

Good and Prolonged Response to Low Dose Capecitabine as Second Line Therapy in a Patient with Advanced Hepatocellular Carcinoma

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Received date: August 22, 2015; Accepted date: December 18, 2015; Published date: December 23, 2015

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Abstract

Sorafenib is the only validated pharmacological treatment option for patients with advanced hepatocellular carcinoma (HCC) in the context of Child-Pugh class A liver function. Effective and safe systemic treatments for advanced disease with severe underlying cirrhosis (Child-Pugh class B and C) are not yet available. A few reports have described capecitabine as an option after failure of sorafenib or for patients who were not eligible for clinical trials. Here, we present a case of good response to low dose capecitabine in a patient with advanced HCC.

Keywords: Hepatocarcinoma (HCC); Cirrhosis; Capecitabine

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer-related death worldwide [1]. Curative treatments for early-stage tumors include liver transplantation, resection, percutaneous ethanol injection therapy, microwave coagulation therapy, or percutaneous radiofrequency ablation. However, the majority of patients are not eligible for curative therapies because of tumor extent or underlying liver dysfunction [2]. Sorafenib, an oral multikinase inhibitor, is the only systemic agent proven to be effective in patients with HCC and Child-Pugh A liver function. Two randomized phase-III studies demonstrated a mean survival advantage of approximately 3 months [3,4] with sorafenib as compared to placebo, thus establishing sorafenib as the reference standard systemic treatment for patients with advanced HCC who still have preserved liver function. Unfortunately, the survival advantage is achieved at the expense of frequent toxicity.

Presently, no approved second line systemic therapies exist for patients who are resistant, intolerant or not eligible for sorafenib.

The use of capecitabine, an oral 5-fluorouracil (FU) prodrug, has been reported in a few small studies, both in advanced HCC and as postoperative adjuvant therapy after curative resection [5,6]. Capecitabine is absorbed in the intestine and then metabolized to FU in a three-step enzymatic reaction, the final one being the conversion in the liver and in the tumor by thymidine phosphorylase (TP). TP is present at higher levels in tumor cells compared to healthy tissue, allowing a selective activation of the drug [7]. Treatment resulted to be safe in patients with cirrhosis, in particular at metronomic dosage [5,8,9]. While standard schedule of capecitabine (2000 mg/m²/die for 14 days every 3 weeks) in cirrhotic patients can deteriorate liver function, increase bilirubin or induce ascites, lower dosage seems to increase tolerability and reduce the risk of liver function deterioration.

The mechanisms of chronic administration of continuous low doses of chemotherapy are not entirely clear. Kamat et al. [10], and Kerbel

[11], found that activated endothelial cells were more sensitive to low-dose chemotherapy than tumor cells, which provides a hint that anti-angiogenesis may involve in the therapeutic effect of metronomic chemotherapy in solid tumors.

HCC is a highly vascular tumor, thus the use of antiangiogenic therapy has a strong biological rationale.

We describe a patient with advanced HCC who obtained long-lasting objective response with low-dose capecitabine monotherapy; hence, we may suggest this capecitabine schedule to optimize the treatment of HCC when sorafenib fails or is not indicated.

Case report

We report the case of a 61-year-old man with exotoxic cirrhosis included in a dedicated surveillance program. His medical history was also significant for the presence of insulin-treated diabetes, euthyroid multinodular goiter and the presence of grade 2 oesophageal varices. In October 2008, due to abdominal tension and epigastric pain, he underwent abdominal magnetic resonance (MRI), showing multiple liver lesions suspicious for HCC. The MRI also documented the presence of enlarged para-aortic lymph nodes and the neoplastic thrombosis of the right portal branch. A biopsy was then performed, which confirmed the presence of a well differentiated HCC. After a global liver function evaluation, the patient was classified as Child-Pugh class B (MELD 8).

Locoregional treatments were excluded by a multidisciplinary team due to neoplastic thrombosis and multifocal dissemination in the liver. Consequently, the patient was referred to our oncologic unit to evaluate possible systemic approaches. At first evaluation, his clinical condition and blood test classified the patient with Child-Pugh B7 liver function. In particular, total bilirubin was 20.3 µmol/L (normal range 1.7 – 17.0), albumine was 35.38 g/L and coagulation tests showed PT 65% and INR of 1.13. Alpha fetoprotein dosage was normal. Abdominal ascites was prominent at physical evaluation.

Since the patient fell within Child-Pugh class B, he was not eligible for sorafenib therapy. First line therapy with pegylated liposomal doxorubicin and gemcitabine in the context of the trial by Lombardi et al. [12], was administered from January to April 2009, for a total of 4 cycles. The radiological evaluation documented the partial response of the liver nodules and the reduction of the abdominal effusion. Thereafter, chemotherapy was suspended due to poor treatment tolerance and clinico-radiological follow up continued to July 2010, when the Computed tomography (CT) scan revealed liver disease progression and the appearance of lung micronodules (Figures 1, 2 and 3).

and he had already received a first line chemotherapy, he was not considered for sorafenib. A second line treatment with low dose capecitabine (1000 mg/m² twice daily for 14 days every 3 weeks) was started in July 2010. Treatment was well tolerated and regularly administered without interruption or toxicities, apart from grade 1 fatigue according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Complete blood tests were performed every 3 weeks. They showed stable platelet count and no worsening in hepatic function test.

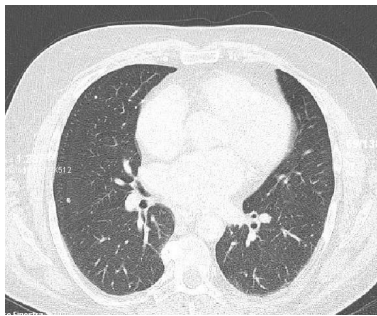


Figure 1: Lung micronodule: baseline.

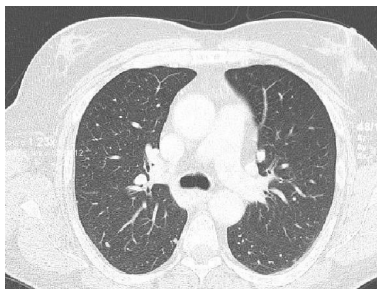


Figure 2: Lung micronodule: baseline.

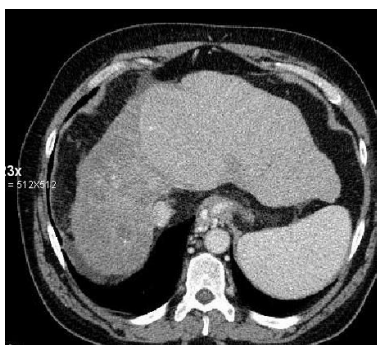


Figure 3: Liver disease: baseline.

Since the patient was still classified as Child-Pugh class B (platelets 89 x10.9/L; total bilirubin 28,6 µmol/L; albumine 38 g/L; PT 78, INR 1,07), abnormal ascites and Barcelona Clinic Liver Cancer (BCLC) B

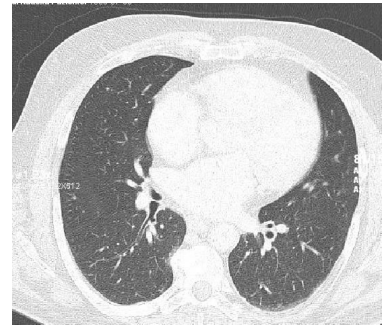


Figure 4: Lung micronodule evaluation.

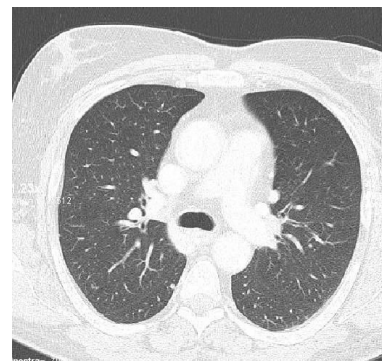


Figure 5: Lung micronodule evaluation.

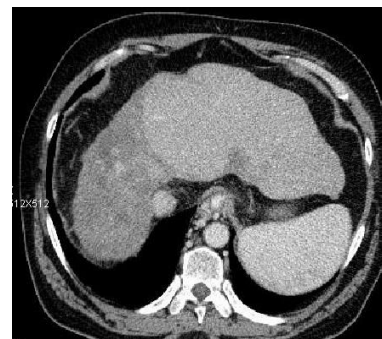


Figure 6: Liver disease evaluation.

Regular quarterly radiological assessment performed during that period documented stable disease (see Figure 4-6). The last evaluation

in September 2014 still documented the absence of disease progression. Overall, progression free survival is 50 months (Figure 7-9).

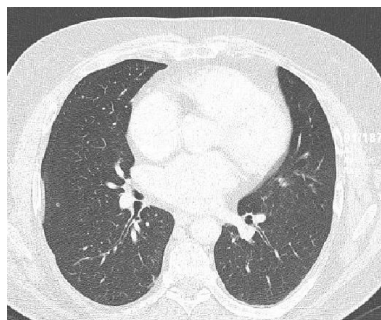


Figure 7: Lung micronodule, last evaluation (September 2014).

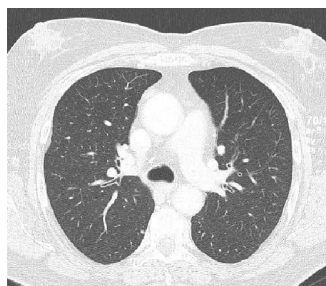


Figure 8: Lung micronodule, last evaluation (September 2014).

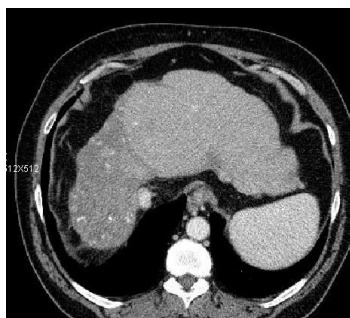


Figure 9: Liver disease, last evaluation (September 2014).

Discussion

Herein, we presented a case of HCC not amenable for either locoregional treatment or sorafenib therapy. Patients with locally advanced or metastatic HCC face a dismal outcome. The high mortality rate for HCC is due to limited treatment options. Only 10%–30% of cases are suitable for the current curative treatments and nearly 90% of HCC develop in the context of liver cirrhosis [13]. Sorafenib is the only available drug administered as first-line treatment in Child-Pugh A liver function patients with advanced HCC, as demonstrated in two randomised placebo-controlled trials [3,14]. Conversely, no standard treatment has been defined for patients who fail, are

intolerant or not eligible for sorafenib. An interesting treatment was described by Lombardi et al. [12], who treated forty-one patients with advanced HCC with a combination chemotherapy with gemcitabine 1000 mg/m² on days 1 and 8, followed by pegylated liposomal doxorubicin 30 mg/m² on day 1. They obtained three (7%) complete responses and seven (17%) partial responses. The median TTP and OS were 5.8 and 22.5 months, respectively. Hematologic toxicity was the most common side effect, including neutropenia (17%) and anemia (7%).

Recently, many Authors [15-18] reported interesting results in advanced HCC with capecitabine, in terms of disease control and tolerability. Capecitabine was administered in both treatment-naïve and pretreated patients with advanced HCC. In particular, in the phase II trial by Brandi and colleagues [16], treatment-naïve patients achieved a median progression free survival (PFS) of 6.03 months and an OS of 14.47 months, while the second cohort achieved a median PFS of 3.27 months and a median OS of 9.77 months. Treatment was also well tolerated and most reported adverse effects were mild or moderate and were manageable with supportive care or a brief drug-free period. No treatment-related deaths were observed and no patient withdrew from treatment because of adverse events. Similarly, Marinelli et al. [15], reported unexpectedly good therapeutic efficacy with metronomic capecitabine in two patients with advanced HCC, one after sorafenib failure and the other not eligible for sorafenib.

Moreover, capecitabine demonstrated a good safety profile even in the context of impaired liver function [17].

The chronic administration of chemotherapeutic agents at minimally toxic doses, as demonstrated in the context of advanced breast cancer, increases antiangiogenic properties of the drugs [19], thus providing a good rationale for its use in a highly vascular tumors, such as HCC.

Capecitabine seems well tolerated, even in patients with impaired liver function. Indeed, capecitabine has an acceptable safety profile and it does not seem to be associated with major events. Capecitabine offers several potential advantages as compared to aggressive chemotherapy in a population with advanced cirrhosis, such as the more favourable haematological toxicity profile and avoidance of intravenous hydration required for treatment with platinum analogs in patients with uncontrolled ascites.

Twelves and colleagues [20] demonstrated that mild to moderate hepatic dysfunction has no clinically significant influence on the pharmacokinetic parameters of capecitabine and its metabolites. In another study, treatment with capecitabine resulted in an overall response rate of 11%, including one complete remission and 22% disease control rate with tolerable toxicity in 37 patients with unresected HCC and underlying liver cirrhosis [9]. In another retrospective series of 11 patients treated with capecitabine monotherapy [18], the median time to tumor progression and median OS were 2.2 months (95% CI 1.7-2.7 months) and 10.1 months (95% CI 3.0-17.2 months), respectively. The therapy was well tolerated, with hand-foot syndrome as the main toxicity. Grade 3 diarrhoea occurred in one patient and grade 3/4 hyperbilirubinemia was seen in five patients, but it was mainly due to tumor progression rather than to drug related adverse event. No other significant toxicities were observed.

Conclusion

In the present clinical case, the patient experienced good response, long progression free survival of 50 months and good safety with low dose capecitabine treatment as second line chemotherapy. We can suggest capecitabine as an active and safe treatment in patients not eligible for sorafenib treatment or in sorafenib-resistant patients. However, further studies are warranted to confirm the role of capecitabine for advanced HCC in various clinical settings.

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