CASE REPORT

Long-term survival of a HCC-patient with severe liver dysfunction treated with sorafenib

Christoph Roderburg, Jhenee Bubenzer, Michael Spannbauer, Nicole do O, Andreas Mahnken, Tom Luedde, Christian Trautwein, Jens JW Tischendorf

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third leading cause of cancer-related death[1-3]. Therapeutic options and prognosis are stage dependent. In the case of localized disease, prognosis has been significantly improved in the last decade due to progress in diagnostic techniques and introduction of combined modality therapy[1-3]. In the case of unresectable or metastatic disease, however, HCC is still associated with a poor prognosis, and systemic therapy with cytotoxic agents provides only marginal benefit[4-6]. The introduction of targeted therapies such as receptor tyrosine kinase inhibitors represents a breakthrough in the management of HCC[5,6].
At present, the multi-tyrosine kinase inhibitor Sorafenib is the first and only molecular targeted drug that has been approved for treatment of patients with advanced HCC. Encouraging preclinical results in several human tumours and a large phase III trial including 137 patients with advanced HCC led to a multi-center trial with a randomized, placebo-controlled design. The phase III Sorafenib HCC Assesment Randomized Protocol (SHARP) trial demonstrated a 31% decrease in risk of death with a median survival of 10.7 mo for the sorafenib arm versus 7.9 mo for placebo. Similar results were acquired by the ASIAN-trial. However both trials were restricted to patients with non-impaired liver function (Child-Pugh class A). Whether patients with impaired liver function can safely be treated with sorafenib and how this treatment might influence liver function and tumour progression is presently unclear.

CASE REPORT

A 47-year-old Egyptian patient was referred to our outpatient unit with clinical signs of chronic liver insufficiency. The patient was diagnosed with liver cirrhosis in 1996, caused by long-term ethanol abuse (stopped in 2001) and a hepatitis C infection after vaccination in Egypt in 1993. Between October 1997 and 2002 different interferon- and interferon/ribavirin-based therapies were conducted and finally discontinued due to non-response and at the request of the patient. Between 2002 and May 2007 no clinical visit was documented. In May 2007 laboratory testing and a sonography of the abdomen were performed every three months. As serum triglycerides were within the normal limits, moreover serum gamma-glutamyl transferase (GGT) as well as serum alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) were within the normal limits, indicating long-term alcohol abstinence. Clinically the patient showed jaundice of skin and sclera and stage 1 encephalopathy. Taken together, these data resulted in a Child-Pugh score of 12 (Child-Pugh class C). Ultrasound examination of the abdomen demonstrated a hepatic mass in liver-segment VIII accompanied by portal hypertension, massive ascites and severe meteorism, limiting the sensitivity of this examination to detect smaller lesions. Arterial phase contrast-enhanced multislice spatial computed tomography (MSCT) confirmed this lesion and further lesions [lobus caudatus (7 mm × 8 mm); segment II (5 mm × 3 mm); segment VI/ VIII (12 mm × 17 mm) and segment VII (17 mm × 18 mm and 23 mm × 14 mm)] became apparent (Figure 1). Furthermore, two lesions smaller than 5 mm in largest diameter (segment IIb and VII) were described. In order to further discriminate between HCC and benign lesions (such as hyperplastic nodules) magnetic resonance imaging (MRI) with a liver specific contrast agent was performed. Here five lesions suspect for HCC became apparent, strongly suggesting the presence of a multifocal HCC. After evacuation of 3.5 L ascites, a CT-guided puncture of the hepatic lesion in segment VII was performed. Pathological analysis confirmed the presence of a well-differentiated hepatocellular carcinoma (G2). Neither on MSCT scan nor in MRI was extrahepatic tumour spread detected.

Overall, the patient was classified as BCLC stage D, suggesting treatment focussed on palliation as the remaining therapeutic option. However, considering the young age of the patient, the presence of a hepatitis C infection and the lack of extrahepatic tumour spread, the potential risks and benefits of a treatment with 800 mg sorafenib daily were discussed with the patient. This therapy was initiated in October 2007 and has continued until now. Regular clinical evaluations have included physical examination and laboratory testing (complete blood count, creatinine, ALT, AST, AP, GGT and Quick) every 4 wk. CT scans with intravenous and oral contrast of the abdomen have been performed every three months. As depicted in Figure 2, on admission the patient presented with a Child-Pugh score of 12 (MELD score: 19). The lesion in segment VIII with a diameter of 22.8 mm was chosen as a reference for evaluation of tumour growth. After the onset of sorafenib treatment a 24% reduction in tumour size was achieved as the best radiological response, corresponding to long-term (27 mo) tumour control. Interestingly evaluation of tumour mass by serum AFP measurements and MSCT were in perfect correlation (Figure 2B). In the meantime an intensified monitoring of tumour kinetics will be performed.

Figure 1 Computed tomography (CT)-scans: Axial IV contrast enhanced CT. Arterial phase image showing the reference lesion at the indicated time points. Size of this lesion remained stable between 2007 and 2009. A: CT liver November, 2007; B: CT liver December, 2009.
has become an option for treatment of patients with advanced HCC. Sorafenib is one of the new molecular targeted agents that inhibits both proangiogenic (VEGFR-1, -2, -3; PDGFR-β) and tumorigenic (RET, Flt-3; c-KIT) receptor tyrosine kinases. It also inhibits the serine/threonine kinase Raf-1. Raf-1 has been shown to be activated in a wide range of human malignancies and is therefore recognized as a strategic target for therapeutic drug development. Thus, sorafenib has been proven to be effective in a wide range of solid tumours comprising renal cell carcinoma, melanoma and hepatocellular carcinoma by inhibiting proangiogenic and pro-apoptotic pathways.

Sorafenib demonstrated a significant survival benefit in patients with non-resectable or advanced HCC in the SHARP- and the ASIAN- trial and has become a treatment standard for HCC-patients in advanced stages of disease. A subgroup analysis of both studies showed that those patients lacking extrahepatic tumor spread and chronic hepatitis C infection benefit particularly from treatment with sorafenib. This may be due to the fact that chronic hepatitis C induces signalling via Ras/Raf-pathway, which is one of the main targets of sorafenib. However, the positive outcome of these studies applied only to Child-Pugh class A and a few of Child-Pugh class B patients. The question of the efficacy and safety of sorafenib treatment of patients with impaired liver function had therefore remained unanswered. In a large phase trial including 137 patients with advanced HCC, 28% of patients were classified as Child-Pugh class B. Pharmacokinetic parameters showed no difference in patients with cirrhosis Child-Pugh class A and B, and common adverse events associated with sorafenib were similar. However, cirrhosis worsened more frequently in Child-Pugh class B patients. It remained unclear whether this was a drug-related effect or was caused by disease progression. While differences in sorafenib pharmacokinetics between Child-Pugh class A and B patients were not clinically significant, study-based safety data are not available for patients with Child-Pugh class C cirrhosis. To our knowledge there are only two reports on sorafenib treatment of HCC patients with Child-Pugh class C cirrhosis. Pinter et al. and Wörns et al. report on ten and four patients, respectively, treated with sorafenib. Based on their data, they concluded that sorafenib had no significant benefit in patients with high grade impaired liver function because of their limited life expectancy (OS < 3 mo) and lack of improvement in clinical parameters.

In sharp contrast to these data, we here report the case of a HCC-patient with Child-Pugh C liver cirrhosis who has experienced a long-term (27 mo) phase of stable tumour disease under treatment with sorafenib. On admission the patient displayed a Child-Pugh score of 12 [at this time since at least 5 months lasting (May 2007-October 2007)] and seven hepatic HCC-lesions, as shown by MRI/ MSCT scan. The AFP level was only slightly enhanced, which is consistent with the fact that up to 20% of HCC patients do not produce AFP during the treatment with sorafenib. Based on their data, they concluded that sorafenib had no significant benefit in patients with high grade impaired liver function because of their limited life expectancy (OS < 3 mo) and lack of improvement in clinical parameters.

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course of the disease\textsuperscript{14,15}. During the period of treatment with sorafenib we observed a reduction in tumour size of 24\%, corresponding to stable disease according to RECIST criteria.

In addition hepatological treatment such as optimization of nutrition and lifestyle as well as optimization of medication (e.g. diuretics) was implemented and resulted in an improvement of Child-Pugh score from class C to class A (score 12 to score 6). Given the improved liver function, the patient became suitable for treatment concepts such as TACE which are currently rejected by the patient due to the risk of worsening of liver function. Furthermore liver transplantation was considered as an option for this patient. Liver transplantation represents a curative treatment modality for a selected patient population as defined by tumour burden. For HCC, liver transplantation only yields good results for patients whose tumour masses do not exceed the Milano-criteria (1 lesion $\leq$ 5 cm, or 2 to 3 lesions $\leq$ 3 cm)\textsuperscript{16}. In recent years living donor liver transplantation has been discussed for patients exceeding these criteria\textsuperscript{17}. However due to tumour load and lack of a liver donor neither cadaveric nor living donor liver transplantation were an option for the patient.

In summary these data suggest that for a highly selected population of HCC-patients (e.g. young age, lack of extrahepatic tumour spread, chronic HCV infection) sorafenib-treatment might be a well tolerated option even in cases of deteriorated liver function.

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