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Long-lasting response with metronomic capecitabine in advanced hepatocellular carcinoma

Pierluigi Ballardini[1], Ivan Marri[2], Guido Margutti[1], Camillo Aliberti[2], Giorgio Benea[2], and Roberto Manfredini[1]

[1]Department of Internal Medicine, and [2]Department of Radiology, Ospedale del Delta, Lagosanto (FE) - Azienda USL of Ferrara, Italy

ABSTRACT

Effective and safe systemic treatment for advanced hepatocellular carcinoma (HCC) with severe underlying cirrhosis is not yet available. Sorafenib, an oral multikinase inhibitor, has proved to be effective in the treatment of patients affected by HCC with Child-Pugh class A liver function. For patients with cirrhosis-associated HCC having Child-Pugh class B and C liver function, no systemic treatments of documented efficacy and safety exist. We report a case of metastatic HCC associated with Child-Pugh class B cirrhosis that was treated with low, "metronomic" doses of capecitabine (1000 mg/day continuously). This treatment was effective and well tolerated and the response was maintained for 18 months. Metronomic capecitabine may represent a possible alternative in the treatment of those patients with advanced cirrhosis-associated HCC who cannot be treated with sorafenib. Free full text available at www.tumorionline.it

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worlwide and has become one of the main global health problems[1]. In Western countries, around 40% of patients are eligible for potential curative treatment (resection, transplantation, or local ablation) and 20% for chemoembolization[2-4]. Patients with advanced tumors or severe underlying cirrhosis can only be palliated by chemotherapy or best supportive care. Recently, encouraging results have been obtained with sorafenib in the treatment of advanced HCC[5]. Sorafenib is an oral multikinase inhibitor that blocks tumor cell proliferation by targeting the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase (Raf/MAPK/ERK) signaling pathway and exerts an antiangiogenic effect by targeting the tyrosine kinases vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3, and platelet-derived growth factor receptor β (PDGFR-β)[6,7]. In the SHARP trial[5], a large randomized phase III study, sorafenib produced a significant improvement in overall survival and time to progression in patients with advanced HCC. However, only patients with Child-Pugh class A liver function were included. Effective and safe systemic treatment for advanced HCC with severe underlying cirrhosis is not yet available. We report the case of a patient suffering from HCC and Child-Pugh B cirrhosis, so not eligible for sorafenib, who was treated with metronomic oral capecitabine.

Case report

This case refers to a 65-year-old woman with hepatitis B virus (HBV)-correlated cirrhosis diagnosed in 2003. In February 2006, after the ultrasonographic finding of a nodular lesion in the liver localized at segment II, she underwent abdominal comput-

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Correspondence to: Pierluigi Ballardini, MD, Ospedale del Delta, Via Valle Oppio 2, 44023 Lagosanto (FE), Italy.
Tel +39-0533-723468;
fax +39-0533-723467;
e-mail p.ballardini@ausl.fe.it

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erized tomography (CT). The scan confirmed the presence of a nodular area with a maximum diameter of 25 mm and tomographic features of HCC (hypervascular pattern with enhancement in the arterial phase, and rapid washout in the portal venous and delayed phases). Brain and thorax CT excluded the presence of metastatic lesions. The alpha-fetoprotein (AFP) level was 4239 ng/mL (normal range, 0-10). According to the Barcelona Clinic Liver Cancer Staging Classification (BCLC)[8], the disease was classifiable as stage A. After having received detailed information, the patient refused the surgical approach and preferred locoregional treatment. Thermoablation was contraindicated because of the lesion's proximity to Glisson's capsule, so transcatheter arterial chemoembolization (TACE) was chosen. In April 2006, the patient underwent TACE by means of drug-releasing microspheres preloaded with 50 mg doxorubicin. One month later, the AFP level had dropped to 18 ng/mL. In February 2008, during a follow-up checkup, AFP levels were increased to 27,860 ng/mL, and total-body CT showed peritoneal metastatic lesions with a maximum diameter of 3 cm, although the liver appeared free from HCC lesions. CT-PET confirmed the presence of 3 peritoneal areas of uptake, with a maximum standardized uptake value (SUV) of 7.3. Since the patient was affected by Child-Pugh B cirrhosis (score 8), and therefore not eligible for sorafenib therapy, she was treated with metronomic capecitabine, administered orally at a fixed dose of 1000 mg daily, continuously. After 3 months of capecitabine treatment, CT examination showed a decrease in the number and size of peritoneal metastases, which had reduced to 1 nodule with a maximum diameter of 6 mm in the left lower quadrant. AFP had dropped to 1480 ng/mL. Capecitabine was continued and 18 months from the start of therapy the patient was asymptomatic, classifiable in Child-Pugh class A (score 6), AFP levels were stable, and CT imaging showed a further slight reduction of the residual peritoneal metastasis (from 6 to 4 mm), without liver tumor relapse (Figure 1). Capecitabine was well tolerated, with grade 3 hyperbilirubinemia and thrombocytopenia being the only toxicities. These were managed by treatment interruptions of 1 week that always resulted in the recovery of values until grade 2 or less, thus allowing resumption of capecitabine administration.

Discussion

Sorafenib is the only drug proven to be effective in advanced-stage HCC patients with Child-Pugh class A liver function. For patients with Child-Pugh classes B and C, however, no systemic treatments with documented efficacy and safety are available. Many systemic chemotherapy regimens have been tested in HCC patients, but none of these were found to significantly improve the patients' survival or progression-free interval[9]. In addition, chemotherapy is poorly tolerated by these patients due to underlying cirrhosis, coexisting cytopenias, and unpredictable pharmacokinetics.

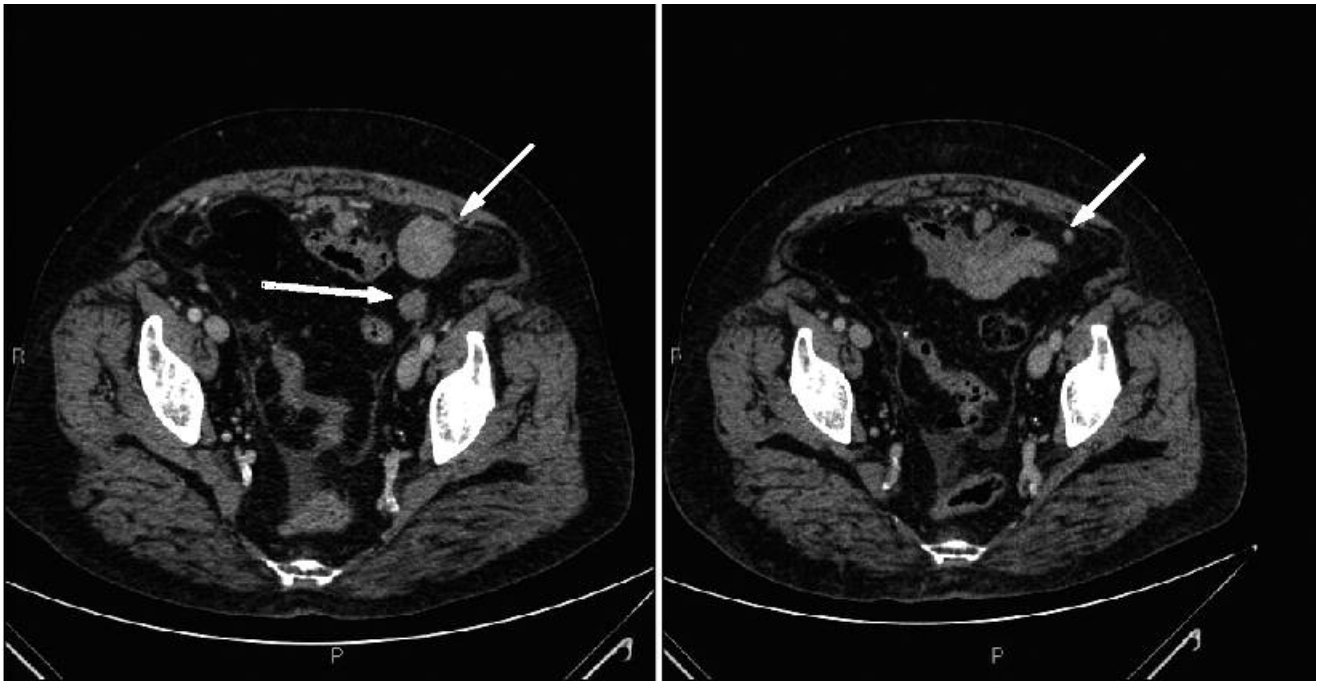

Figure 1 - Peritoneal metastasis from HCC before (left) and after (right) treatment with metronomic capecitabine.

Capecitabine, an oral fluoropyrimidine, was found to be safe for treatment of patients with HCC, although the objective response rate was limited[10]. In an animal model, a metronomic capecitabine regimen was found to have an antiangiogenic effect[11]. Metronomic chemotherapy has been proposed as an alternative to conventional chemotherapy. The therapeutic effects of this modality of drug administration seem to be secondary to a higher antiangiogenic effect combined with a reduction of acute toxicity[12]. These features of metronomic therapy are particularly useful in patients with HCC, since this type of cancer is characterized by a rich vascularization and angiogenesis. Metronomic therapy is also associated with a reduction of conventional chemotherapy-related toxicity, which is more harmful in cirrhotic patients. In a rat model of HCC with liver cirrhosis, low-dose metronomic chemotherapy with cyclophosphamide showed antitumor and antiangiogenic effects, and improved the survival of the animals without major toxicities[13]. Preliminary studies on humans have also shown that metronomic capecitabine treatment was better tolerated than standard schedules in patients with advanced HCC[14].

In our patient, metronomic capecitabine was well tolerated and effective in the control of HCC metastases and in the prevention of liver relapses.

Conclusions

In recent years the concept of metronomically delivered therapy has become relevant to the treatment of cancer[15-19]. The clinical case reported here seems to provide further evidence that metronomic capecitabine treatment could be a possible treatment option also for patients with advanced HCC.

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