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Pharmacokinetic and Clinical Phase II Trial of Imatinib in Patients with Impaired Liver Function and Advanced Hepatocellular Carcinoma

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Key Words
c-kit · Hepatocellular carcinoma · Imatinib · Phase II clinical trials · Platelet-derived growth factor receptor

Abstract
Objectives: No effective chemotherapy for advanced hepatocellular carcinoma (HCC) exists. Expression of the platelet-derived growth factor receptor (PDGFR) has been demonstrated in HCC, which may derive from hepatic stem cells that express c-kit. The aim of this trial was to evaluate imatinib, a tyrosine kinase inhibitor of PDGFR and c-kit, in patients with advanced HCC and impaired liver function. ***Patients and Methods:*** Patients were treated with 400–600 mg imatinib daily. Immunohistochemical staining was performed for PDGFR and c-kit. Response was assessed by CT scans every 8 weeks. For pharmacokinetics studies, 74 plasma samples were assessed. ***Results:*** Of the 17 patients enrolled in the study, 15 were evaluable for response. Only 1 tumor was positive for PDGFR and none was positive for c-kit. Grade 3/4 neutropenia occurred in 2 patients (1 had neutropenic fever). There was no objective response, and 5 (33%) patients had stable disease. Median time to treatment failure was 1.8 months in the whole study cohort and 3.7 months in the patients with stable disease. Patients treated with 400 mg imatinib did not significantly differ in pharmacokinetics from patients with chronic myelogenous leukemia (CML). ***Conclusion:*** In this small group of patients with advanced, mostly PDGFR- and c-kit-negative HCC, imatinib showed no therapeutic effect. In contrast to CML patients, the pharmacokinetics of imatinib were not significantly affected by impaired liver function.

Introduction

Although known to be a common type of cancer worldwide, hepatocellular carcinoma (HCC) has long been considered a rare tumor in the United States. However, this impression is no longer correct. Liver cancer is the most rapidly increasing cause of cancer and cancer death in the United States, accounting for at least 14,000 deaths yearly and ranking eighth as a cause of cancer mortality in men [1, 2]. In 80% of cases HCC develops in cirrhotic livers, and cirrhosis is the strongest predisposing factor [3]. In the United States and the developed world, the rapid increases in HCC rates correlate with the rising incidence of hepatitis C viral infection [1].

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HCC is a highly fatal cancer. However, liver cirrhosis may be as limiting as the malignancy itself. The only curative therapies of HCC are resection and liver transplantation, but recurrence is common. More importantly, the vast majority of patients with HCC are not candidates for these therapies due to advanced and unresectable tumors at the time of diagnosis. For patients with HCC who are not candidates for resection or liver transplantation, an increasing array of localized semisurgical treatments has become widely accepted. These include ethanol injection, radiofrequency ablation, cryotherapy and newer forms of radio-wave therapy. It is important to note that local ablative therapies are generally useful for patients with 1 or 2 tumor lesions with a maximum diameter of 3 cm, i.e. for localized tumors only [4]. A large number of clinical trials evaluating the usefulness of cytotoxic chemotherapy for HCC have been published. Only few studies have been able to show response rates of more than 20%, and there is no evidence of improved survival. Consequently, for patients with advanced disease, vascular involvement, extrahepatic spread or physical impairment, treatment with new antitumoral agents is recommended [3, 5].

Platelet-derived growth factors (PDGFs) and their cognate tyrosine kinase receptors (PDGFRs) are involved in multiple tumor-associated processes, including autocrine growth stimulation of tumor cells, stimulation of tumor angiogenesis and recruitment and regulation of tumor fibroblasts [6]. PDGFR was one of the genes preferentially expressed in tumor samples of HCC compared to the adjacent noncancerous tissues [7]. Furthermore, mainly c-kit-positive oval cells, which are the somatic stem cells of the liver, might play an important role in the development of HCC [8]. Furthermore, PDGF plays a critical role in the progression and initiation of liver cirrhosis, and it has been suggested that anti-PDGF intervention should have a therapeutical impact on the treatment of liver fibrogenesis and therefore might stop progression of liver cirrhosis [9, 10].

Imatinib mesylate (imatinib, Gleevec®, Glivec® and STI571) is an inhibitor of specific protein tyrosine kinases targeting PDGFR. In addition, it was found to inhibit the constitutively active bcr-abl fusion product arising from the Philadelphia chromosome of chronic myelogenous leukemia (CML) and the stem cell factor receptor (c-kit, CD117) [11]. Nowadays, imatinib is the standard treatment of CML and gastrointestinal stromal tumors, the latter being characterized by a gain-of-function mutation of c-kit in most cases. However, due to the usual inclusion criteria of clinical trials, pharmacokinetics of imatinib in patients with impaired liver function have never been assessed. A case report of successful treatment of HCC with imatinib has been published recently [12].

Consequently, this phase II trial was initiated to evaluate the safety and efficacy of imatinib in patients with advanced HCC. In addition, pharmacokinetics of imatinib in these patients with impaired liver function was evaluated and compared to CML patients.

Patients and Methods

Patients

To be eligible for the trial, patients were required to have a histologically or cytologically proven HCC, measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST), and neither suitable for surgery nor for locoregional therapy. They also met the following laboratory criteria: total bilirubin $<2.0 \times$ upper limit of normal (ULN), SGOT (AST) and SGPT (ALT) $<5 \times$ ULN, creatinine $<1.5 \times$ ULN, absolute neutrophil count $>1.0 \times 10^9$/l and platelet count $>70 \times 10^9$/l. Performance status had to be less than 3. Patients with acute liver failure, decompensated liver cirrhosis (Child-Pugh C), active infections, unstable cardiovascular conditions, brain metastases, or other serious medical illnesses were excluded from this trial. They must not have uncontrollable vomiting nor diarrhea and had to be able (reliably) to ingest test medication each day. Informed consent was obtained from all patients included in the study, which was approved by local ethics committees.

Immunohistochemistry

Immunohistochemical staining of c-kit (Dako, Glostrup, Denmark) and PDGFR type A/B (Upstate Biotechnology, Lake Placid, N.Y., USA) was performed on serial paraffin sections of the diagnostic liver biopsies with the help of an automated immunostainer (Ventana Benchmark, Ventana Medical Systems, Tucson, Ariz., USA), using established protocols. Appropriate controls mounted on the same slide were used for each case. A paraffin-embedded cell pellet of NIH 3T3 cells stimulated with PDGF served as positive control for the PDGFR staining. Immunohistochemistry could not be performed in 3 (c-kit) and 2 cases (PDGFR) due to insufficient tissue or only cytological material, respectively.

Treatment

Imatinib (Novartis, Nuremberg, Germany) was orally administered at a dose of 400 mg once daily. After 2 weeks, the daily dose of imatinib was increased to 600 mg in the absence of toxicity. Dose modification due to toxicity was as follows: for non-hematologic toxicity $\geq$ grade 2, imatinib was discontinued until the toxicity has resolved to less than grade 1. Imatinib was then resumed at the same daily dose. In case of non-hematological toxicity grade 3/4 or recurrence of toxicity grade 2, imatinib was reduced from 400 to 200 or from 600 to 400 mg. For hematological toxicity grade 3/4, imatinib was discontinued until toxicity has resolved to less than grade 2. Doses were not interrupted in patients with an absolute neutrophil count $>2.0 \times 10^9$/l independent of the white blood cell count. If the hematological toxicity grade 3/4 recurred or persisted longer than 2 weeks, imatinib was reduced from 400 to 300 or from 600 to 400 mg. No dose reductions were performed for anemia.

Pharmacokinetic Studies

Plasma samples were collected on days 1 and 57 before the daily dose and after 4 and 24 h (days 2 and 58 before the daily dose). Analysis of imatinib and N-desmethyl-imatinib, the main metabolite, was done by HPLC [13]. Pharmacokinetics were calculated with the 'Topfit' program. Mean curve parameters were calculated by linear interpolation of a 400-mg once-daily imatinib dose. Steady-state conditions were assumed after an application interval of 12 days. Dose-dependent parameters were proportionally calculated for a dose assuming a 100% imatinib absorption. N-desmethyl-imatinib parameters were proportionally calculated for a 400-mg once-daily dose assuming 100% imatinib absorption and a 20% metabolized amount of imatinib. All parameters were calculated for the first dose application. Results of pharmacokinetic studies were compared with data from CML patients [14].

Patient Evaluation

The primary end point of this trial was objective response. Secondary end points included toxicity, pharmacokinetics, time to treatment failure and overall survival. CT scans were performed every 8 weeks. Additionally, α-fetoprotein (AFP) was assessed every 4 weeks. Response to treatment was evaluated in this study using the new international criteria proposed by the RECIST Committee [15]. Partial response (PR) was defined as at least 30% reduction in the sum of the longest diameters (LD) of all target lesions, taking the baseline sum of LD as a reference. Progressive disease (PD) was defined as at least 20% increase in the sum of the LD of all target lesions, taking the smallest sum of LD recorded since the treatment started as a reference or development of new lesions in a previously uninvolved site. Stable disease (SD) was defined as disease that showed neither sufficient shrinkage nor increase to qualify as either PR or PD. Each patient was assigned to one of the following criteria: (1) PR, (2) SD, (3) PD, (4) early death from HCC, (5) early death from toxicity, (6) early death because of other causes or (7) not evaluable. To be evaluable for response, patients must have received the trial drug for at least 21 days. Patients in response categories 3–6 were considered as treatment failure. All patients enrolled were evaluated for safety if they received the trial drug at least once and if the documentation was adequate. Adverse events were classified according to Common Toxicity Criteria (version 2.0).

Statistical Analysis

According to Fleming [16], we tested the null hypothesis (H_0) that the true response rate was $\leq 10\%$ versus the alternative hypothesis (H_A) that the true response rate was $\geq 30\%$. The significance level (i.e. the probability of rejecting H_0 when true) was 0.031. The power (i.e. the probability of rejecting H_0 when the alternative hypothesis was true) was 0.839. Rules for early treatment discontinuation were provided to stop treatment in the event of lack of efficacy. Sufficient responses (>1 in 15 evaluable patients) were required to trigger the second phase of enrollment for a maximum of 30 patients. The 95% confidence interval (CI) was calculated by the method of Clopper and Pearson. Overall survival and time to treatment failure were calculated by the Kaplan-Meier method using SPSS (version 12.0) software.

Results

A total of 17 patients were enrolled in the study between May 2003 and March 2004. Median duration from diagnosis of unresectable HCC to enrollment in this trial was 1.6 months. Table 1 depicts their baseline characteristics. Eleven patients had liver cirrhosis, and 7 had a history of alcohol abuse. Of 16 patients screened, 5 had hepatitis C (anti-HCV positive), but none had hepatitis B (hepatitis B surface antigen positive). In 1 patient, hereditary hemochromatosis was detected. Liver function was impaired as indicated by elevated bilirubin (8 patients) and low albumin levels (8 patients). Seven patients had metastatic disease in the adrenal gland (n = 4), lung (n = 2) and bone (n = 1). Vascular invasion and portal vein thrombosis was present in 8 (47%) and 7 (41%) patients, respectively. The majority of the patients had advanced disease and unfavorable prognostic scores. Nine patients were classified in Okuda stage II and 12 had an advanced score of 3 or more according to the Cancer of the Liver Italian Program (CLIP) investigators [17]. Only 1 of 15 (7%, 95% CI 0.2–32%) tumors assessed was positive for PDGFR and none of 14 (95% CI 0–23%) was positive for c-kit by immunohistochemistry.

Adverse Events

Imatinib was well tolerated in the majority of the patients. After at least 2 weeks of treatment with 400 mg of imatinib, doses were increased to 600 mg in 4 patients without toxicity. The most commonly reported adverse events of all grades were edema, renal failure, diarrhea, ascites and leukopenia. Table 2 summarizes the clinically relevant adverse events. Neutropenia was the only grade 4 adverse event and occurred in 2 patients (1 had neutropenic fever). When acute toxicity had resolved in the patient with neutropenic fever, doses were reduced from 400 to 300 mg and treatment was safely continued. In the 2 patients with grade 4 neutropenia, the neutrophil counts were 1 and 10%, and white blood cell counts were 2.73 and 1.77×10^9/l, respectively.

Many adverse events were judged complications of advanced malignant disease, underlying liver cirrhosis or comorbidities. After 7 months of treatment, acute renal failure occurred in 1 patient. Despite discontinuation of imatinib and initiation of dialysis, the patient did not recover and died probably due to progression of malignant disease. One patient developed progressive jaundice. Treatment was stopped on day 15, because the bilirubin level was >5 mg/dl. Despite no further doses of the study drug, bilirubin levels increased up to 19.3 mg/dl. There were 2 ear-

Table 1. Patient characteristics (n = 17)

Characteristics	
Age, years	
Mean	61
Range	34–75
Sex	
Male	9 (53%)
Female	8 (47%)
Karnofsky score	
100	1 (6%)
90	4 (24%)
80	8 (47%)
70	3 (18%)
60	1 (6%)
Anti-HCV positive[1]	5 (31%)
Liver cirrhosis	11 (65%)
Child-Pugh score	
A	13 (77%)
B	4 (24%)
Distant metastases	7 (41%)
Okuda stage	
I	8 (47%)
II	9 (53%)
CLIP score	
1	2 (12%)
2	3 (18%)
3	8 (47%)
4	4 (24%)
Bilirubin (normal <1.2)	
1.2–1.9 mg/dl	4 (24%)
≥2.0 mg/dl	4 (24%)
Albumin (normal 3.5–5.0)	
<2.8 g/dl	2 (12%)
2.8–3.5 g/dl	6 (35%)
AFP, IU/ml	
Median	1,453
Mean	31,269
Range	3.8–330,600
Prior therapies	
Resection	1 (6%)
TACE	3 (18%)
Octreotide	1 (6%)
Chemotherapy	2 (12%)

CLIP = Cancer of the Liver Italian Program [17]; TACE = transcatheter arterial chemoembolization.

[1] Only 16 patients were screened for hepatitis C virus.

Table 2. Adverse events (n = 17)

Adverse event	All grades	Grade 3 and 4
Edema	11 (65%)	0
Creatinine	6 (35%)	2 (12%)
Diarrhea	5 (29%)	2 (12%)
Ascites	5 (29%)	2 (12%)
Leukopenia	5 (29%)	1 (6%)
Neutropenia	4 (24%)	2 (12%)
Bilirubin	4 (24%)	2 (12%)
Anemia	4 (24%)	1 (6%)
Muscle cramps	3 (18%)	0
Thrombocytopenia	2 (12%)	0
Cardiovascular disorder[1]	1 (6%)	1 (6%)

[1] One grade 5 cardiovascular disorder.

Table 3. Best overall objective response (n = 17)

	n	% (95% CI)
Not evaluable for response	2	
Early death, unclear	1	
Progressive jaundice	1	
Evaluable for response	15	100
PR	0	0 (0–22)
SD	5	33 (12–62)
PD	9	60 (32–84)
Early death from HCC	4	27 (8–55)
Early death from toxicity	0	0 (0–22)
Early death from other causes	1	7 (0.2–32)

ly deaths, which were apparently not associated with imatinib treatment. One patient had an acute myocardial infarction after 1.1 months of treatment. Coronary angiography demonstrated diffuse coronary heart disease. No revascularization could be performed, and the patient died the following day. Since this patient received the study drug for more than 21 days, the patient was therefore evaluable for response according to RECIST. The other patient died only 6 days after study entry at home. Apart from mild diarrhea, which already existed before imatinib therapy, there were no signs or symptoms suspicious of any relation with the study drug. This early death remained unclear because postmortem examination was not performed.

Efficacy

The objective response data for all 17 study patients are shown in table 3. Two patients received the trial drug for less than 21 days, resulting in 15 patients evaluable for response. There was no objective response. Five patients had SD after 8 weeks, with 2 being stable after 16 weeks. Others failed treatment mainly due to PD, including 4 early deaths. Median time to treatment failure was

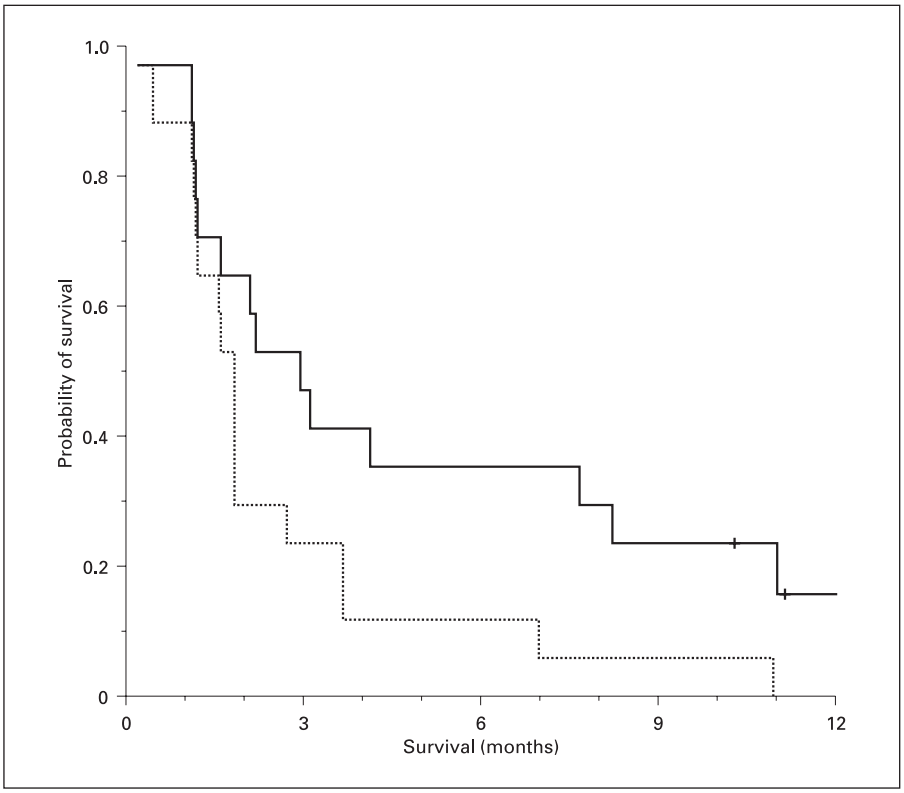

Fig. 1. Kaplan-Meier failure-free (dotted line) and overall survival (solid line) of all 17 patients enrolled. The median failure-free survival was 1.8 months and the median overall survival 3.0 months.

1.8 and 3.7 months in all patients enrolled and patients with SD, respectively. Overall and failure-free survival is shown in figure 1.

One female patient initially refused consent for enrollment in the study. Eight weeks later, PD was documented by CT scan. Then she gave informed consent and was enrolled in the trial. Immunostaining of tumor tissue was positive for PDGFR in this patient. After 8 weeks of imatinib treatment, tumor assessment showed SD despite an increased AFP level.

AFP levels decreased by 40, 36 and 19% in 3 patients, respectively. Best response (RECIST) of these 3 patients was SD (AFP –36%), PD (AFP –19%) and early death due to HCC (AFP –20% after 2 weeks and –40% after 3 weeks). Six and 3 patients had an increase in their AFP levels of less than 20% at 4 and 8 weeks, respectively, and were classified as stable.

Pharmacokinetics

Of the 17 patients enrolled, 74 plasma samples were analyzed. In patients treated with 400 mg imatinib, there were no significant differences in pharmacokinetics compared with CML patients. Results of pharmacokinetic studies are shown in table 4 and figure 2.

Table 4. Pharmacokinetic parameters of imatinib 400 mg once daily

Parameter	Imatinib		N-desmethyl-imatinib	
	HCC	CML	HCC	CML
$t_{1/2\ terminal}$, h	22.0	26.6	55.4	74.3
$t_{1/2\ absorption}$, h	1.8	2.2	–	–
$t_{1/2\ metabolism}$, h	–	–	1.3	2.0
AUC, μg × h/ml	32.0	31.7	5.6	6.1
C_{max}, μg/ml	1.2	1.4	0.13	0.13
t_{max}, h	3.7	3.7	2.5	3.2
V_{SS}, liters	340	374	1,040	1,058
$Clearance_{total}$, ml/min	210	221	240	211

Differences in all parameters between HCC and CML patients (n = 6) were not statistically significant. AUC = Area under the concentration-time curve; C_{max} = peak concentration; t_{max} = time to C_{max}; V_{SS} = volume of distribution.

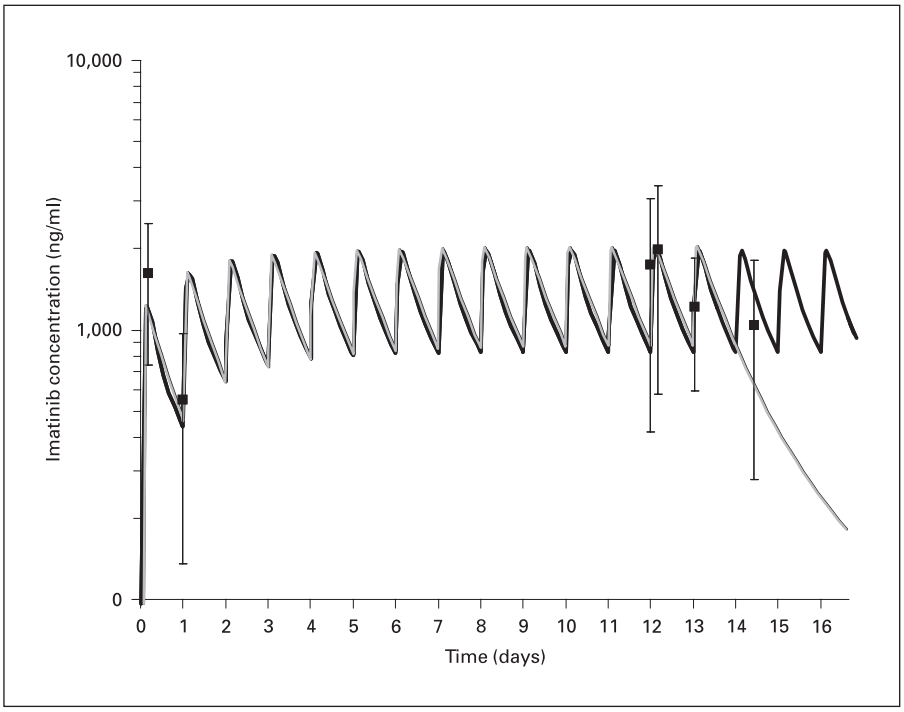

Fig. 2. Mean plasma curve of imatinib at a dose of 400 mg once daily for HCC (black line) and CML patients (grey line). Squares are mean data of HCC patients.

Discussion

In Western countries, surveillance programs for patients at risk of HCC have led to an increase in the application of radical and local ablative therapies, which are nowadays indicated in 30–40% of patients [3]. Several therapies have been proposed for patients who cannot benefit from a radical approach. In randomized controlled trials, only chemoembolization has been shown to improve survival in well-selected candidates [5]. However, in a recent randomized controlled European trial, only 12% of more than 900 consecutively evaluated HCC patients were suitable for this treatment [18]. Furthermore, despite significant improvement in survival, chemoembolization does not offer a curative option, and palliative therapies are needed for progressive disease.

At specialized centers, the majority of patients with HCC present with bilobar cancer (75%), portal vein thrombosis (72%) and three or more tumor masses in their livers (65%), indicating advanced tumor stage and poor prognosis [4]. All patients included in the present trial had advanced tumors, 47% had vascular involvement, and 41% had extrahepatic spread. Consequently, 47 and 24% of the patients enrolled had CLIP scores 3 and 4, respectively. In large patient series, median survival was only 4.5–8 and 2–2.5 months in patients with CLIP scores 3 and 4, respectively [17, 19].

Several protein kinases are deregulated and overexpressed in human cancers and are thus attractive targets for selective pharmacologic inhibitors. The most extensively studied is the BCR-ABL tyrosine kinase of CML. In a large randomized trial, 39% of all patients treated with imatinib but only 2% of all those given interferon plus cytarabine had a reduction in BCR-ABL transcript levels of at least 3 log ($p < 0.001$) [20]. Meanwhile, the frequency of major molecular responses observed in this trial with imatinib serves as a benchmark against which future studies aiming to optimize therapy for CML will be measured. Furthermore, gastrointestinal stromal tumors (GISTs) are characterized by a gain-of-function mutation of the KIT receptor and, occasionally, of PDGFR. Unresectable or metastatic tumors have been judged to be untreatable, because GISTs are insensitive to conventional chemotherapy. Nowadays, response rates of more than 50% and SD in additional 30% of patients have been observed in randomized trials of imatinib in patients with GIST [21, 22].

In contrast, no responses were observed in our study, and only 33% of patients experienced disease control for at least 8 weeks. Remarkably, 1 patient was treated with imatinib for 11 months. However, this patient was pre-

treated with gemcitabine for 10 months and with capecitabine for 15 months supposing less aggressive tumor biology of individual HCC rather than success of imatinib therapy.

These negative overall results may be due to the lack of PDGFR- and c-kit-positive tumors in this trial. Perhaps, treatment with imatinib should have focused on PDGFR- or c-kit-positive tumors only. In contrast to our results with no (95% CI 0–23%) c-kit-positive tumors, others found 26% (95% CI 17–36%) c-kit-positive HCCs by immunohistochemical staining and confirmed mRNA expression by RT-PCR [23]. Even supposing a relevant number of c-kit-positive tumors, imatinib therapy may fail in patients with HCC as c-kit expression was surprisingly found to be a positive prognostic factor in a recent trial [23]. However, significant overexpression of c-kit in HCCs was not found in another trial, which reported only 1 c-kit-positive tumor (4%, 95% CI 0.1–20%) in 25 HCCs examined [24]. Discrepant results may be due to a wide variety of different KIT antibodies, protocols and scoring systems to identify KIT-positive tumors. The antibody A4502 (DAKO) was found to yield a high frequency of positivity in GISTs and low staining background in other tissues. However, analysis of HCC with this antibody was negative in 40 tumors assessed [25]. Taken together, these results make c-kit a questionable target in the treatment of patients with HCC.

Several malignancies are associated with mutational activation of PDGF and PDGFRs such as a subset of GISTs expressing wild-type c-kit, bcr-abl-negative CML, hypereosinophilic syndrome and dermatofibrosarcoma protuberans. Furthermore, gliomas, soft-tissue sarcomas and other tumors are associated with autocrine PDGFR signaling. In addition to the mechanism of autocrine PDGFR signaling, pro-angiogenic effects of different PDGF isoforms have been demonstrated. These findings have led to speculations that PDGFs also are involved in tumor angiogenesis. Moreover, recent studies have provided experimental support for this notion [6]. Typically, HCC is a hypervascular tumor. Many angiogenic factors have been studied in HCC, and several anti-angiogenic therapies have been tested in animal models [26].

However, the low rate (7%, 95% CI 0.2–32%) of PDGFR-positive tumors and failure of imatinib therapy in the present study do not support the hypothesis that PDGF might play an important role in HCC. Consequently, it must be assumed that vascular endothelial growth factor, basic fibroblast growth factor or other angiogenic factors play a more important role than PDGF. Furthermore, positive trials of systemic use of anti-angiogenic drugs in patients with HCC are lacking to date [26]. In this context, novel tyrosine kinase inhibitors that block vascular endothelial growth factor receptor, PDGFR and c-kit, like PTK787, may be more active. For example, SU5416 is a potent inhibitor of VEGF receptor, c-kit, PDGFR and hepatocyte growth factor receptor (c-Met) that blocks hepatocyte-growth-factor-induced invasiveness of human HepG2 hepatoma cells in vitro [27].

After oral administration to normal volunteers, imatinib is well absorbed with an absolute bioavailability of 98%. At clinically relevant concentrations, total binding of imatinib to plasma proteins is about 95%, mostly to albumin and α_1-acid glycoprotein. CYP3A4 is the major enzyme responsible for imatinib metabolism. Other cytochrome P_{450} enzymes play a minor role in its metabolism. Approximately 81% of the dose is eliminated within 7 days (68% in feces and 13% in urine). Unchanged imatinib accounted for 25% of the dose (5% in urine and 20% in feces), the remainder being metabolites [28]. These data suggest relevant impact of hepatic metabolic function in imatinib pharmacokinetics. Indeed, in a phase I study of imatinib in patients with varying degrees of liver dysfunction, mostly due to liver metastases of colorectal cancer, a single episode of dose-limiting toxicity (grade 3 vomiting/diarrhea) was seen at 400 mg. In a preliminary analysis, the average dose-normalized exposure to imatinib was increased by about 50% at steady state in patients with liver dysfunction compared with controls [29].

In the present trial, the majority of patients had impaired liver function due to HCC and underlying liver disease. Liver dysfunction was mild and moderate in 77 and 24% of patients, respectively (data not shown), according to the definition used by Ramanathan et al. [29]. Interestingly, analysis of pharmacokinetic parameters of imatinib after continuous oral administration at steady state showed no statistically significant difference compared to CML patients without liver disease. In addition, pharmacokinetics assessed in this trial are in the range of results published for CML patients [30]. These findings do not confirm the results of the phase I study mentioned above [29]. However, liver function was not decompensated in our patients according to inclusion criteria. Despite impaired liver function indicated by elevated bilirubin and low albumin levels on the one hand, liver function was compensated as indicated by the coagulation system, which was nearly normal in all patients.

According to the advanced disease of our patients included, several adverse events observed in this trial were

more likely caused by progression of malignancy or the underlying liver disease than by the study drug. Ascites, edema, jaundice, renal failure (hepatorenal syndrome), leukopenia and thrombocytopenia are frequent complications in liver cirrhosis and hepatocellular carcinoma [31]. Altogether, rate of adverse events of any grade and of grade 3/4 toxicities is in the range of previously reported results of CML and GIST patients treated with imatinib at a dose of 400–600 mg daily [21, 28, 32]. It is worthy to note that patients included in this small trial had at least compensated liver function according to Child-Pugh stages A and B, whereas decompensated states (Child-Pugh C) were excluded.

In conclusion, in this small group of patients with advanced HCC, imatinib showed no therapeutic effect in terms of overall response. Unexpectedly, the majority of tumors were PDGFR and c-kit negative, a fact that may have contributed to our negative results. Imatinib pharmacokinetics were not significantly different in these patients with impaired liver function as compared to CML patients. In addition, adverse events observed in this trial were mostly complications of HCC and liver cirrhosis but otherwise within the expected range of those observed in patients without liver diseases. These findings suggest that imatinib treatment may be well tolerated in patients with mildly/moderately impaired liver function.

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