Research Article

JOURNAL OF HEPATOLOGY

Sorafenib therapy for hepatocellular carcinoma with extrahepatic spread: Treatment outcome and prognostic factors

Won Sohn, Yong-Han Paik*, Ju-Yeon Cho, Ho Yeong Lim, Jem Ma Ahn, Dong Hyun Sinn, Geum-Youn Gwak, Moon Seok Choi, Joon Hyeok Lee, Kwang Cheol Koh, Seung Woon Paik, Byung Chul Yoo

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background & Aims: Sorafenib is recommended as the treatment of choice for hepatocellular carcinoma (HCC) with extrahepatic spread (EHS). However, early discontinuation of sorafenib treatment is not uncommon because of adverse events, deterioration of liver function and/or performance. This study aimed to investigate the treatment outcome and prognostic factors of sorafenib treatment in HCC patients with EHS in which sorafenib was administered for at least 8 weeks.

Methods: From May 2007 to December 2012, a total of 254 HCC patients with EHS were treated with sorafenib monotherapy for at least 8 weeks. The treatment outcome, risk factors for disease progression, and overall survival were retrospectively analyzed.

Results: The median duration of radiologic progression and overall survival after sorafenib was 2.5 and 9.6 months, respectively. Prognostic factors for radiologic progression were intrahepatic tumor with macrovascular invasion (MVI) (hazard ratio (HR) 2.38, p <0.001), intrahepatic tumor without MVI (HR 2.37, p <0.001), age <60 years (HR 1.44, p = 0.008), peritoneal involvement (HR 1.57, p = 0.03), and underlying hepatitis B (HR 1.46, p = 0.05). Prognostic factors for overall survival were lack of disease control with sorafenib (HR 2.98, p <0.001), intrahepatic tumor with MVI (HR 2.23, p <0.001), intrahepatic tumor without MVI (HR 1.70, p = 0.003), Child-Pugh class B (HR 1.90, p = 0.009), serum AFP ⩾200 ng/ml (HR 1.45, p = 0.009), and ALT ⩾40 U/L (HR 1.34, p = 0.041). In patients with chronic hepatitis B, the use of antiviral treatment was associated with favorable overall survival after sorafenib therapy (HR 0.64, p = 0.003).

Conclusion: Sorafenib prolonged survival in HCC patients with EHS who achieved disease control. Intrahepatic tumor is a poor prognostic factor for both disease progression and overall survival in HCC patients with EHS treated with sorafenib.

Keywords: Hepatocellular carcinoma; Extrahepatic spread; Sorafenib.
Received 19 June 2014; received in revised form 1 December 2014; accepted 2 December 2014; available online 13 December 2014

* Corresponding author. Address: Department of Medicine, Sungkyunkwan University School of Medicine, 81 Irwon-Ro Gangnam-Gu, Seoul 135-710, Republic of Korea. Tel.: +82 2 3410 3878; fax: +82 2 3410 6983.
E-mail address: yh.paik@skku.edu (Y.-H. Paik).

Abbreviations: HCC, hepatocellular carcinoma; EHS, extrahepatic spread; HR, hazard ratio; SHARP, sorafenib HCC assessment randomized protocol; MVI, macrovascular invasion; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; AST, aspartate transaminase; ALT, alanine transaminase; ECOG, Eastern Cooperative Oncology Group; PV, portal vein; IVC, inferior vena cava; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; HBV, hepatitis B virus.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1]. The therapeutic modality for HCC is based on the tumor stage. Curative or loco-regional therapies are recommended for the treatment of early or intermediate stage HCC [2,3]. Whereas, sorafenib is recommended as the treatment of choice for advanced HCC because it provided survival benefit over placebo in two phase III randomized clinical trials (SHARP trial and Asia-Pacific trial) [4,5].

Extrahepatic spread (EHS) of HCC is regarded as an advanced stage in most staging systems and is associated with poor prognosis [6]. Also, EHS of HCC is not a simple but a complex condition where co-existence of intrahepatic tumor, macrovascular invasion (MVI), and the sites of EHS should be considered in a clinical situation. There are several studies on the prognostic factors for HCC with EHS. Liver function, serum tumor maker such as alpha-fetoprotein (AFP), vascular tumor invasion, intrahepatic tumor, and performance status were associated with disease prognosis in HCC patients with EHS [7–9]. However, there have been few studies assessing the prognostic factors after sorafenib treatment in HCC patients with EHS.

The above two randomized clinical trials showed that sorafenib was much less effective in the treatment of advanced HCC with EHS or MVI than in treatment of HCC without EHS/MVI [4,5]. Thus, sorafenib treatment for HCC with EHS is an important but difficult issue. Real-life clinical data showed that sorafenib was administered for less than 4–8 weeks in a substantial number of patients with advanced HCC because of adverse events or deterioration of liver function [10,11]. Therefore, data regarding the treatment outcome of advanced HCC patients with adequate administration of sorafenib is currently limited. The present

Cancer

study enrolled HCC patients with EHS who were administered sorafenib for at least 8 weeks to evaluate the effect of the drug.

The aim of this study was to investigate the treatment outcome of sorafenib therapy in HCC patients with EHS. We examined the effect of sorafenib on disease progression and overall survival in HCC patients with EHS in which sorafenib was administered for at least 8 weeks. Also, the prognostic factors for disease progression and overall survival after sorafenib treatment were assessed in HCC patients with EHS.

Patients and methods

Study patients

A total of 829 patients with HCC were treated with sorafenib between May 2007 and December 2012 at Samsung Medical Center, Seoul, Korea (Fig. 1). Among them, 106 patients were excluded due to the following reasons: (i) combined HCC and cholangiocarcinoma (n = 10); (ii) loss to follow-up before the first assessment of response to sorafenib (including transfer to other hospitals) (n = 92); (iii) preemptive therapy without viable HCC (n = 4). Thereafter, we excluded 134 patients who were treated with combination therapies (transarterial chemoembolization (TACE), radiofrequency ablation (RFA), radiation therapy, systemic chemotherapy, other targeted agents, and metastasectomy) and 159 patients who received treatment for intrahepatic HCC without EHS. Thus, 430 patients with HCC and EHS were treated with sorafenib monotherapy. To evaluate the treatment outcome of sorafenib therapy, 176 patients who were treated with sorafenib for less than 8 weeks were additionally excluded due to the short duration of sorafenib administration. Finally, this study included 254 HCC patients with EHS who were treated with sorafenib monotherapy for at least 8 weeks. HCC was diagnosed on the basis of the American Association for the Study of Liver Diseases (AASLD) guideline [2]. The study was approved by the institutional review board of Samsung Medical Center.

Clinical parameters

We reviewed the following clinical parameters: age, gender, etiology, prothrombin time, serum albumin, total bilirubin, blood cell count, aspartate transaminase (AST), alanine transaminase (ALT), alpha-fetoprotein (AFP), hepatitis B surface antigen, antibody to hepatitis C virus, Child-Pugh classification, and performance status. The scoring of performance status was based on the criteria of the Eastern Cooperative Oncology Group (ECOG) [12]. We checked for history of any treatment for HCC before sorafenib therapy (e.g., surgical resection, liver transplantation, RFA, TACE, radiation therapy, and systemic chemotherapy). We also assessed the following tumor characteristics related to metastasis: co-existence of intrahepatic tumor with MVI, number of EHS sites, and location of EHS. The patients were classified into three groups according to co-existence of intrahepatic tumor and MVI such as portal vein (PV) or inferior vena cava (IVC) invasion. Group 1 included cases of HCC with EHS only. Group 2 included cases of HCC with EHS and intrahepatic tumor without MVI. Group 3 included cases of HCC with EHS and intrahepatic tumor with MVI. Abdominal dynamic computer tomography (CT) and/or magnetic resonance imaging (MRI) was used to evaluate intra-abdominal metastases. Chest radiography plus CT and/or positron emission tomography-CT (PET-CT) was performed to evaluate intra-thoracic metastases. Whole body bone scan and/or PET-CT were performed to assess bone metastasis.

Sorafenib administration

In principle, sorafenib administration was started at a dose of 400 mg twice daily (800 mg/day). However, the initial dose of sorafenib could be reduced (400 or 600 mg/day) according to the physician's judgment based on the liver function. The patients were treated with the initial dose during the first 2 weeks, and thereafter sorafenib was continued every 4 weeks if there were no side effects. After starting sorafenib, dose reduction or temporary interruption was performed when drug-related adverse events occurred. If the patient could tolerate sorafenib, the therapy was continued until disease progression. However, even after confirmation of disease progression, sorafenib could be continuously administered if there was no other therapeutic option and the patients agreed to continue the treatment.

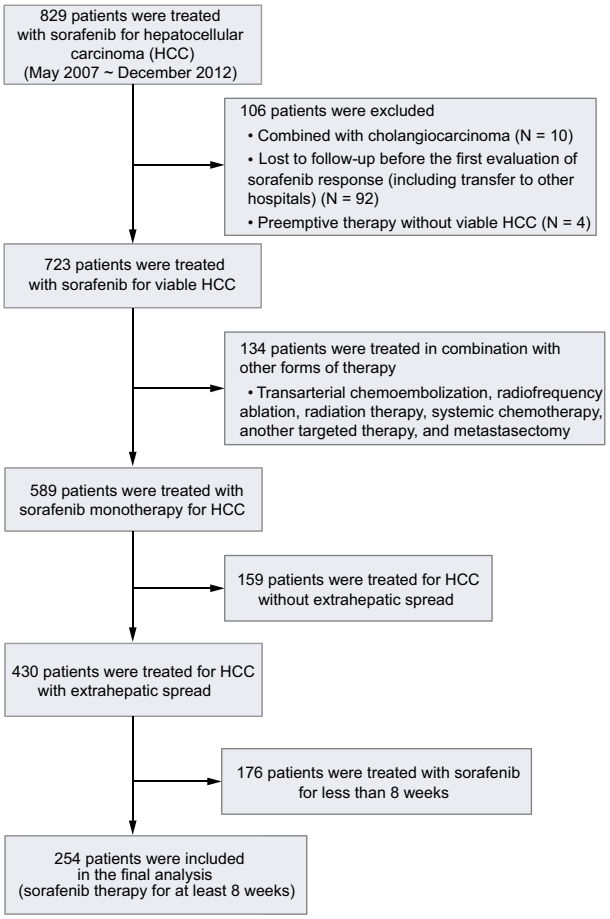

Fig. 1. Flow diagram of enrolled patients in this study.

Outcome measurement

Overall survival, tumor response to sorafenib, time to radiologic progression, and adverse events after starting sorafenib therapy were retrospectively investigated in HCC patients with EHS. Overall survival was defined as the time from the start of sorafenib therapy to death. The response to sorafenib therapy for HCC with EHS was assessed on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13]. Disease control was defined when the tumor response was satisfactory in the form of complete remission (CR), partial remission (PR), or stable disease (SD) according to the RECIST criteria. Radiologic progression of MVI was regarded as a $\geqslant$25% increase of the tumor thrombus in the greatest cross-sectional diameter compared to a baseline tumor thrombus. However, radiologic progression of HCC was assessed by overall tumor response including intrahepatic tumor and extrahepatic spread as well as MVI. The first evaluation of the radiologic response was performed between 8 and 10 weeks after starting sorafenib therapy. Thereafter, imaging studies were performed to assess the tumor response every 8–12 weeks. Time to radiologic progression was defined as the time from the start of sorafenib therapy to disease progression on imaging studies. The symptoms of patients including adverse events, physical examination, and serum laboratory tests were assessed at baseline and every 4 weeks thereafter.

Statistical analysis

Continuous variables were presented as mean ± standard deviation unless otherwise mentioned. Categorical variables were expressed as frequency and percentages. Cumulative overall survival and time to radiologic progression after sorafenib administration was calculated by the Kaplan–Meier method. Univariable and multivariable Cox proportional hazards models were used to identify risk factors that predict the overall survival and radiologic progression