in advanced HCC, Patients (ECOG 0-2 and Child-Pugh A) with advanced measurable HCC without prior systemic treatment achieved a median OS of 10.7 months after sorafenib (400 mg b.i.d.) treatment, as compared to 7.9 months of those received placebo. The median TTP and disease-control rate were 5.5 vs. 2.8 months (P<0.001) and 43% vs. 32% (P=0.002), respectively.

The findings of this international clinical trial were further confirmed by a randomized clinical trial conducted in the endemic regions of HCC. In the Asian phase III trial reported by Cheng et al. [8], sorafenib was found to provide improved OS and TTP in patients with advanced HCC from the Asia-Pacific region. The median OS time and TTP were 6.5 vs. 4.2 months (P=0.014) and 2.8 (2.63-3.58) vs. 1.4(1.35-1.55) months (P=0.0005) for patients received sorafenib or placebo, respectively.

The results of the aforementioned clinical trials are detailed in Table 1. Despite the improved outcome with sorafenib treatment, objective response of the gross lesion(s) is usually limited. The Partial Response (PR) rates reported were merely 1.3-3.3%, and CR was not observed in any of the prospective trials [6-8]. An exhaustive search of published literature revealed one case report showing CR of HCC after sorafenib treatment. A 78-year old male with unresectable metastatic HCC achieved a rapid and complete clinical response following therapy with sorafenib (400 mg, b.i.d.) for 6 months. No evidence of recurrence had been noted for 6 months after discontinuation of therapy, this report is detailed in Table 2 [9]. Furthermore, for another clinical indication of sorafenib, i.e., renal cell carcinoma, and clinical response after treatment is equally limited despite a significant improvement in TTP [10]. Results from phase II clinical trials on sorafenib for the treatment of advanced breast and thyroid cancers also demonstrated very limited evident response rates, despite its potential clinical efficacy in improving TTP [11,12].

Sorafenib is associated with a number of adverse-effects [13]. Although hypertension and hand-foot skin reactions are commonly observed, the only adverse-reactions of our patient to sorafenib treatment were transient hypertension and grade 1 hand-foot skin reaction [14,15]. The adverse-reactions seen in the similar case study reported by So et al. was mild diarrhea. The observation of mild side-effects is perplexing as finding of large-scale clinical trials have demonstrated that response in terms of TTP is related to the severity of adverse-effects especially skin reaction [16,17]. The clear contrast between our finding and those of the case study reported by So et al. versus the results of the prospective trials suggested that a distinct but rare mechanism might exist for sorafenib in the treatment of HCC of our case.

Angiogenesis and signaling through the RAF/Mitogen Activated Protein (MAP)/extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK (RAF/MEK/ERK) cascade play important roles in the development of HCC [18]. Sorafenib that targets receptor tyrosine and serine/threonine of the cancer cell and tumor vessels is suggested to

	Abou-Alfa GK, et al.	J. Llovet, et al.		Cheng AL, et al.	
	Sorafenib alone	Sorafenib vs Placebo		Sorafenib vs Placebo	
Patients' Characteristics					
Number	137	299	303	150	76
Median Age,years	69	64.9	66.3	51	52
Sex(male/female)	97/40	260/39	264/39	127/23	243/81
CP A/CP B/Missing	98/38/1	284/14/0	297/6/0	146/4/0	74/2/0
Hepatitis B/Hepatitis C/other	23/66/48	56/87/156	55/82/166	106/16/28	59/3/14
Disease stage at study entry					
(TNM classification)II,IIIA/IIIB,IV	4/42/91	NA	NA	NA	NA
BCLC B/C	NA	54/244	51/252	NA/143	NA/73
ECOG(0/1/2)	68/69/0	161/114/24	164/117/22	38/104/8	21/51/4
Outcome					
OS(mo)	9.2	10.7	7.9	6.5	4.2
TTSP(mo)	NA	4.1	4.9	3.5	3.4
TTP(mo)	4.2	5.5	2.8	2.8	1.4
Disease control rate,%	NA	43	32	35.3	15.8
Complete response,n (%)	0	0	0	0	0
Partial response, n (%)	3(2.2)	7 (2.3)	2 (0.7)	5(3.3)	1(1.3)
Stable disease, n (%)	8(5.8)	211 (70.6)	204 (67.3)	81(54.0)	21(27.6)
Progressive disease, n (%)	46(33.6)	54 (18.6)	73 (24.1)	46(30.7)	41(54.0)
Not available for independent review	32(23.5)	NA	NA	18(12.0)	13(17.1)
Adverse Events					
Hand-foot skin reaction,n	42	21	3	67	2
Rash or desquamation,n	23	16	11	30	5
Alopecia,n	14	14	2	37	1
Fatigue,n	41	22	16	30	6
Diarrhea,n	59	39	11	38	4
Nausea,n	22	11	8	17	8
Anorexia,n	19	14	3	19	2
Vomiting,n	14	5	3	NA	NA
Bleeding,n	NA	7	4	NA	NA
Hypertension,n	NA	5	2	28	1

CP: Child-Pugh; NA: Not Available; mo: month; n: number; OS: Overall survival; TTSP: Time to symptomatic progression; TTP: Time to tumor progression

Table 1: Clinical trials on sorafenib in the treatment of HCC.

have a direct effect on cell proliferation that involves the RAF/MEK/ERK signaling pathway [19,20]. However, the exact mechanism of sorafenib on HCC is unknown. In a preliminary report of early results of assessing potential predictive biomarkers from the SHARP study, Llovet and colleagues found that sorafenib significantly decreased plasma levels of soluble c-KIT, vascular endothelial growth factor receptor(VEGFR)-2,3 and increased Vascular Endothelial Growth Factor (VEGF) levels at 12 weeks. HCC patients with high baseline levels of soluble c-KIT demonstrated a trend of better response to sorafenib in terms of OS and TTP. In addition, baseline higher pERK immunostaining correlated with a trend towards longer TTP [21]. Nevertheless, as CR was not reported in SHARP or other randomized trials; the applicability of the results mentioned above to our patients with CR is unknown.

As such, we consider both tumor response and adverse-effects observed in this case important as they may indicate a unique but rare mechanism of sorafenib in the treatment of HCC. If this mechanism of optimal response is identified, biomarkers for predicting of such response can then be targeted, and adjuvant treatment to enhance the therapeutic effect of sorafenib should be researched and developed, with an aim of long-term disease-free survival in patients of advanced HCC with minimal invasive treatments.

The use of TACE in this patient acts as a confounding factor for determining the underlying mechanism of the superb outcome from our patient. TACE is often used for local palliation in patients with unresectable HCC [22]. Complete resolution of gross liver lesions have not been observed in reported controlled clinical trials on TACE [23-25]. A comprehensive review of literatures also revealed that CR after TACE is rare [3]. It has been suggested that tumor tissue ischemia and hypoxia after TACE may promote the expression of VEGF [26]. However, current understanding of HCC and its treatment with either modality preclude an explanation for the observation of this case, and clinical outcome of combined use of TACE and sorafenib is lacking. Currently, two interventional clinical trials of sorafenib and TACE to treat HCC are ongoing at University of Pittsburgh and Heinrich-Heine University, Duesseldorf [27,28]. The findings in these studies will be crucial for the understanding of the clinical implication of our observation.

Conclusion

Sorafenib induced complete resolution of gross liver lesions of a patient with unresectable and locally advanced HCC. This phenomenon may represent a unique but rare therapeutic mechanism of sorafenib or its use with TACE. Translational clinical trials are needed to identify and exploit the underlying mechanism for this superb but rare observation.

	Brian J So, et al.		Lianyu Chen, et al.	
Patient's Characteristics				
Age,years	78		64	
Sex	Male		Female	
Related Diseases				
Hepatitis	NA		B	
Hypertension	Yes		Yes	
Diabetes	Yes		Yes	
Cirrhosis	Yes		Neg	
Previous Therapy				
Surgical Resection	Neg		Neg	
Liver Transplantation	Neg		Neg	
RFA,PEI,TACE,HAI	Neg		TACE	
Pathological Diagnosis	NA		HCC	
Disease Stage(BCLC)	NA		C	
	First Visit	Last Visit	First Visit	Last Visit
Number of lesion	Multiple	Neg	multiple	Neg
Longest Diameter,cm	4.5×5.0	Neg	3.0×2.5	Neg
Metastatic Lesion	Lung	Lung	Neg	Neg
Biochemical Analysis				
Child-Pugh Class	NA	NA	A	A
AFP(ng/ml)	13599	3.8	2.22	2.67
ECOG	2	1	1	0
Maintain dose level	400 mg,bid	0	400 mg,bid	400 mg,bid
Main adverse-reactions	Diarrhea		HFSR	
Time of treatment(mo)	6		>8	
Outcome	CR		CR	

NA: Not Available; Neg: Negative; mo: months; HFSR: Hand foot skin reaction; CR: Complete response; PR: Partial response; >: more than

Table 2: Clinical reports on sorafenib in the treatment of HCC.

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