

Sorafenib for Patients with Hepatocellular Carcinoma and Child-Pugh B Liver Cirrhosis: Lessons Learned from a Terminated Study

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TRIAL INFORMATION

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- **Sponsor:** Amsterdam University Medical Center
- **Principal Investigator:** Heinz-Josef Klümpen
- **IRB Approved:** Yes

LESSONS LEARNED

- Recruitment of patients with advanced hepatocellular carcinoma and Child-Pugh B for sorafenib treatment and additional pharmacokinetic studies is challenging.
- Patients with Child-Pugh B liver cirrhosis have high rates of cirrhosis-related adverse events.

ABSTRACT

Background. Few data are available on the pharmacokinetics (PK) of sorafenib in patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh B liver cirrhosis. This study aimed to explore the sorafenib PK and its relationship with efficacy and toxicity in these patients.

Methods. Patients with advanced HCC and Child-Pugh B7-8 liver function were prospectively recruited at a tertiary center. Adverse events (AEs), progression-free survival (PFS), and overall survival (OS) were recorded. Patients received a starting dose of 200 b.i.d. with toxicity-adjusted dose escalation to a target dose of 400 mg b.i.d. with PK sampling at fixed time points.

Results. Between May 2014 and March 2017, 12 patients were screened, of whom 7 progressed to a terminal stage during the screening ($n = 6$) or shortly after recruitment ($n = 1$). The five included patients had median PFS of 3.8 months (range, 1.7–10.8) and OS of 7.4 months (range, 1.7–25.8). Three patients had severe AEs and one patient had a partial response with an OS of 25.8 months. In 2017, the trial was aborted for lack of accrual.

Conclusion. Because of low accrual, no conclusion can be drawn on the sorafenib PK in patients with advanced HCC and Child-Pugh B liver cirrhosis. The poor survival and frequent cirrhosis-related AEs suggest limited benefit for most of these patients. *The Oncologist* 2020;25:e1274–e1279

DISCUSSION

Sorafenib, a tyrosine kinase inhibitor, is recommended for patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh class A liver function [1–3]. Nonetheless, real-life studies showed that sorafenib is still commonly (12%–44%) prescribed to patients with Child-Pugh B liver function [4–14]. Sorafenib undergoes hepatic metabolism and biliary excretion, which could potentially be influenced by concomitant liver cirrhosis [15]. Prior studies analyzing the association between hepatic impairment and sorafenib's pharmacokinetics (PK) had small Child-Pugh B subgroups ($n < 20$) [16–19]. The present study aimed to prospectively recruit 45 patients to study sorafenib PK parameters and identify potential predictors for sorafenib exposure (i.e., bilirubin, CYP3A4 activity) and its relationship with toxicity, progression-free survival (PFS), and overall survival (OS).

Patients with advanced HCC, an Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, and a Child-Pugh score of B7 or 8 were recruited at a large referral center. Patients received a starting dose of 200 b.i.d. with ramp-dosing to a target dose of 400 mg b.i.d. with PK sampling at fixed time points [20].

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Table 1. Patient characteristics

Characteristic	Number
Gender	
Male	5
Female	0
Age, years, median (range)	69 (63–79)
HCC etiology	
Alcohol	5
Other	0
ECOG performance status	
0	1
1	4
Child-Pugh classification	
B7	4
B8	1
BCLC stage	
Intermediate stage (BCLC-B)	1
Advanced stage (BCLC-C)	4
Received prior treatment	
No	4
Yes: TACE	1

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Despite extensive accrual efforts for almost 3 years (May 2014 to March 2017), our study had to be terminated prematurely after inclusion of 5 patients. Foremost, there were competing studies also recruiting patients with Child-Pugh B7 (i.e., SORAMIC trial and STOP-HCC trials [21, 22]), which were prioritized by patients and physicians. The accrual was further hampered by a rapidly deteriorating liver function (Child-Pugh \geq B9) or clinical condition (ECOG PS \geq 3) in 7 of 12 (58%) screened patients who had a median OS of 2.5 months (range 0.5–5.7 months). Six of these patients progressed to a terminal stage during the screening period, whereas one patient had a variceal bleeding and progressive ascites 5 days after starting sorafenib. The patient characteristics are summarized in Table 1.

Unfortunately, this incomplete study is limited in drawing definitive conclusions on the impact of Child-Pugh B liver function on sorafenib PK, efficacy, and safety. This is the second study in patients with Child-Pugh B patients treated with sorafenib that had to be terminated due to slow enrollment [23]. This reflects the difficulty in recruiting and treating these patients, mainly due to the higher risk of cirrhosis-related adverse events.

TRIAL INFORMATION

Disease	Hepatocellular carcinoma
Stage of Disease/Treatment	Advanced/palliative
Prior Therapy	No designated number of treatments
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Sorafenib exposure
Secondary Endpoint	Toxicity/adverse events
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival

Additional Details of Endpoints or Study Design

The main endpoint was sorafenib and *N*-oxide sorafenib exposure as a marker of the PK. The population PK analysis was planned to be done using nonlinear mixed effects modelling (NONMEM). Power calculations are not possible in NONMEM. As a rule of thumb, 40 patients allow one to identify approximately three clinically significant correlations between PK parameters and patients characteristics. To be sure to have 40 evaluable patients, we aimed to recruit 45 patients.

Investigator's Analysis

Poor accrual in fragile population. High rates of cirrhosis-related adverse events. Sorafenib is unlikely to be beneficial for most patients with Child-Pugh B.

DRUG INFORMATION

Drug 1	
Generic/Working Name	Sorafenib
Trade Name	Nexavar
Company Name	Bayer
Drug Type	Small molecule
Drug Class	Tyrosine Kinase inhibitor

Dose	400 mg b.i.d.
Route	oral (p.o.)
Schedule of Administration	Starting dose: 200 mg b.i.d. with ramp-dosing to the maximum dose of 400 mg b.i.d.

PATIENT CHARACTERISTICS

Number of Patients, Male	5
Number of Patients, Female	0
Age	Median (range): 69 years (63–79 years)
HCC Etiology	Alcohol: 5; other: 0
ECOG Performance Status	0 — 1 1 — 4
Child-Pugh Classification	Child-Pugh score: B7, 4; B8, 1
BCLC Stage	Intermediate stage (BCLC-B), 1; advanced stage (BCLC-C), 4
Received Prior Treatment	No: 4; Yes: 1 (TACE)

PRIMARY ASSESSMENT METHOD

Number of Patients Screened	12
Number of Patients Enrolled	5
Number of Patients Evaluable for PK Analysis	4
Number of Patients Evaluable for Toxicity	5
Number of Patients Evaluated for PFS	5
Number of Patients Evaluable for OS	5
Radiological Evaluation Method	mRECIST
Radiological Response	Complete response: <i>n</i> = 0 (0%) Partial response: <i>n</i> = 1 (20%) Stable disease: <i>n</i> = 3 (60%) Progressive disease: <i>n</i> = 0 (0%) Response unknown: <i>n</i> = 1 (20%)
Median Duration Assessments PFS	3.8 months (range, 1.7–10.8)
Median Duration Assessments OS	7.4 months (range, 1.7–25.8)
Median Duration of Treatment	13 weeks (range, <1–46)
Median Total Tolerated Dose	400 mg (range, 200–600)

ADVERSE EVENTS, ACCORDING TO CTCV4.03

Variable, <i>n</i>	All grades	Grade 1–2	Grade 3–4
Any adverse events	5	2	3
Fatigue/asthenia	3	3	0
Diarrhea	3	3	0
Vomiting	1	1	0
Constipation	1	1	0
Hand-foot skin syndrome	3	2	1
Mucositis	2	2	0
Other			
Sepsis	1	0	1
Hyperkalemia	1	1	0
Hyponatremia	1	0	1

Neuropathy	1	1	0
Tinnitus	1	1	0
Hiccups	1	1	0
Cirrhosis-related adverse events			
Ascites	3	1	2
Hypoalbuminemia	2	1	1
Hyperbilirubinemia	5	4	1
Thrombocytopenia	4	4	0
Variceal bleeding	1	0	1

PHARMACOKINETICS/PHARMACODYNAMICS

Analysis not feasible because of small number of patients

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study terminated before completion

Terminated reason

Did not fully accrue

Investigator's Assessment

High rates of cirrhosis-related adverse events. Sorafenib is unlikely to be beneficial for most patients with Child-Pugh B

Advanced stage hepatocellular carcinoma (HCC) bears a poor prognosis with an expected median survival of 6–8 months without treatment [24]. Sorafenib, a multi-tyrosine kinase inhibitor, was the first treatment showing a modest survival benefit in these patients. Two randomized phase III studies showed that sorafenib improved the overall survival with 2–3 months compared with placebo [25, 26]. In these landmark studies, enrollment was restricted to patients with Child-Pugh class A liver function, regardless of presence or absence of underlying liver cirrhosis. International guidelines therefore recommend sorafenib treatment for patients with advanced HCC (Barcelona Clinic Liver Cancer [BCLC] stage C and Child-Pugh A only [1–3]. Nonetheless, several real-life studies showed that sorafenib is still commonly (12%–44%) prescribed to patients with Child-Pugh B liver function [4–14].

Although prior studies suggested similar adverse event profiles in patients with Child-Pugh B liver function [7, 10, 13], there is currently no data showing that sorafenib offers a significant survival benefit in Child-Pugh B patients. Sorafenib undergoes hepatic metabolism (predominantly CYP3A4) and biliary excretion, which could potentially be influenced by the presence of underlying liver disease [15]. Eight sorafenib metabolites have been identified of which pyridine N-oxide, the main circulating metabolite of sorafenib in plasma, has shown in vitro potency similar to that of sorafenib [15]. Prior studies describing the impact of the severity of hepatic impairment on sorafenib's pharmacokinetics (PK) did not find significant differences in the PK profile of sorafenib or the N-oxide metabolite in patients with decreased liver function [16–19]. In these preliminary studies, subgroups with Child-Pugh B were small ($n < 20$). In order to assess the tolerability and potential efficacy of sorafenib treatment in patients with advanced HCC and Child-Pugh B liver cirrhosis, the main aim

of our study was to explore the PK of sorafenib and its metabolites. This prospective, open-label observational study aimed to recruit 45 patients to study various PK parameters (i.e., exposure and variability of sorafenib and N-oxide sorafenib) and identify potential predictors for sorafenib exposure (i.e., bilirubin, CYP3A4 activity). Secondary aims were to correlate PK parameters with sorafenib toxicity and progression-free survival (PFS).

Between May 2014 and March 2017, patients were recruited at a large referral center for patients with HCC (Amsterdam University Medical Center, Meibergdreef, Amsterdam). Patients were eligible for the study in case of advanced HCC (BCLC-C) with a preserved Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 and a Child-Pugh score of B7 or 8. Patients received a starting dose of 200 b.i.d. with ramp-dosing to a target dose of 400 mg b.i.d. with PK sampling at fixed time points [20].

Despite the clear study design targeting a clinically relevant study population with a well-known systemic treatment (sorafenib), our study met some major obstacles and had to be terminated prematurely within 3 years after inclusion of 5 patients. Foremost, it proved difficult to recruit enough patients due to competing studies in advanced HCC that also recruited patients with Child-Pugh B7 for combined selective internal radiation therapy (SIRT) with sorafenib treatment (i.e., the SORAMIC trial and STOP-HCC trials [21, 22]). Understandingly, these studies were prioritized by patients and physicians. One patient refused the study due to the burden of hospital visits for sorafenib treatment and the additional PK sampling. For logistical reasons, expansion to a multicenter study was not feasible. Efforts to improve the accrual, including promoting the study on patient information websites and referral of potential candidates within the national study collaboration

(Dutch Hepatocellular & Cholangiocarcinoma Group [DHCG]), did not lead to a sufficient increase in accrual. In addition, the accrual was further hampered by a rapidly deteriorating liver function (Child-Pugh \geq B9) or clinical condition (ECOG PS \geq 3) in 7 of 12 (58%) screened patients. Six of these patients progressed to a terminal stage (BCLC-D) during the screening period, whereas one patient was admitted with a variceal bleeding and progressive ascites 5 days after starting sorafenib, leading to permanent sorafenib discontinuation in this case. These patients died after a median of 2.5 months (range 0.5–5.7), indicating a poor prognosis if patients with advanced HCC develop decompensated liver cirrhosis.

Lastly, the focus of this trial on patients with Child-Pugh B7-8 exposed the limitations of the Child-Pugh score as a tool for patient selection. Prior studies have reported up to 12.1% discrepancies in Child-Pugh score, caused by interobserver variation of subjective parameters (severity of ascites, encephalopathy) or incorrect categorization of continuous parameters (albumin, bilirubin, prothrombin-time) [6]. Small fluctuations in serum test can also lead to migration of patients across Child-Pugh classes.

In total, 5 male patients were enrolled with a median age of 69 years (range 63–79 years). Patients were treated for a median of 13 weeks (range, 5 days to 46 weeks) with a median tolerated daily dose of 400 mg (range 200–600 mg). All patients died, with a median PFS of 3.8 months (range 1.7–10.8 months) and OS of 7.4 months (range 1.7–25.8 months). Three patients experienced severe adverse events, including one patient admitted with a variceal bleeding and refractory ascites, 1 patient with grade 3 hyperbilirubinemia and refractory ascites, and 1 patient with grade 3–4 hand-foot syndrome complicated by a sepsis with grade 3 hypoalbuminemia and grade 3 hyponatremia.

Unfortunately, this incomplete study is limited in drawing definitive conclusions on impact of Child-Pugh B liver function on sorafenib PK, efficacy, and safety. This is the second study in patients with Child-Pugh B patients treated with sorafenib that had to be terminated prematurely due to slow enrollment [23]. This reflects the difficulty in recruiting and treating these patients, mainly due to the higher risk of cirrhosis-related adverse events. In a prior study, we extensively discussed this topic and pled for adherence to the current

guidelines and restriction of sorafenib to patients with Child-Pugh A liver function [9]. Interestingly, one patient with a partial response to sorafenib had an OS of 26 months, showing that longer survival is possible in patients with Child-Pugh B and underscoring limitations of Child-Pugh as a prognostic tool when considering sorafenib. Novel algorithms, such as the recently proposed “Prediction of Survival in Advanced Sorafenib-treated HCC” (PROSASH) score have refined survival prediction based on prognostic and predictive clinical features [27, 28]. This approach offers an individualized survival prediction with a higher accuracy than the Child-Pugh score and BCLC-algorithm [29]. These algorithms may improve clinical decision making and optimize the prognostic stratification of future clinical studies in which sorafenib is the control arm. Further studies in the mechanisms leading to the onset of sorafenib toxicity and treatment effect are needed to find additional biomarkers that may aid in improved survival prediction and patient-tailored treatment.

In conclusion, patients with Child-Pugh B liver function are unlikely to benefit from sorafenib treatment due to a higher risk of cirrhosis-related adverse events. Further studies in the mechanisms leading to the onset of sorafenib toxicity and treatment effect are needed to find additional biomarkers that may aid in improved survival prediction and patient-tailored treatment.

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DISCLOSURES

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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