Phase I Adjuvant Trial of Sorafenib in Patients with Hepatocellular Carcinoma after Orthotopic Liver Transplantation

NING JIA[1], IRIS LIOU[2], JEFFREY HALLDORSON[3], ROBERT CARITHERS[2], JAMES PERKINS[3], JORGE REYES[3], MATTHEW YEH[4], ELIZABETH STOHR[5], SUJATA RAO[5,6] and EDWARD H. LIN[5]

[1]*Department of Medical Oncology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Tsinghua University Health System, Beijing, P.R.C;*
[2]*Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, WA, U.S.A.;*
[3]*Division of Transplantation, Department of Surgery, University of Washington, Seattle, WA, U.S.A.;*
[4]*Department of Pathology, University of Washington, Seattle, WA, U.S.A.;*
[5]*Department of Medicine, University of Washington, Seattle, WA, U.S.A.;*
[6]*Onyx Pharmaceuticals, South San Francisco, CA, U.S.A.*

Abstract. *Background: Post-transplant hepatocellular carcinoma recurrence has been reported to be between 15-18% and is higher among patients with high-risk features (bilobar tumor, macrovascular invasion, or multifocality). There are no known treatments which reduce risk of recurrence post-transplant. Sorafenib is currently approved for the treatment of advanced hepatocellular carcinoma. The objective of this phase I trial was to establish the safety and toxicity profile of sorafenib in high-risk patients with hepatocellular carcinoma who have undergone orthotopic liver transplantation. Patients and Methods: Patients with hepatocellular carcinoma on explant with above high risk features were eligible to start the study drug between 28 and 60 days after liver transplantation. Sorafenib was administered and escalated twice daily on three cohort dose levels: i) 400 mg/day, ii) 600 mg/day and iii) 800 mg/day. Results: Four patients newly transplanted were enrolled and received standard post-transplant medications. Dose-limiting toxicity was reached at the first cohort dose, with three out of four patients experiencing grade 3 toxicities. One patient experienced emerging grade 3 hand foot skin reaction leading to discontinuation of the study drug. Duration of sorafenib in the four patients was 0.7 months, 1.6 months, 3.5 months and 1.6 months, respectively. Conclusion: Although a small number of patients were studied, toxicity seen at 400 mg/day is consistent with toxicity reported by a small parallel study by Siegel AB.*

Correspondence to: Edward H. Lin, Seattle Cancer Care Alliance, 825 Eastlake Ave E, G3-630, Seattle, WA 98019, U.S.A. Tel: +1 2062886678, Fax: +1 2062882054, e-mail: elin88@u.washington.edu

Key Words: Phase I, sorafenib, hepatocellular carcinoma, orthotopic liver transplantation, adjuvant therapy.

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor worldwide. Surgical tumor resection and local ablation therapy are potentially curative for selected patients with adequate liver function. For those patients with poor liver function reserve, orthotopic liver transplantation (OLT) represents the only curative modality in this selected group of patients. Post-transplant hepatocellular carcinoma recurrence has been reported at between 15-18% (1, 2), typically within the first two years following OLT, and is higher among patients with high-risk features (bilobar tumor, macrovascular invasion, or multifocality). Those with high risk features may be at risk for recurrence as high as 66.7% (3). Traditional adjuvant systemic chemotherapy has not been shown to prolong survival in HCC with or without local neoadjuvant treatment modalities after OLT (4). The median survival for patients with tumor recurrence is only around nine months (1). Thus, there is a clinical urgent need to develop an effective adjuvant therapy following OLT.

Sorafenib is a signal transduction inhibitor that prevents tumor cell proliferation and angiogenesis through blockade of the Raf/mitogen-activated protein kinase-extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway. Sorafenib as compared to placebo demonstrated modest improvement in overall survival in two large phase III trial in advanced HCC (5, 6). Sorafenib is the only approved medication in the US and Asia for the treatment of advanced HCC. This phase I study aimed at establishing the safety profile of sorafenib post OLT in patients with high risk features for HCC recurrence.

Patients and Methods

Patient eligibility. Patients with high risk HCC histological features (bilobar tumor, macrovascular invasion, or multifocality) on explant who had not received prior systemic anticancer treatment for HCC were eligible. If patients had well-differentiated HCC, they were required to have all three features. Other inclusion criteria were: age >18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2; life expectancy of at least 12 weeks; four weeks beyond and less than 60 days from liver transplant surgery (to first study treatment); adequate hematopoiesis (absolute platelet count $\geq 60\times10^9$/L, hemoglobin ≥8.5 g/dl), normal coagulation (prothrombin time ≤6 above the control and international normalized ratio ≤2.3); normal renal function [serum creatinine concentration ≤1.5×the upper limit of normal (ULN)]; normal liver (serum total bilirubin level ≤3.0 mg/dl, serum aspartate and alanine transaminase levels ≤5.0×ULN) and pancreatic laboratory tests (serum amylase and lipase levels ≤1.5×ULN); and written informed consent from the patient.

Exclusion criteria included clinically evident congestive heart failure, serious cardiac arrhythmia, active or symptomatic coronary artery disease or ischemia, uncontrolled hypertension, active clinically serious infection, history of human immunodeficiency virus (HIV) infection, central nervous system tumors including metastatic brain disease, clinically significant gastrointestinal bleeding within 30 days prior to study entry, previous or concurrent malignancy that was distinct in primary site or histology from HCC (any cancer treated curatively more than three years prior to entry was not excluded), prior use of systemic anticancer therapy, any condition that was unstable or which could jeopardize the safety of the patient and their compliance in the study, and pregnancy or lactation for women. The study was approved by the Fred Hutchinson Cancer Research Center (#6697).

Treatment methods. Patients started the study medication between 28 and 60 days after liver transplantation. Sorafenib was administered twice daily, and the dose was escalated on three cohort dose levels: i) 400 mg, ii) 600 mg and iii) 800 mg. Sorafenib was given to all patients orally twice daily, in the morning and in the evening (every 12 h, as far as possible). Planned treatment was six 28-day cycles of adjuvant therapy. The sorafenib dose was determined by the escalation dose level at the time of entry into study. Patients continued therapy with the study medication until a criterion was met for stopping therapy. Criteria for discontinuing therapy included recurrence of HCC, deterioration of ECOG PS to greater than 3, intolerable adverse events, and withdrawal of consent.

Examination and observation for safety was conducted every week in the first four weeks then monthly during the treatment period, and administration of the drug was terminated immediately when the patient met the criteria for removal from the study, as described in this protocol with due consideration for the patient's safety.

Study design. This phase I trial was conducted to establish the safety and toxicity profile of sorafenib administered twice daily to HCC patients who had undergone OLT. The study was designed to evaluate 20 patients who had undergone transplant for HCC to establish the dose-limiting toxicity (DLT). There was no formal pharmacokinetics analysis. The DLT was defined as: non-hematological/hematological toxicity≥grade 3 as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (7) that occurred during the first 28-day cycle of sorafenib. In the absence of a DLT at the end of the initial four weeks of treatment, the next cohort of three patients was enrolled. If any patient developed a DLT, three additional patients were enrolled at that dose level. These three patients were to complete the first 28-day cycle without developing DLTs before additional patients could be entered at the next dose level. If DLTs occurred in two or more patients at any dose level, then accrual at that dose level stopped. The maximum tolerated dose (MTD) was the dose level below which two or more patients developed DLT.

Clinical assessments. Medical history, physical examination and electrocardiogram were carried out at baseline. All patients underwent complete blood cell counts, serum chemistries and coagulation panel at baseline and at least once weekly in the first four weeks, then monthly during the treatment period after initiating treatment with sorafenib. During treatment, patients had weekly assessment of non-hematological toxicities in the first four weeks, and then monthly. Computed tomographic (CT) scan and serum alpha-fetoprotein (AFP) measurements were performed at study entry and every three months thereafter.

Results

A total of four patients newly receiving transplants out of a planned 20 were enrolled. Patient characteristics are shown in Table I. The mean age was 49 years (range 18-65 years; male: female=3:1). Three patients had multifocal tumor on explants, and two had bilobar disease. Patients received standard post-transplant medications, including anti-herpes virus prophylaxis (acyclovir or ganciclovir), *Pneumocystis jirovecii* prophylaxis (trimethoprim/sulfamethoxazole), anti-fungal prophylaxis (clotrimazole or fluconazole), and immunosuppressant agents (sirolimus and/or tacrolimus). Adverse events in these four patients are shown in Table II. The most common drug-related adverse event was hand foot skin reaction (4/4). The other adverse events were mostly grade 1 headache and pleural and abdominal pain, which is atypical in the sorafenib experience with advanced HCC. One out of three patients on tacrolimus experienced grade 1 neuropathy. We reached the DLT among the first cohort of four patients with three patients who experienced grade 3 hand foot skin reaction, diarrhea, and abnormal liver function tests, respectively, and the fourth patient begin to experience emerging grade 3 hand foot skin reaction, which led to withholding of study medication due to safety concerns for this patient (Table II). There were no drug-related grade 4 or 5 toxicities. The duration of sorafenib use in the four patients was: 0.7 months, 1.6 months, 3.5 months and 1.6 months, respectively. One patient died from progressive HCC and the other three patients are currently free of HCC recurrence as of last follow-up after 23.4 months, 16.8 months and 19.2 months, respectively.

Table I. *Patient characteristics*.

Characteristic	Patient			
	No.1	No. 2	No. 3	No. 4
Gender	Male	Female	Male	Male
Age years	59	18	55	65
Site of tumor	Bilobar,multifocal tumor	Bilobar tumor	Multifocal tumor	Multifocal tumor
Pathology	Poorly differentiated HCC	Poorly differentiated HCC	Moderately differentiated HCC	Moderately differentiated HCC
Tumor stage (T) on explant	2	3	2	2
Duration of sorafenib (months)	0.7	1.6	3.5	1.6
Concurrent medications	TMP-SMZ, sirolimus, tacrolimus	TMP-SMZ, tacrolimus, ganciclovir	TMP-SMZ, sirolimus, acyclovir	TMP-SMZ, sirolimus, Tacrolimus

HCC: Hepatocellular carcinoma; TMP-SMZ: Trimethoprim/sulfamethoxazole.

Discussion

We were among the first two groups to study adjuvant sorafenib in patients post OLT and found DLT at the first cohort of patients at the 400 mg dose level. Siegel *et al* also found DLT for sorafenib at the 400 mg level (8). Thus, our data supports the recommended MDT for sorafenib post OLT of 200 mg once daily. The expanded cohorts were continued at this dose.

The heightened toxicities at the exceedingly low dose of sorafenib in patients post OLT raises the question of whether there is a potential drug drug interaction between sorafenib and concomitant medications. Sorafenib is metabolized through the Cytochrome P450, family 3, subfamily A (CYP3A) system in the liver and acyclovir is also metabolized through the same liver microsome, thus raising the possibility of this agent being a potential culprit. Unfortunately, the current study did not employ the use of pharmacokinetics, thus, we could not ascertain if increased drug levels or metabolites were present. Interestingly, patients with recurrent HCC post OLT are able to initiate sorafenib at a dose of 400 mg twice daily; however, 36% to 66% of patients typically require dose modification due to untoward side-effects (9-11). There was no drug-drug interaction between sorafenib and immunosuppressant agents in a study with a limited number of patients and follow-up period (9). In the sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) and Asian studies, dose reduction for sorafenib occurred in 26% and 30.9% of the patients who had Child A cirrhosis, respectively (5,6).

Tacrolimus is associated with neurotoxicity (12). The degree of neurological toxicity may be underestimated due to the concurrent hand foot skin reaction caused by sorafenib.

Previous groups had attempted to deliver adjuvant conventional chemotherapy based on doxorubicin for patients post OLT in randomized trials and found no net benefits (13, 14). Licartin, a ^{131}I-radiolabeled murine monoclonal antibody that specifically binds to HCC cells that express an HCC-specific molecule, Hab18G/CD147, was tested in a randomized study (15). The HCC recurrence rate significantly decreased (27% *vs*. 57%). However, the number of patients was limited, and the follow-up was only once per year. This encouraging agent therefore needs further evaluation. Currently, sorafenib as adjuvant treatment in the prevention of recurrence of hepatocellular carcinoma

Table II. *Adverse events*.

	CTC Grade 1/2 (n=4)	CTC Grade 3 (n=4)	All grades (n=4)
Hematological			
Leucopenia	1	-	1
Non-hematological			
Hypertension	2	-	2
Fatigue	2	-	2
Hand foot skin reaction	3*	1	4
Rash	1	-	1
Pruritus	1	-	1
Diarrhea	-	1	1
Ascites	-	1	1
Edema: limb	-	1	1
AST	-	1	1
ALT	-	1	1
GGT	-	1	1
Alkaline phosphatase	1	-	1
Neuropathy: sensory	2	-	2
Insomnia	1	-	1
Colitis, infectious	1	-	1
Pain	3	-	3

CTC: Common terminology criteria for adverse events; ALT: Serum alanine transaminase; AST: Serum aspartate transaminase; GGT: γ-glutamyl transpeptidase; *One patient experienced grade 2 (emerging grade 3) hand foot skin reaction.

(STORM) trial has completed accrual of patients, and this study randomized patients to placebo *versus* sorafenib in patients who underwent HCC resection. This study will shed light on the potential role of adjuvant sorafenib for resected HCC akin to adjuvant sorafenib in the post OLT setting.

In summary, sorafenib in the patients post OLT was complicated by DLT at the 400 mg dose level and it appears that MTD at 200 mg daily is established in this cohort of patients. Further studies are needed to establishe safety and efficacy in the adjuvant setting in this disease.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

Acknowledgements

This study was supported by Onyx Pharmaceutical.

References

1 Roayaie S, Schwartz JD, Sung MW, Emre SH, Miller CM, Gondolesi GE, Krieger NR and Schwartz ME: Recurrence of hepatocellular carcinoma after liver transplant: Patterns and prognosis. Liver Transpl *10*: 534-540, 2004.

2 Grasso A, Stigliano R, Morisco F, Martines H, Quaglia A, Dhillon AP, Patch D, Davidson BR, Rolles K and Burroughs AK: Liver transplantation and recurrent hepatocellular carcinoma: Predictive value of nodule size in a retrospective and explant study. Transplantation *81*: 1532-1541, 2006.

3 Chan EY, Larson AM, Fix OK, Yeh MM, Levy AE, Bakthavatsalam R, Halldorson JB, Reyes JD and Perkins JD: Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: Implications for surveillance studies and new adjuvant therapies. Liver Transpl *14*: 956-965, 2008.

4 Kim R, Tan A, Estfan B and Aucejo F: Adjuvant treatment after orthotopic liver transplantation: Is it really necessary? Oncology *23*: 1276-1281, 2009.

5 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med *359*: 378-390, 2008.

6 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D and Guan Z: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol *10*: 25-34, 2009.

7 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003(http://ctep.cancer.gov), Publish Date: August 9, 2006.

8 Siegel AB, Hidalgo R, Tsushima D , Zaretsky J, Emond J, Kato T and Brown RS: Phase I trial of sorafenib in hepatocellular carcinoma (HCC) patients after liver transplantation (LT). J Clin Oncol *29*: abstr TPS172, 2011.

9 Yoon DH, Ryoo BY, Ryu MH, Lee SG, Hwang S, Suh DJ, Lee HC, Kim TW, Ahn CS, Kim KH, Moon DB and Kang YK: Sorafenib for recurrent hepatocellular carcinoma after liver transplantation. Jpn J Clin Oncol *40*: 768-773, 2010.

10 Kim R, El-Gazzaz G, Tan A *et al*: Safety and feasibility of using sorafenib in recurrent hepatocellular carcinoma after orthotopic liver transplantation. Oncology *79*: 62-66, 2010.

11 Dharancy S, Romano O, Lohro R, Pageaux GP, Ledinghen VD, Hurtova M, Vanlemmens C, Salame E, Cattan S, Boleslawski E, Mathurin P and Pruvot FR: Tolerability of Sorafenib in recurrent hepatocellular carcinoma after liver transplantation: A case control study. Liver Transpl *14*: S216, 2008.

12 Bechstein WO: Neurotoxicity of calcineurin inhibitors: Impact and clinical management. Transpl Int *13*: 313-326, 2000.

13 Pokorny H, Gnant M, Rasoul-Rockenschaub S, Gollackner B, Steiner B, Steger G, Steininger R and Mühlbacher F: Does additional doxorubicin chemotherapy improve outcome in patients with hepatocellular carcinoma treated by liver transplantation? Am J Transplant *5*: 788-794, 2005.

14 Söderdahl G, Bäckman L, Isoniemi H, Cahlin C, Höckerstedt K, Broomé U, Mäkisalo H, Friman S and Ericzon BG: A prospective, randomized, multi-centre trial of systemic adjuvant chemotherapy *versus* no additional treatment in liver transplantation for hepatocellular carcinoma. Transpl Int *19*: 288-294, 2006.

15 Xu J, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, Xu HY, Song F, Yang XM, Mi L, Zhao QC, Tian R, Feng Q, Zhang SH, Li Y, Jiang JL, Li L, Yu XL, Zhang Z and Chen ZN: A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. Hepatology *45*: 269-276, 2007.

Received April 17, 2013
Revised May 21, 2013
Accepted May 22, 2013