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Metronomic capecitabine as second-line treatment in hepatocellular carcinoma after sorafenib failure

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ABSTRACT

Background: No standard second-line treatments are available for hepatocellular carcinoma patients who fail sorafenib therapy. We assessed the safety and efficacy of metronomic capecitabine after first-line sorafenib failure.
Methods: Retrospective analysis of consecutive hepatocellular carcinoma patients receiving metronomic capecitabine between January 2012 and November 2014. The primary end-point was safety, secondary end-point was efficacy, including time-to-progression and overall survival.
Results: Twenty-six patients (80% Child–Pugh A, 80% Barcelona Clinic Liver Cancer stage C) received metronomic capecitabine (500 mg/bid). Median treatment duration was 3.2 months (range 0.6–31). Fourteen (53%) patients experienced at least one adverse event. The most frequent drug-related adverse events were bilirubin elevation (23%), fatigue (15%), anaemia (11%), lymphoedema (11%), and hand–foot syndrome (7.6%). Treatment was interrupted in 19 (73%) for disease progression, in 4 (15%) for liver deterioration, and in 1 (3.8%) for adverse event. Disease control was achieved in 6 (23%) patients. Median time-to-progression was 4 months (95% confidence interval 3.2–4.7). Median overall survival was 8 months (95% confidence interval 3.7–12.3).
Conclusions: Metronomic capecitabine was well tolerated in hepatocellular carcinoma patients who had been treated with sorafenib. Preliminary data show potential anti-tumour activity with long-lasting disease control in a subgroup of patients that warrants further evaluation in a phase III study.

1. Introduction

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals, Montville, NJ, USA) is the only systemic drug approved for the treatment of hepatocellular carcinoma (HCC). In two randomised phase III trials sorafenib was shown to increase the median survival of approximately 3 months, with an adequate safety profile [1,2].

Despite the evidence of efficacy, a significant number of sorafenib-treated patients experience disease progression. There is currently no proven second-line therapy and current guidelines recommend either best supportive care or clinical trial enrolment for this patient population [3]. According to recent studies, only 41–56% of patients failing first-line systemic therapy are potentially eligible for second-line clinical trials on the basis of clinical and biochemical eligibility criteria [4,5]. In fact, although the exact clinical course of patients at the end of sorafenib treatment is unclear, their prognosis is influenced by both tumour progression pattern and residual liver function, which frequently deteriorates after sorafenib failure [5]. Liver-related toxicity is therefore a key factor to consider in the development of second-line therapies [6].

Capecitabine (Xeloda®, Roche) is an oral prodrug of 5-fluorouracil (5-FU), which is metabolised to 5-FU in a three-step enzymatic reaction, the final one being conversion in the liver and in the tumour by thymidine phosphorylase [7].

In recent years the concept of metronomic chemotherapy has been introduced into oncology [8]. It is based on the chronic administration of chemotherapeutic agents at low doses without prolonged drug-free breaks to optimise the anti-angiogenic properties of the drug and to reduce toxicities [9–11].

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It has been proposed that the metronomic dose should be the highest one within a metronomic schedule, to avoid bone marrow suppression, which may act as a pro-angiogenic stimulus [10].

This therapeutic approach could be of particular interest in HCC patients who present more severe and advanced disease when they experience first-line therapy failure.

Preliminary studies suggest that capecitabine may be safe and effective in HCC patients. However, study design and patient characteristics of these studies are heterogeneous and few data are available on metronomic capecitabine (MC) as second-line therapy in patients who had been previously treated with sorafenib [12–17].

The aim of this study was to retrospectively evaluate the safety and efficacy of MC as second-line treatment in patients who progressed or were intolerant to first-line sorafenib.

2. Patients and methods

2.1. Patients

In this single-centre study we retrospectively analysed data of HCC patients unresponsive or intolerant to sorafenib, who were consecutively treated with MC between January 2012 and November 2014 at our centre.

During this time period, after sorafenib discontinuation, patients were evaluated for second-line clinical trials.

If no second-line study was open locally or when a patient was ineligible for second-line trials according to the eligibility criteria or refused clinical trial entry, MC was proposed if the following clinical criteria were also satisfied: Child–Pugh (CP) score ≤B8, total bilirubin ≤3 mg/dl, Eastern Cooperative Oncology Group performance status (PS) ≤2, platelet count ≥50,000/mmc, Hb >9 g/dl, WC >1500/mmc, transaminases <5× the upper normal level, creatinine <1.5 mg/dl, INR <2, no decompensated ascites (defined as diuretic uncontrolled ascites), no encephalopathy, no history of heart disease.

Patients who did not satisfy the criteria for second-line clinical trials nor for treatment with MC underwent best supportive care (BSC).

Patients treated with MC between January 2012 and November 2014 fulfilling the following inclusion criteria constituted the study population: age >18 years, written informed consent to the study, previously therapy with only sorafenib as first-line systemic treatment.

The study was performed according to the revised version of the Declaration of Helsinki and was approved by the local ethics committee of our hospital.

2.2. Metronomic capecitabine treatment

The use of capecitabine for HCC patients was approved at our centre in the Emilia-Romagna region. Patients started capecitabine therapy at the metronomic dosage of 500 mg every 12 h. They were closely monitored clinically and by laboratory tests.

Capecitabine was continued until the occurrence of unacceptable toxicity or radiological or symptomatic progression of HCC.

Adverse events (AEs) and laboratory abnormalities were summarised by category and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Liver function deterioration was defined as an increase of at least 2 points in the CP score.

Grade 3/4 AEs lead to dose modification (500 mg daily) or temporary interruption, until symptoms resolved to grade ≤2. Other causes of dose modification or temporary interruption were clinically relevant grade 2 AEs or liver function deterioration.

2.3. Clinical follow-up and response to treatment

Patients were assessed for physical examination within 7 days of treatment initiation, and every 4 weeks thereafter. Haematology and liver tests, and serum alpha-fetoprotein (AFP), were determined by conventional assays and were performed within 7 days of start of treatment, and every 2 weeks thereafter. The following baseline parameters were recorded: sex, age, aetiology of liver disease, comorbidities, previous HCC treatment, haematology and liver tests, AFP, CP score, oesophageal varices, portal vein thrombosis (PVT), PS and Barcelona Clinic Liver Cancer Clinic Liver Cancer (BCLC) stage.

HCC was staged by multiphase computed tomography (CT) or magnetic resonance imaging (MRI) and classified according to the BCLC staging system.

Chest and abdominal CTs were routinely performed, while additional investigations were made when clinically appropriate.

During follow-up, radiological examination was scheduled every 3 months ± 2 weeks and performed using CT or MRI.

The tumour response was evaluated by the modified Response Evaluation Criteria In Solid Tumours (mRECIST) [18].

The mRECIST overall response assessment includes the evaluation of target lesion response, non-target lesion response and the occurrence of new lesions. Objective response (OR) was defined as complete response (CR) + partial response (PR), and disease control (DC) as CR + PR + stable disease (SD).

2.4. Statistical methods

Overall survival (OS) was measured from the first day of capecitabine treatment to death, with values censored at 5th November 2014 (end of study).

Time to progression (TTP) was defined as the time from the date of the first capecitabine application to radiological disease progression. In the absence of radiologically confirmed disease progression, TTP was censored at the date of last follow-up visit.

Frequency counts and percentages are provided for response and disease control rates. For analyses of TTP and OS, the median time to event and 95% confidence intervals (CI) are calculated using the Kaplan–Meier method.

All statistical analyses were performed using the SPSS 17.0 statistical package (SPSS Incorporated, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

During the period January 2012 to November 2014, sorafenib was discontinued in 54 patients. Patient enrolment is shown in Fig. 1. Fifteen underwent BSC (27%), 13 were enrolled in randomised, double-blind, placebo-controlled phase III trials (24%), and 26 were treated with MC (48%).

Baseline characteristics of the 26 capecitabine-treated patients are shown in Table 1. Twenty-three (88%) of them were ineligible for second-line clinical trials according to clinical/biochemical inclusion and exclusion criteria. Conditions precluding eligibility were: platelet count <60,000/mmc (9 patients), total bilirubin levels >2 mg/dl (4 patients), CPT B7 (3 patients), platelet count <60,000/mmc and CPT B7 (2 patients), grade 3/4 AEs under sorafenib treatment (3 patients), and human immunodeficiency virus infection (2 patients).

In 21 patients (81%) sorafenib had been discontinued because of disease progression (10 for extrahepatic progression, 11 for intrahepatic progression), 3 (11%) owing to adverse events, and 2 (7.6%) for worsening of liver function.