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Original Article

Increased cumulative doses and appearance of hand-foot skin reaction prolonged progression free survival in sorafenib-treated advanced hepatocellular carcinoma patients

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Abstract Sorafenib has been recommended as a new palliative therapy for advanced hepatocellular carcinoma (HCC). However, the clinical outcome of patients receiving sorafenib therapy varies. This study sought to identify which clinical method could be used to predict clinical outcome of sorafenib monotherapy in patients with advanced HCC. A total of 146 advanced HCC patients with Child-Pugh A liver function were enrolled from June 2011 to September 2015. Sorafenib doses ranged from 200 mg once daily to 400 mg twice daily. Clinical and pathological parameters were collected. There was no predefined primary endpoint. Tumor response rate, adverse events, overall survival (OS), and progression-free survival (PFS) were analyzed. The follow-up period was 1718 days (median: 859 days). The median dosage of sorafenib was 562.35 mg.Forty patients (27.4%) had stable disease and 106 patients (72.6%) had progression disease. The OS was 432.21 ± 360.52 days (median: 329 days) and PFS was 167.05 ± 166.50 days (median: 102.5 days). No sorafenib toxic effect-related mortality was encountered. The most common severe adverse events (≧grade 3) were hand-foot skin

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reactions (HFSR) (16, 11.0%), diarrhea (7, 4.8%), and alopecia (1, 0.7%). The following patients had longer median PFS (mPFS): those receiving total dosage > 55000 mg (217 vs.63 days; HR = 0.20,95%CI = 0.11–0.38; p < 0.001), those receiving daily dosage <562 mg (140 vs.69 days; HR = 0.27, 95%CI = 0.17–0.46; p < 0.001), those with treatment durations > 112 days (231vs.64 days; HR = 0.37, 95%CI = 0.19–0.74; p < 0.001), and those with HFSR (105 vs.75 days; HR = 0.60,95% CI = 0.6–0.98; p = 0.04). In conclusion, increased cumulative doses of sorafenib as well as the appearance of HFSR were indicators of prolonged mPFS in sorafenib-treated advanced HCC patients.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women worldwide and the second most common cancer-related cause of death worldwide [1,2]. Partial liver resection, local ablation therapy, and liver transplantation have been considered as curative therapies and used to improve long term survival [3–5]. Because most HCC patients (>70%) had liver cirrhosis, poor performance status or advanced stages of HCC, only 10%–37% of these patients can receive liver resection or ablation therapy and only a few HCC patients can receive liver transplantation due to shortage of donors [5,6]. Therefore, only palliative treatments were suggested for advanced stage HCC patients cannot receive curative or TACE treatments [4,7,8].

Recently, sorafenib was introduced for use in palliative oral targeted therapy for advanced HCC patients after the phase III SHARP trial [7–9]. This drug is a tyrosine kinase receptor inhibitor taken orally to inhibit tumor angiogenesis and tumor cell proliferation by blocking the activity of Raf serine/threonine kinase isoforms and blocking vascular endothelial growth receptors −2 and −3, platelet-derived growth factor receptorβ,C-KIT,FLT-3 [3,4,7,8,10–12].

However, sorafenib has been used with various outcomes in advanced HCC patients. The reported disease-control rate of sorafenib-treated HCC patients ranged from 32.1% to 43.0% [7,11,13]. And its safety has been a concern as sorafenib has been associated with several adverse events, including hand-foot skin reaction (HFSR), diarrhea, hypertension, and alopecia [13–17]. Rates of severe sorafenib-related adverse events (grade 3/4) ranging from 6.0% to 25.0%, have been reported [11,13]. Although most of these adverse effects can be managed, they can lead to dose modifications, temporary suspension or discontinuation of sorafenib, which may reduce the drug's therapeutic efficacy [16–18]. Besides, appearance of these adverse effects or not have also been found to possibly predict survival, evaluate efficacy, and determine dosage of use of sorafenib in advanced HCC patients reported in US, Europe, and Asia–Pacific trials [16,17,19]. Therefore, the identification of clinical parameters that may predict the safety and efficacy of sorafenib is very important because the response rate to this drug is low, it has been associated with a high rate of adverse events, and the cost of using it to treat advanced HCC is high [13,15,16].

Thus, in this study, we collected medical records and biochemical data in advanced HCC patients in south Taiwan to investigate any associations they may have on the efficacy, adverse events, and clinical outcome of sorafenib.

Patients and methods

Patients

This study enrolled patients diagnosed with advanced HCC by pathological or radiological examination at two tertiary referred medical centers in south Taiwan, where sorafenib for treatment of this patient population is covered by the National Health Insurance (NHI) program [20]. To be classified as advanced HCC, patients should have macrovascular invasion of major branches of portal or hepatic veins, or extra-hepatic metastases. To be included, all patients were required to have at least one newly found HCC or recurrent HCC measurable lesion after curative treatments, liver resection or local ablation therapy, or transarterial chemoembolization (TACE) diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI)). Also to be included, patients should have a Child-Pugh Classification Class A score of 5 or 6 and had to be≧18 years old, have a life expectancy of at least 3 months, and be deemed to have an Eastern Cooperative Oncology Group Performance status of two or less, as well as have adequate renal and bone marrow function [7,13,15,21].

Patients were excluded if they were eligible for curative treatment (including liver transplantation) or if they had been previously treated by tyrosine kinase inhibitors or systemic or hepatic artery infusion chemotherapy. They were also excluded if they had uncontrolled hypertension, QTc prolong >450 ms, unstable angina, recent (<6 months) myocardial infarction, a known history of human immunodeficiency virus infection, central nervous system tumor or metastases, gastrointestinal bleeding <30 days prior to study entry, organ transplantation, pregnancy or lactation [13,15].

The protocol for this study was approved by the Institutional Review Board of Kaohsiung Medical University