Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Phase II study of combining sorafenib with metronomic tegafur/uracil for advanced hepatocellular carcinoma

Chih-Hung Hsu[1,4], Ying-Chun Shen[1,2], Zhong-Zhe Lin[1,4], Pei-Jer Chen[2,3], Yu-Yun Shao[1], Yea-Hui Ding[1], Chiun Hsu[1,4,*], Ann-Lii Cheng[1,3,4,5,**]

[1]*Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan;* [2]*Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan;* [3]*Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan;* [4]*Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan;* [5]*Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan*

Background & Aims: Sorafenib, a multi-kinase inhibitor with anti-angiogenic activity, was recently approved for the treatment of advanced hepatocellular carcinoma (HCC). Metronomic chemotherapy using tegafur/uracil (4:1 molar ratio), an oral fluoropyrimidine, has been shown to enhance the anti-tumor effect of anti-angiogenic agents in preclinical models. This phase II study evaluated the efficacy and safety of combining metronomic tegafur/uracil with sorafenib in patients with advanced HCC.

Methods: Patients with histologically- or cytologically-proven HCC and Child-Pugh class A liver function were treated with sorafenib (400 mg twice daily) and tegafur/uracil (125 mg/m^2 based on tegafur twice daily) continuously as first-line therapy for metastatic or locally advanced disease that could not be treated by loco-regional therapies. The primary endpoint was progression-free survival (PFS).

Results: The study enrolled 53 patients. Thirty-eight patients (72%) were hepatitis B surface antigen-positive. The median PFS was 3.7 months (95% C.I., 1.9–5.5) and the median overall survival was 7.4 months (95% C.I., 3.4–11.4). According to RECIST criteria, 4 patients (8%) had a partial response and 26 patients (49%) had a stable disease. Major grade 3/4 toxicities included fatigue (15%), abnormal liver function (13%), elevated serum lipase (10%) hand-foot skin reaction (HFSR) (9%), and bleeding (8%). HFSR was the major adverse event resulting in dose reduction (19%) or treatment delay (21%).

Conclusions: Metronomic chemotherapy with tegafur/uracil can be safely combined with sorafenib and shows preliminary activity to improve the efficacy of sorafenib in advanced HCC patients.

Cancer

Keywords: Sorafenib; Tegafur/uracil; Metronomic chemotherapy; Hepatocellular carcinoma.

Received 7 November 2009; received in revised form 12 December 2009; accepted 27 January 2010; available online 30 March 2010

*Correspondence to: Chiun Hsu, Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan 10002. Tel.: +886 2 231 23456x67789; fax: +886 2 23711174.

**Correspondence to: Ann-Lii Cheng, Departments of Internal Medicine and Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan 10002. Tel.: +886 2 23123456x67251; fax: +886 2 23711174.

E-mail addresses: chsu1967@ntu.edu.tw (C. Hsu), alcheng@ntu.edu.tw (A.-L. Cheng).

Abbreviations: HCC, hepatocellular carcinoma; PFS, progression-free survival; C.I., confidence interval; RECIST, response evaluation criteria in solid tumors; HFSR, hand-foot skin reaction; VEGFR, vascular endothelial growth factor receptor; EU, European Union; US, United States; VEGF, vascular endothelial growth factor; 5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; PT, prothrombin time; AE, adverse event; ORR, overall response rate; DSR, disease stabilization rate; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; OS, overall survival; ITT, intent-to-treat; BCLC, Barcelona Clinic Liver Cancer; CLIP, the Cancer of the Liver Italian Program; AFP, alpha-fetal protein; CEC, circulating endothelial cell.

Introduction

Patients with metastatic or advanced hepatocellular carcinoma (HCC) that cannot be treated by loco-regional therapies face a dismal outcome [1–3]. In Asian countries, the median survival of these patients is in the range of 2–4 months with the best supportive care [1,2]. Until recently, conventional cytotoxic chemotherapy has shown little effect. This limited success has been attributed to the inherent chemo-resistance of HCC cells, as well as chemo-intolerance of HCC patients as a result of concomitant chronic liver disease.

Since 2007, sorafenib, a multi-kinase inhibitor against Raf kinase and vascular endothelial cell growth factor receptor (VEGFR) [4], has been approved for the indication of unresectable HCC by regulatory agencies of the EU, US, and other countries. This approval was based on the positive results of a placebo-controlled randomized phase III study in advanced HCC patients with good liver reserve [5]. Subsequently, another phase III study conducted in the Asia–Pacific region where hepatitis B virus infection is the dominant etiologic factor of chronic liver disease, also demonstrated the survival benefits of sorafenib [1]. Sorafenib is generally well tolerated [1,5–10] and combination therapy may further improve the efficacy of sorafenib in advanced HCC.

Metronomic chemotherapy refers to administrating chemotherapeutics at doses significantly less than the maximum-tolerated doses on a frequent basis for a prolonged period of time [11]. In preclinical models, metronomic chemotherapy is identified to have anti-angiogenic activity. The anti-angiogenic mechanisms of

metronomic chemotherapy include inhibiting proliferation of activated endothelial cells in tumor neovasculature, suppressing mobilization of endothelial progenitor cells from bone marrow, and inducing anti-angiogenic factors [11,12]. The combination of metronomic chemotherapy and inhibitors of vascular endothelial growth factor (VEGF)/VEGFR has shown synergistic anti-tumor effects in experimental tumor models [12,13]. Recently, metronomic chemotherapy, alone or in combination with anti-VEGF agents, has demonstrated clinical benefits without eliciting serious toxicity in heavily pretreated breast cancer patients [14,15].

Tegafur/uracil, composed of tegafur and uracil in a molar ratio of 4:1, is an orally active fluoropyrimidine [16]. Tegafur, as a prodrug, is metabolized to 5-fluorouracil (5-FU) mainly in the liver. Uracil, an inhibitor of dihydropyrimidine dehydrogenase which is the rate-limiting enzyme of 5-FU degradation, helps maintain a stably high concentration of 5-FU in the liver and in the circulation [17]. Tegafur/uracil has been approved for the treatment of various types of advanced gastrointestinal (GI) cancers in Japan and Taiwan. The single-agent activity of tegafur/uracil in advanced HCC was previously reported in small-scale phase II studies in Japan, with response rates of 3.8–17% [18,19]. Interestingly, tegafur and its metabolites have shown potent anti-angiogenic effects in preclinical models [20,21]. In mice bearing high-volume metastatic breast cancer, metronomic chemotherapy with tegafur/uracil is effective in reducing tumor metastasis and prolonging survival [22].

We hypothesized that the efficacy of sorafenib in advanced HCC can be improved by adding metronomic tegafur/uracil, and the toxicity profiles of this combination would not be significantly different from those of sorafenib alone.

Patients and methods

Study design and conduction

The study was an open-labeled, single-arm, single-institute, investigator-initiated phase II clinical study. The study was approved by the Institute Research Ethical Committee of National Taiwan University Hospital, and was conducted in accordance with the principles of the Declaration of Helsinki. The recruitment notification has been posted on www.clinicaltrials.gov (NCT 00464919).

Eligibility of patients

The study targeted HCC patients with metastatic diseases or locally advanced diseases that were not amenable to loco-regional therapies, including surgery, transcatheter arterial (chemo)embolization, or local ablation. The eligibility criteria included an age $\geqslant$18 years; histologically- or cytologically-documented HCC; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; serum creatinine $\leqslant$1.5$\times$ upper limit of normal (ULN); adequate liver function reserves defined by Child-Pugh classification A, liver transaminases $\leqslant$5$\times$ ULN, albumin $\geqslant$2.8 g/dl, serum total bilirubin $\leqslant$3 mg/dl, prothrombin time (PT)-international normalized ratio $\leqslant$2.3 or PT $\leqslant$6 s prolongation; and adequate bone marrow reserves, defined by white blood cells $\geqslant$3000/μl, neutrophil count $\geqslant$1500/μl, platelets $\geqslant$100,000/μl, and hemoglobin $\geqslant$8.5 g/dl. Patients needed to have at least one measurable lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST) [23], which was not previously treated with any loco-regional therapy. However, patients with prior local treatments were allowed if the local treatments were completed at least 6 weeks prior to enrollment. Any treatment-related acute toxicity should have returned to $\leqq$grade 1, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE) v3.0.

Key exclusion criteria included prior or concomitant systemic anti-cancer treatment for HCC, metastatic brain or leptomeningeal tumors, a history of organ transplantation, and life expectancy <2 months. Patients with significant gastrointestinal bleeding within 30 days prior to enrollment were not eligible. All patients were required to provide written informed consent.

Treatment

Patients received sorafenib (400 mg orally, twice per day), and tegafur/uracil (UFUR®, 125 mg/m^2 based on tegafur orally, twice per day; TTY Biopharm Co., Ltd., Taipei, Taiwan) continuously. The treatment was continued until disease progression or development of unacceptable toxicity. The dose of tegafur/uracil was based on the published report of adjuvant tegafur/uracil in patients with completely resected pathological stage I adenocarcinoma of the lung [24].

Dose modification of sorafenib and tegafur/uracil was according to the toxicities, graded by NCI-CTC AE v3.0. When symptomatic grade 2 or grade 3 hypertension occurred, sorafenib was held and the patients were treated accordingly. When the AEs recovered to $\leqq$grade 1, sorafenib was resumed with the dose of 400 mg per day. If symptomatic grade 2 or grade 3 hypertension recurred, sorafenib was further reduced to 400 mg every 2 days. Sorafenib was discontinued permanently when grade 4 hypertension occurred, when more than 2 dose reductions for the toxicities of hypertension were required, or when treatment delay was more than 30 days due to insufficient recovery from toxicities.

When grade 2 or 3 HFSR occurred, sorafenib was held until HFSR recovered to $\leqq$grade 1. Sorafenib was resumed with the original dose without dose reduction for the first occurrence of grade 2 HFSR, and was resumed with the dose of 400 mg per day for the second grade 2 HFSR and first grade 3 HFSR. Sorafenib was further reduced to 400 mg every two days if similar toxicities recurred. Sorafenib was discontinued permanently when more than two dose reductions for the toxicity of HFSR were required, or when treatment delay was more than 30 days due to insufficient recovery from toxicities.

When grade 3 diarrhea or mucositis occurred, tegafur/uracil was withheld, and was resumed with the dose of 62.5 mg/m^2 twice per day when the toxicities recovered to $\leqq$grade 1. Tegafur/uracil was discontinued permanently when similar grade 3 toxicities recurred despite a dose reduction, or when treatment delay was more than 30 days.

For grade 3 or 4 hematologic toxicities, hepatic toxicities, and other adverse events (AEs) which were considered treatment-related, the dose modification was as follows: reduced dose level 1, sorafenib 400 mg twice per day and tegafur/uracil 62.5 mg/m^2 based on tegafur twice per day; reduced dose level 2, sorafenib 400 mg per day and tegafur/uracil 62.5 mg/m^2 based on tegafur twice per day; and reduced dose level 3, sorafenib 400 mg every 2 days. The combination was discontinued permanently when more than 3 dose reductions were required, or when treatment delay was more than 30 days.

Disease assessment

Tumor assessment was performed every 8 weeks using RECIST criteria [23]. Confirmation of responses was required at least 4 weeks after the initial response was recorded.

Statistical analyses

The primary endpoint of the study was progression-free survival (PFS). At the time when this study was designed, the available data about the clinical efficacy of sorafenib was a phase II trial of sorafenib involving 137 advanced HCC patients, reported by Abou-Alfa et al. [6]. In that trial, 40% of patients treated with sorafenib monotherapy remained progression-free at 6 months. It was estimated that adding metronomic chemotherapy of tegafur/uracil to sorafenib would improve the 6-month PFS rate from 40% to 60%. To detect an improvement of at least 20%, a sample size of 50 patients was required to provide a power of 80% with an one-sided 5% significance level according to sample size planning by Makuch and Simon [25].

The secondary endpoints included 6-month PFS rate, objective tumor response rate (ORR), disease stabilization rate (DSR; defined as the sum of complete response [CR], partial response [PR], and stable disease [SD] for at least 2 months), overall survival (OS), and the safety profile of the combination.

All the statistics were performed for an "intent-to-treat (ITT) population", which was defined as patients who received at least one dose of the study drugs. The PFS and OS were analyzed using Kaplan–Meier method.

Results

Patient characteristics

Between April 2007 and April 2008, a total of 53 patients with advanced HCC were enrolled at the National Taiwan University