Successful treatment of hepatocellular carcinoma with the tyrosine kinase inhibitor imatinib in a patient with liver cirrhosis

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Several mechanisms of development of hepatocellular carcinoma (HCC) in patients with liver cirrhosis have been discussed. One hypothesis suggests that the somatic stem cells of the liver, the so-called oval cells, may undergo malignant transformation. Oval cells are derived from the biliary cells of the canal of Hering and are characterized by c-kit-positivity, the transmembrane receptor of stem cell factor. Constitutively activated tyrosine kinases have been identified as major pathogenetic mechanisms in the development of malignant diseases like gastrointestinal stromal tumors (c-kit) and chronic myelogenous leukemia (bcr–abl). The prognosis of these diseases improved enormously since the drug imatinib, a tyrosine kinase inhibitor of c-kit and bcr–abl, was introduced. Here we report the successful cure of a patient with liver cancer by this tyrosine kinase inhibitor. *Anti-Cancer Drugs* 15:405–409 © 2004 Lippincott Williams & Wilkins.

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Introduction

Hepatocellular carcinoma (HCC) is among the five most common cancers worldwide; about 1 million people die annually of this cancer [1]. Chronic viral hepatitis, alcohol abuse and repeated aflatoxin β_1 intake are the major risk factors in the different areas of the world [2].

Most of the cancers arise in cirrhotic livers. In fact, patients with cirrhosis of any etiology are at significant risk of developing HCC. Prospective studies performed in different areas of the world show an annual incidence of 1–6% in patients with cirrhosis [3]. Tumor resection, liver transplantation or local ablation are the only therapeutic options [4]. However, the number of patients suitable for resection is low due to the underlying cirrhosis [5]. On the other hand, the number of transplantations is small because of limited organ supply [6]. Local ablative measures (ethanol injection, radiofrequency or laser ablation) are of palliative importance. Chemotherapeutical regimens have been disappointing and not a single drug can now be suggested for therapy of HCC [7].

So far, three main mechanisms of development of HCC in patients with liver cirrhosis have been discussed [8]. One hypothesis suggests that hepatocytes of regenerative nodules become 'dysplastic' and then neoplastic ('nodule in the nodule') [9]. The second mechanism implicates a possible role of hepatitis viruses which may directly promote neoplastic transformation of hepatocytes [10].

The third hypothesis suggests that the somatic stem cells of the liver, the so-called oval cells [11], which are supposed to replace dead hepatocytes when these cannot proliferate, may undergo malignant transformation [12]. Oval cells derive from the biliary cells of the canal of Hering and are characterized by c-kit-positivity [13]. This transmembrane receptor of stem cell factor (SCF, CD117) is essential in development [14]. In the adult, c-kit is expressed by hematopoetic stem cells, mast cells and Cajal cells, the pacemaker cells of the gut. Gain of function mutations of c-kit [15] have recently been identified as the major pathogenetic mechanism in the development of gastrointestinal stromal tumors which are supposed to derive from Cajal cells [16]. The prognosis of these tumors improved enormously since the drug imatinib (STI 571, Glivec; Novartis, Basel, Switzerland), an inhibitor of the tyrosine kinase of c-kit, has been introduced into the therapy of this relatively rare tumor [17].

We used the same drug in a patient with liver cirrhosis complicated by appearance of a small hepatocellular carcinoma.

Case report

In 1994, a 58-year-old patient presented with decompensated liver cirrhosis due to alcohol consumption. The patient recovered and remained abstinent to date.

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Echography of the abdomen and α-fetoprotein controls were performed every 3–6 months. Seven years later, in May 2001, hepatic ultrasound examination detected a hypoechogenic lesion of 13 mm diameter in liver segment VI. Magnetic resonance imaging (MRI) scanning revealed a coarse nodular shrunken cirrhotic liver with hypertrophy of the left lobule. Pictures taken during the arterial phase after i.v. administration of 20 ml Magnevist (Schering, Berlin, Germany) showed a hypervascular lesion in segment VI. The control MRI 8 months later showed an increase of the lesion to 1.9 × 1.6 cm (January 2002).

Echo-guided biopsy was performed in February of 2002. Histological examination showed a well-differentiated HCC (Fig. 1A). The cells reacted weakly with antibodies against c-kit (Fig. 1B) and cytokeratin 7 (Fig. 1C), but were cytokeratin 19-negative, and 20% of the tumor cells were positive for MIB-1 (detecting the nuclear cell proliferation-associated antigen Ki-67, Fig. 1D). None of the tumor cells was positive for CD34 (Fig. 1E) or α-fetoprotein (Fig. 1F).

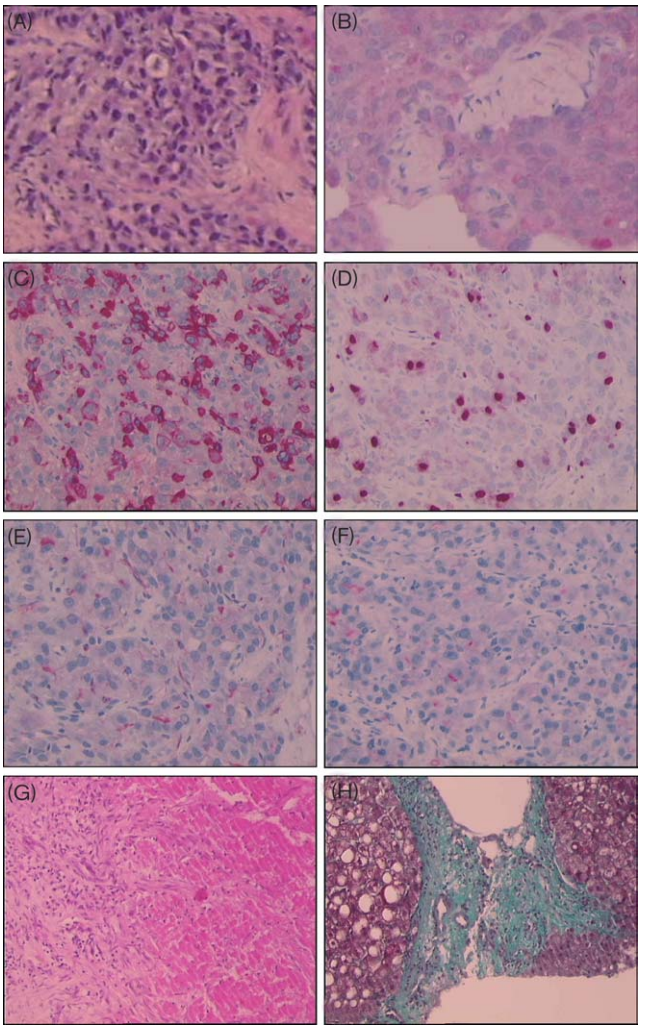
The now 66-year-old diabetic patient (non-insulin dependent, liver cirrhosis in Child-Pugh stage A) refused surgical resection of the tumor. He also refused liver transplantation. Instead, he agreed to start therapy with imatinib. The therapy was started in March 2002 with one 100 mg capsule twice daily. This dosage was selected considering the underling cirrhosis and that imatinib is eliminated by the liver. Toxicity was assessed at follow-up visits 1, 3 and 5 weeks later, and every 4–6 weeks thereafter. At every visit blood chemical values as well as echography of the abdomen were performed. The response to treatment was also assessed by dynamic MRI 2 months after beginning treatment and every 6 months thereafter. Echo-guided biopsy of the lesion was performed 1 year after the beginning of the therapy. The patient (body weight 70 kg) is now in a good health.

Results

Safety and tolerability of the drug

Imatinib was well tolerated with no mental or physical changes as observed by the patient. No change of blood chemical values was observed throughout the observation period of 15 months. Aminotransferases and cholestatic parameters ranged within reference values immediately before treatment and throughout the follow-up. Body weight remained constant; ascites or peripheral edema

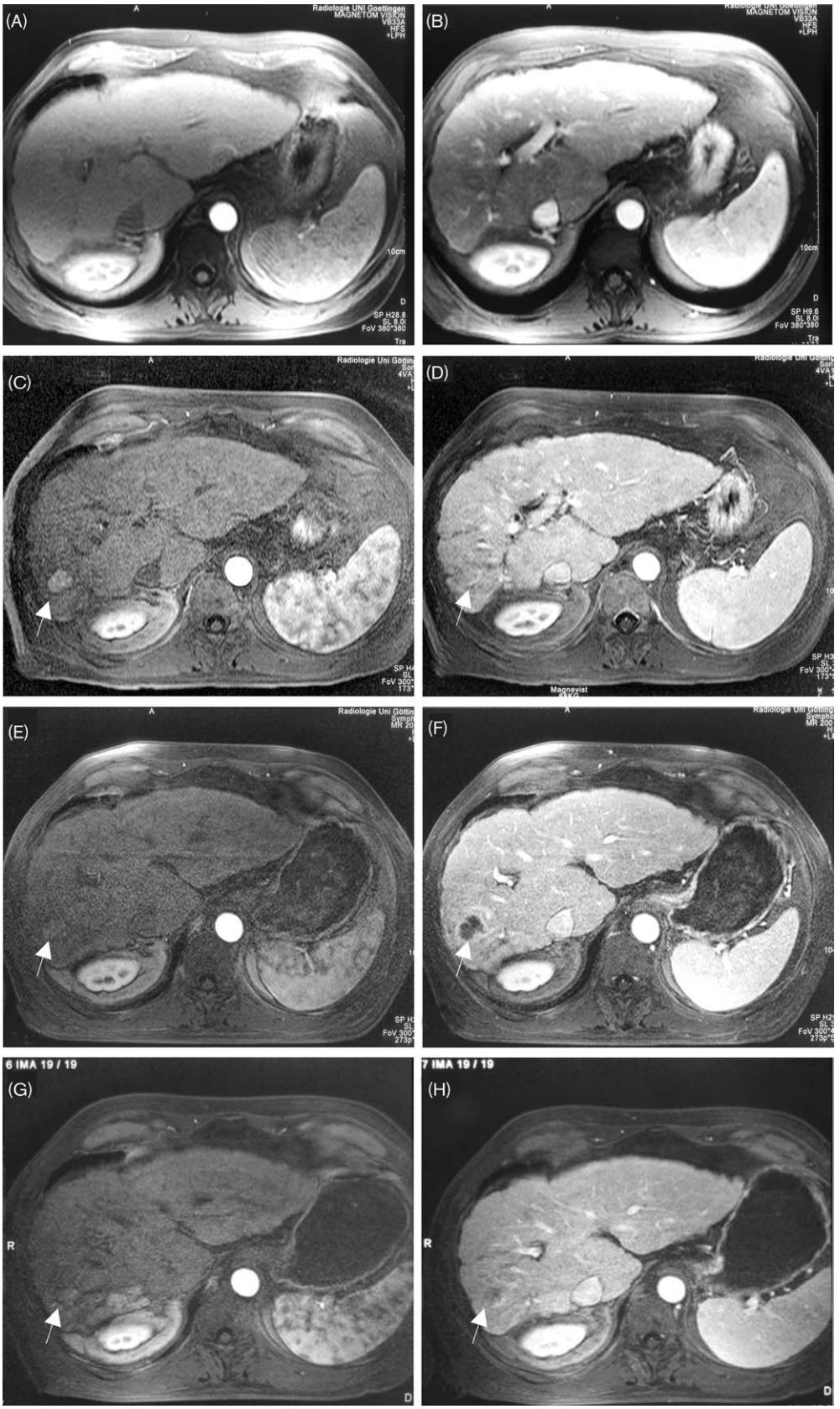
Fig. 1



Histochemical and immunohistochemical study of tumor biopsies obtained before imatinib therapy (A–F) and after 1 year of imatinib therapy (G and H). Hematoxylin & eosin staining showing well-differentiated tumor cells (A). Immunostaining of the tumor with antibodies against c-kit (B), cytokeratin 7 (C), MIB1 (D), CD34 (E) and α-fetoprotein (F). Biopsy after 1 year of treatment showing acellular necrotic tissue after hematoxylin & eosin staining (G) and cirrhotic tissue with steatosis outside the tumor (H, Masson–Goldner staining).

Transaxial Gd-enhanced T_s-weighted MRI studies of the upper abdomen before and during imatinib therapy. MRI scan in October 1999 before development of HCC. Arterial phase (A) and portalvenous phase (B) after i.v. application of Magnevist. Note the nodular surface of the liver implicating the presence of liver cirrhosis, normal sized spleen and lack of ascites. MRI scan in May 2002, 2 months after initiation of imatinib therapy (C and D). A hyperarterialized lesion of 2.1 × 1.7 cm is seen in segment VI in the arterial phase (C, arrow), but undetectable during the portalvenous phase (D, arrow). MRI scan 1 year after imatinib therapy (E and F). Contrast medium enhancement of the lesion is drastically reduced during the arterial phase (E, arrow) and a lack of contrast medium enhancement during the portalvenous phase (F, arrow). A hypodensity of the center of the tumor with a small rim of contrast medium enhancement in the periphery can be seen. MRI scan 3 months later when the tumor became undetectable by hepatic ultrasound showing a reduction of the tumor size (G, arterial phase; H, portalvenous phase; arrows).

Fig. 2



were not detected. No interaction with the antidiabetic drug glibenclamide (3.5 mg twice a day) was notable.

Evaluation of the response to imatinib by conventional ultrasound and by MRI

Evaluation of the size of the lesion by conventional ultrasound performed by different investigators revealed an increase of the size from 1.3 × 1.3 cm at the initial diagnosis (May 2001) to 1.9 × 1.6 cm (January 2002). Eight weeks after the start (March 2003) of imatinib the size of the tumor on a subsequent MRI scan was 2.1 × 1.7 cm. Enhancement by Magnevist in the arterial phase was similar to that seen in the MRI scan before imatinib. Six months after beginning the imatinib therapy the size of the lesion was unchanged. However, the enhancement observed in the periphery of the lesion after Magnevist administration was reduced when compared to the earlier examinations (Fig. 2C and D). One year after beginning the therapy (April 2003) the lesion was hardly visible during the arterial liver passage of the contrast medium in a follow-up MRI scan (Fig. 2E). Moreover, during the portal perfusion of Magnevist, the lesion presented with a central hypodensity and a peripheral hyperdensity (Fig. 2F). The size was similar to that seen before (2.1 × 1.8 cm). In contrast, no change of the echogenicity of the lesion was detectable by ultrasound. Echo-guided biopsy of the lesion was performed and histological examination showed beside cirrhotic tissue with extensive fibrosis and steatosis necrotic material without vital tumor tissue. There were no signs of inflammation.

At this point of time measurement of imatinib serum concentrations became available (HPLC analysis). Whereas the serum concentration of imatinib was within the normal range (550 ng/ml), the level of the main metabolite (*N*-DesM-imatinib, 70 ng/ml) was reduced to about 50% of the expected value consistent with impaired hepatic metabolic activity, but without accumulation of imatinib.

Moreover, fluorodeoxyglucose positron emission tomography (FDG-PET) performed in April 2003 could not detect any accumulation of the tracer within the liver or at any other location that could be due to vital metastases.

Another follow-up ultrasound in June 2003 failed to detect the lesion. The lesion was then hardly detectable by MRI during the arterial and venous passage of the contrast medium (Fig. 2G and H).

Discussion

HCC arises very often in cirrhotic liver. After cirrhosis has been diagnosed the probability of HCC development varies from 1 to 6% per year when inflammation with consequent hepatocellular death and continuous reduction of the functional liver mass and ineffective regeneration are present [18–20]. The risk is lower when inflammation is stopped as is the case for eradicated viral infections (HCV, HBV) or quitting alcohol consumption.

The precursor of the malignant cell is supposed to be the dysplastic hepatocyte [18], but a possible origin from 'oval cells' has been discussed [21]. Those cells are known to show c-kit-positivity [13]. For this reason we tested the tumor for c-kit-positivity by immunohistochemistry. As tumor cells, but not stromal cells reacted with the antibody against c-kit to a moderate extent (the patient refused any invasive treatment) we started treatment with imatinib. In consideration of the fact that the patient had fully established liver cirrhosis and imatinib is metabolized by the liver, we decided to reduce the dose usually given to patients with gastrointestinal stromal tumors (400 mg daily) by 50% and started with 200 mg imatinib/day. When determination of imatinib serum concentrations became available, the measured values of imatinib and its main metabolite indicated a reduced hepatic metabolization, but no accumulation. It may be concluded that the patient would have tolerated a higher dosage. As the lesion did not increase during the first 6 months, effectiveness was supposed and treatment was continued. After the next 6 months the MRI showed a significant reduction of Magnevist enhancement during the arterial phase of the contrast medium. Moreover, the contrast medium failed to accumulate in the central part of the lesion during the portalvenous passage. Only a small rim in its periphery was left with contrast medium enhancement. Moreover, histological examination revealed the disappearance of tumor cells, the appearance of necrotic material and scaring. The echographic pattern did not change during the 12 months of therapy. Three months later ultrasound failed to detect the lesion.

Although the results obtained from one case cannot be generalized, it can be concluded from the presented case that imatinib may be well tolerated in patients with liver cirrhosis and that it may be effective against HCC. There are three lines of evidence for the latter conclusion. First, stable size during the first 12 months and then decrease of the tumor size, whereas growth was observed before. Second, loss of contrast medium enhancement during the arterial and portalvenous phase. Third, disappearance of vital tumor cells as assessed by histology. Arguing that the biopsy was taken from the rim of the tumor showing a continuous transition from necrosis to non-neoplastic liver tissue, the stringent conclusion is a complete necrosis of the tumor. FDG-PET after 1 year of treatment was negative and may be another clue for tumor necrosis. However, FDG-PET had not been performed before imatinib was started, leaving an uncertainty whether the vital tumor would have been detectable by this method. This is particularly true for well-differentiated HCC [22].

The mechanism by which imatinib may have been effective in this particular patient can be suggested from its known inhibitory activities blocking the kinase activity of c-kit and platelet-derived growth factor receptor α (PDGF-RA). c-kit and PDGF-RA are closely connected to chronic liver disease and possibly to (hepato-)carcinogenesis. c-kit-positivity of HCC as shown in this report then could be a hint that (c-kit$^+$) HCC tumors derive from oval cells since hepatocytes are supposed to be c-kit-negative. However, recent data indicated that only single HCC may overexpress c-kit [23].

Alternatively, the inhibition of PDGF-R kinase activity known to be expressed in a variety of hepatoma cell lines may induce tumor necrosis. We only performed a bioptic control 1 year after treatment and cannot exclude that efficacy of the therapy could have been seen much earlier.

This success encourages the initiation of a study on patients with liver cancers which are small in size and which are c-kit$^+$. To this purpose, the stage of liver cirrhosis should also be of major importance.

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