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Pancreatic Atrophy in Hepatocellular Carcinoma Patients Receiving Long-Term Treatment with Sorafenib

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Key Words
Hepatocellular carcinoma · Sorafenib · Pancreatic atrophy

Abstract
Objective: To date, sorafenib is the only approved systemic therapy for advanced hepatocellular carcinoma (HCC). Pancreatic atrophy has recently been reported in 2 patients as a novel side effect after long-term sorafenib treatment. ***Methods:*** We retrospectively analyzed clinical and radiological data of patients with advanced HCC with long-term treatment of sorafenib (median 279 days, range 153–826 days). Pancreata were semi-manually segmented section by section to calculate the pancreas volumes before and under sorafenib treatment. ***Results:*** Sorafenib reduced pancreatic volume in 18/19 (95%) HCC patients with a mean pancreatic volume loss of 25% (p = 0.002). Pancreatic volume loss depended on the dose (r = 0.36) and exposure time of sorafenib (r = 0.35) and was detectable as early as after 3 months of sorafenib treatment and already after a cumulative sorafenib dose of <100 g. Median overall survival was 13.2 months (range 7.8–31.3 months) but did not correlate with sorafenib-induced pancreatic volume reduction (hazard ratio 1.002, 95% confidence interval 0.981–1.060, p = 0.24). ***Conclusion:*** We could confirm pancreatic atrophy as a novel adverse event of sorafenib therapy in HCC patients, correlating with sorafenib dose and exposure time.

Introduction

The multikinase inhibitor sorafenib is the first chemotherapeutic drug that showed a survival benefit in advanced hepatocellular carcinoma (HCC) [1, 2]. However, sorafenib therapy is limited by side effects and lack of long-term efficacy. The most frequent side effects include diarrhea and hand-foot skin reaction (HFSR) and often lead to discontinuation or dose reduction of sorafenib. However, development of early skin toxicity [3] or diarrhea [4, 5] under sorafenib treatment was associated with a better outcome in HCC patients. Recently, pancreatic atrophy has been reported as a novel, long-term side effect of sorafenib treatment in 2 HCC patients receiving sorafenib for 2.5 and 3 years, respectively [6]. Having developed grade 2 diarrhea after 3 months of sorafenib treatment, the first patient showed a 20% volume reduction of the pancreas after 7 months of sorafenib. The second pa-

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tient developed grade 1 diarrhea 2 months after initiation of sorafenib and showed a 35% volume reduction of the pancreas after 37 months of sorafenib treatment.

The aim of our current study was to reappraise the finding of sorafenib-associated pancreatic atrophy in a larger cohort of HCC patients and to determine the correlation between pancreatic atrophy and both the duration and the cumulative dose of sorafenib exposure. Furthermore, we aimed to analyze the correlation between pancreatic atrophy and the patients' survival.

Material and Methods

Patients

We retrospectively analyzed clinical and radiological data from advanced HCC patients with long-term sorafenib treatment who were monitored by computed tomography (CT) at a 3-month interval at our institution between January 2008 and December 2012. Diagnosis of HCC was established according to the recommendations of the American Association for the Study of Liver Diseases [7]. Inclusion criteria were age >18 years, compensated liver cirrhosis (Child-Pugh score A–B), sorafenib treatment >5 months, and ECOG performance status 0–3. Exclusion criteria comprised patients with pancreatic lesions, previous pancreatic operations, and pretreatment with sorafenib or other chemotherapies. This study was approved by the local Ethics Board (S-300/2011). Of 88 HCC patients treated with sorafenib, we had to exclude 47 who were on sorafenib for <5 months, 6 who were lost to follow-up, 1 with sorafenib pretreatment, and 36 who were not monitored by CT at a 3-month interval (mainly due to MRI follow-up). We identified 19 eligible patients with available consecutive high-quality CT scans before and under sorafenib treatment. Clinical data were retrospectively collected regarding age, gender, underlying liver disease, treatment duration and cumulative dose of sorafenib, onset and grade of sorafenib side effects according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (diarrhea, HFSR), second-line treatment (n = 1), and overall survival. The patient with second-line therapy received the oral histone deacetylase-inhibitor resminostat after progression under sorafenib treatment. Detailed data on the study population is given in table 1.

Sorafenib Treatment

Sorafenib treatment was performed as previously described [4]. Briefly, the starting dose of sorafenib was 400 mg b.i.d. In patients with impaired liver function (bilirubin >3 mg/dl), the initial sorafenib dose was 200 mg b.i.d., which, in case of good tolerability, was escalated after 2–4 weeks up to 400 mg b.i.d. Dose reduction was performed in patients with moderate toxic side effects (grade 2), with a dose reescalation upon resolution of side effects. In case of grade 3 toxicity, sorafenib therapy was interrupted until improvement of side effects to grade 0–1, followed by a permanent dose reduction. In parallel, mild and moderate diarrhea was treated with loperamide. All patients received prophylaxis of skin toxicity with urea-containing ointment. Cumulative sorafenib exposure time and dose at the time point of each CT scan was quantified for all patients.

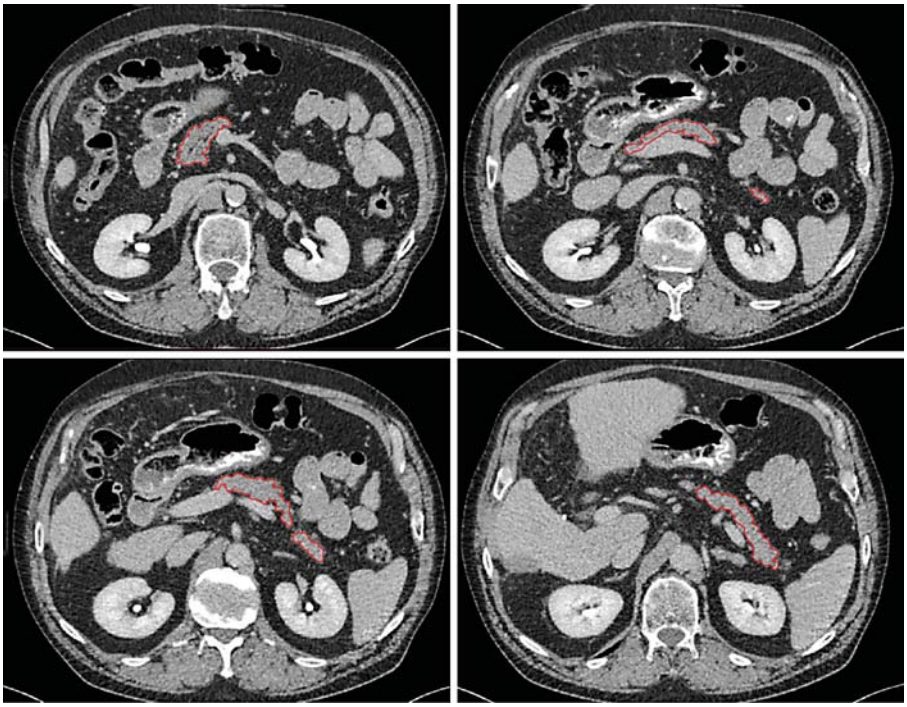
Table 1. Patient characteristics

Total number	19
Male/female	14 (74)/5 (26)
Median age at sorafenib start, years	71.0 (46–85)
Liver cirrhosis/no cirrhosis	17 (89)/2 (11)
Median body mass index	26.1 (19.8–35.6)
Etiology of liver cirrhosis	
Alcohol	5 (29)
Viral hepatitis	3 (18)
Nonalcoholic steatohepatitis	2 (12)
Hemochromatosis	2 (12)
Cryptogenic	5 (29)
Median exposure time to sorafenib, days	279 (153–826)
Median cumulative sorafenib dose, g	144 (12–516)
Median daily sorafenib dose, mg	565 (400–800)
Diarrhea, grade	
0	3 (16)
1	11 (58)
2	3 (16)
3	2 (11)
HFSR, grade	
0	11 (58)
1	2 (11)
2	2 (11)
3	4 (21)
Weight loss, grade	
0	7 (37)
1	8 (42)
2	4 (41)
Median overall survival, days	396 (233–940)

Values in parentheses are percentages (percentage of cirrhotic patients for etiology of liver cirrhosis) or ranges. Adverse events are graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0.

CT Scanning and Image Processing

Tumor response was evaluated by contrast-enhanced abdominal CT scans with portal venous phase on a 128-slice dual-energy CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector, Forchheim, Germany) with the following scan parameters: contrast-enhanced dual-energy CT was performed on the 64-slice dual-energy CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector). All patients were scanned in craniocaudal direction from the dome of the liver to the iliac crest during inspiratory breath hold. Iodinated contrast medium (Iomeprol-400, Iomeron, Bracco Imaging SpA, Milan, Italy) was intravenously administered via an automated dual-syringe power injector (Accutron CT-D, Medtron, Saarbrücken, Germany) according to a body weight (mean 68 ± 15 kg)-adapted injection protocol. Mean contrast amount was 97 ± 9 ml. The flow rate was 3.9 ± 0.3 ml/s. The timing for the arterial phase scan was determined using the care bolus technique (Siemens Healthcare), i.e., arterial phase scan was automatically started 7 s after the attenuation coefficient of abdominal aortic blood



Color version available online

Fig. 1. Measurement of the pancreatic volume. An example of the semi-manual segmentation of the organ is shown. The boundaries of the pancreas are highlighted in red (in the online version only).

reached 120 Hounsfield units. The portal venous phase images were acquired another 30 s after the arterial phase examination. Contrast application was the same for the individual patient at every imaging time point. The scan was acquired with a detector collimation of 32 × 0.6 mm, slice 3.0 mm, rotation time 0.5 s, and pitch 0.6.

Abdominal CT scans were performed before and approximately every 12 weeks under sorafenib treatment. For volumetric analysis, the complete pancreas was semi-manually segmented section by section in both coronal and sagittal reconstruction by 2 radiologists (M.-K.G. and M.S.), who were blinded for the treatment phase of the respective CT scan. Arterial phase images were included in our analysis in order to differentiate organ borders using an in-house-developed software (MITK Version 2011; DKFZ, Heidelberg, Germany) [8, 9]. The organ was segmented by exploiting the local gray-value statistics of the pancreas tissue (fig. 1). To minimize potential measurement errors, organs were segmented three times, and the mean value of these volume measurements was used for further analysis.

Statistical Analysis

The variables were analyzed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means, standard deviations, medians as well as minimum and maximum or absolute and relative frequencies, respectively, were reported. Survival of the patients was reported using the Kaplan-Meier method. A possible association between continuous variables was investigated using Pearson's correlation coefficients. Descriptive p values of the corresponding statistical tests were calculated. Wherever appropriate, statistical graphics were used to illustrate the findings.

Results

Patient Characteristics

For our analysis, we included 19 patients who were treated with sorafenib for advanced hepatocellular cancer over a median of 279 days (range 153–826 days). The baseline characteristics of our population are listed in table 1. In all patients, treatment with sorafenib was finally stopped due to significant and/or symptomatic tumor progression. Only 1 patient received a second-line treatment after HCC progression after 8.2 months (245 days) of sorafenib therapy. This patient demonstrated an overall survival of 28.9 months (866 days).

Sorafenib-Induced Side Effects

Diarrhea and HFSR were common side effects of sorafenib treatment. Their frequencies are listed in table 1. Diarrhea occurred on average after 89 days of sorafenib treatment (range 3–385 days), HFSR after 53 days of sorafenib treatment (range 14–249 days). Accordingly, 'early' and 'late' HFSR were defined when occurring <50 days versus >50 days after the onset of sorafenib, respectively. However, due to consequent prophylaxis of HFSR with urea-containing ointment, this side effect was comparably mild and rare.

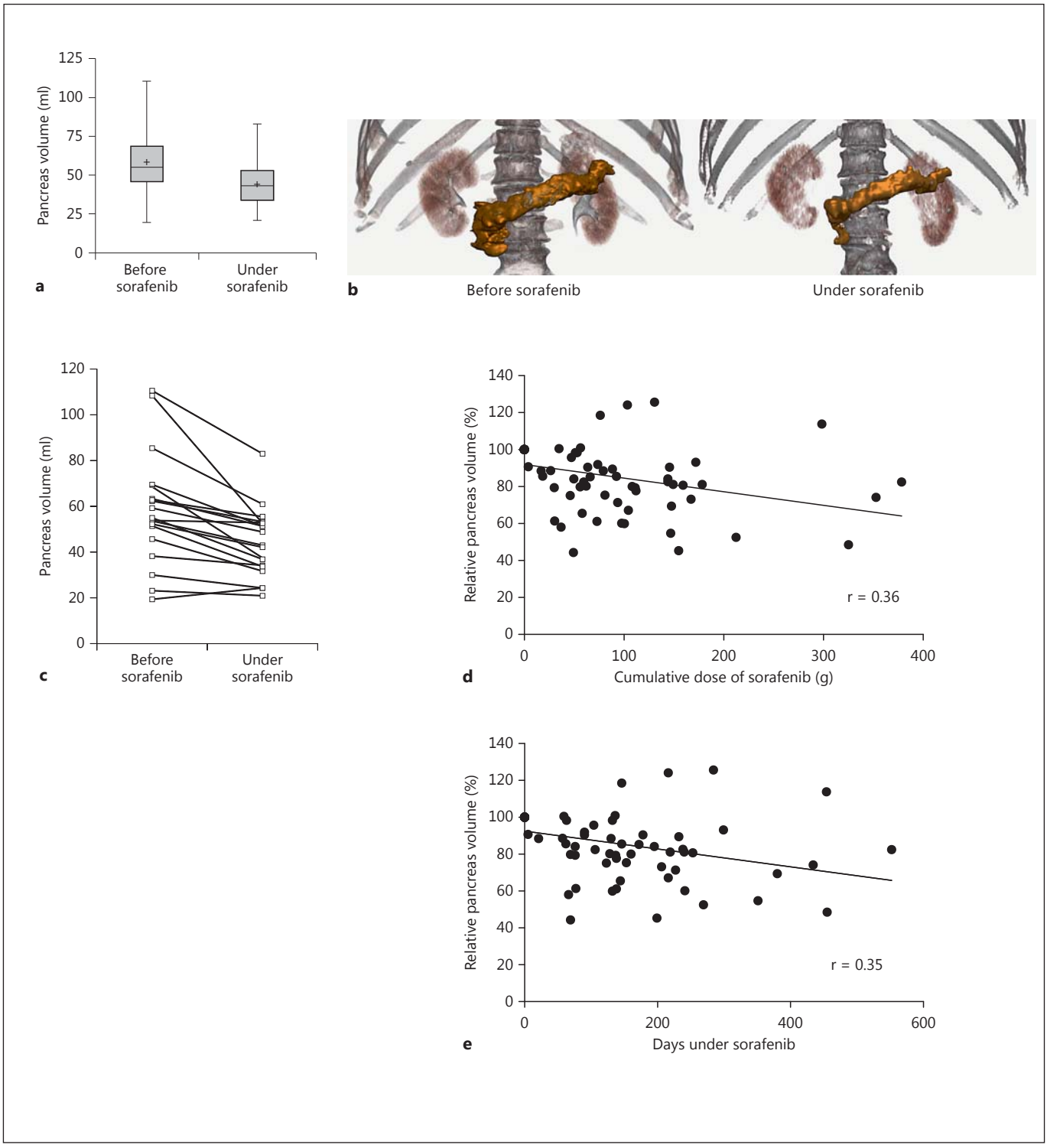


Fig. 2. Sorafenib-induced pancreatic atrophy. **a** Mean pancreas volume reduction from 58.6 ml (median volume 55.0 ml) before the onset of sorafenib to 44.1 ml (median volume 43.0 ml) under sorafenib treatment (p = 0.0002). **b** Example of a three-dimensional volume reconstruction of the pancreas before and after a 240-day treatment interval with sorafenib with a cumulative dose of 51.2 g. **c** Absolute pancreas volumes of all individual patients before sorafenib treatment are compared to the last CT scan under sorafenib treatment. **d**, **e** Relative pancreas volumes (compared to a starting volume of 100%) under sorafenib treatment are shown as a function of the cumulative dose (**d**) and the exposure time to sorafenib (**e**). The correlation coefficient r is given for both graphs.

Volumetric Analysis of the Pancreas under Sorafenib Treatment

The last CT scan before the onset of sorafenib, defining the reference CT with the relative pancreas volume set to 100%, was performed at a mean of 42 days (range 0–207 days) before the start of treatment. However, radiological imaging was performed in all patients at least 30 days before sorafenib treatment. Some imaging was performed by MRI, ruling out significant pancreatic volume changes before sorafenib treatment. For a better comparability of volumetric data before and under treatment, only CT scans were considered for this analysis. On average, 2.7 CT scans (range 1–5) were performed per patient under sorafenib treatment. The final CT scan under sorafenib was performed after a median sorafenib treatment time of 227 days (range 123–552 days). These data sets were used to calculate the pancreas volume before and under sorafenib treatment, measured after the respective maximal sorafenib exposure time.

Sorafenib treatment of HCC patients significantly reduced the mean pancreas volume from 58.6 ml before the onset of sorafenib to 44.1 ml under sorafenib treatment ($p = 0.0002$), resulting in a mean volume reduction by 14.5 ml (25%; fig. 2a). An example of a three-dimensional volume reconstruction of the pancreas before and under sorafenib treatment is shown in figure 2b, demonstrating a significant sorafenib-induced volume loss of the pancreatic head.

Figure 2c compares the individual changes of pancreas volumes before and under sorafenib treatment for all 19 patients. Sorafenib reduced pancreatic volume in all but 1 patient. The maximal pancreas volume reduction was 55.8 ml (51%) after 455 days of sorafenib treatment, with a cumulative sorafenib dose of 325 g at the time point of the last CT scan under sorafenib. Only 1 patient showed an increase of the pancreas volume from 19.4 to 24.3 ml (increase by 25%) after 284 days of sorafenib treatment, with a cumulative dose of 131 g at the time point of the last CT scan under sorafenib.

In figure 2d and e, the relative pancreas volumes under sorafenib treatment compared to the reference CT scan before the onset of treatment (set as 100%) are plotted as a function of the administered cumulative dose of sorafenib (fig. 2d) or the exposure time of sorafenib (fig. 2e) for all patients and including all available CT scans under therapy. Pancreatic atrophy demonstrates a dependence on the dose ($r = 0.36$) and exposure time of sorafenib ($r = 0.35$), with a wide variety of initial pancreas volumes within the whole population (fig. 2c).

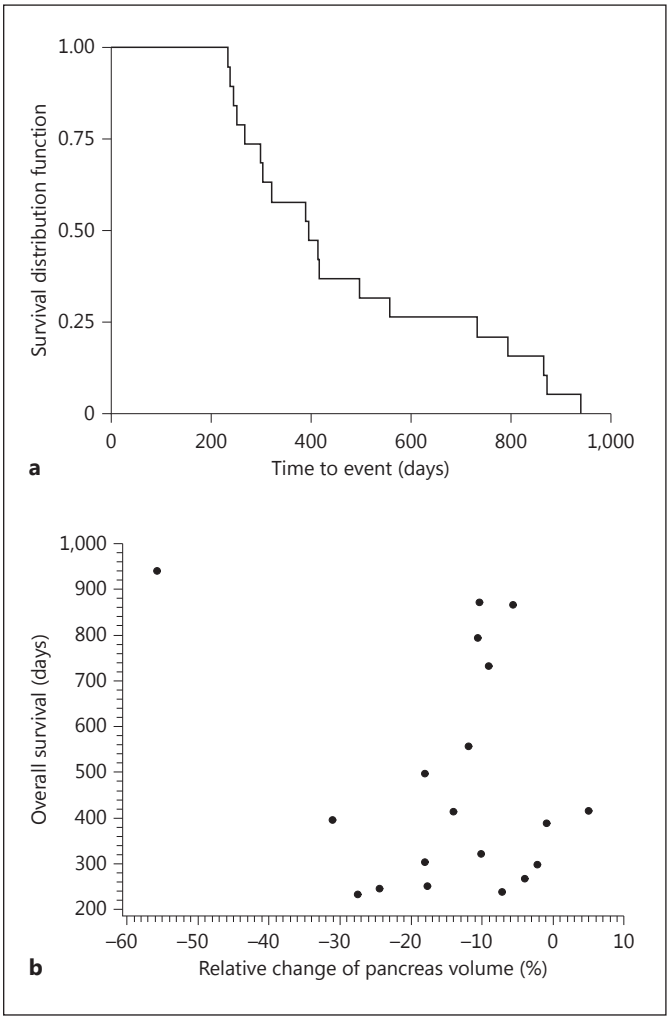


Fig. 3. Sorafenib-induced pancreatic atrophy and survival. **a** Kaplan-Meier curve for the overall survival of all sorafenib-treated HCC patients. **b** Pancreatic volume reduction does not correlate with the overall survival (hazard ratio 1.002, 95% confidence interval 0.981–1.060, $p = 0.24$).

Correlation of Pancreatic Atrophy with Clinical Parameters

Since sorafenib-induced diarrhea and HFSR have been discussed as predictors of positive outcome under sorafenib therapy [4, 5], we sought to investigate whether these side effects are interlinked with the newly described sorafenib-induced pancreatic atrophy [6] and whether pancreatic atrophy is correlated with better outcome of HCC patients as well. In our cohort, there was no correlation between the degree of pancreatic shrinkage and the onset ($r = –0.05$) or grade ($r = 0.11$) of sorafenib-induced diarrhea. However, sorafenib-induced volume reduction

of the pancreas positively correlated with a later onset (>50 days after sorafenib onset, r = 0.52) but not with the grade (r = –0.07) of HFSR. Analyzing the overall survival of our cohort, we found a median overall survival of 13.2 months (396 days), with a median sorafenib exposure time of 9.3 months (279 days). The Kaplan-Meier curve for the overall survival of the whole study population is shown in figure 3a. Sorafenib-induced pancreatic volume loss did not correlate with the patients' overall survival (hazard ratio 1.002, 95% confidence interval 0.981–1.060, p = 0.24; fig. 3b).

Discussion

To date, sorafenib is the only approved systemic therapy for patients with advanced HCC (Barcelona Clinic Liver Cancer stage C) [10]. Recently, pancreatic atrophy has been reported in 2 patients as another novel side effect of long-term sorafenib treatment [6]. In that report, a 20 and 35% decrease in the volume of the pancreas was observed after 7 and 37 months of sorafenib treatment, respectively. A cumulative sorafenib dose of >1,000 g and a treatment duration of >24 months was reported in these 2 long-term treated HCC patients.

In our current study we sought to confirm this observation in a larger cohort. We found that 18/19 (95%) of our HCC patients developed pancreatic volume reduction as a continuous process under sorafenib treatment, being detectable already in the first control CT scan after 3–4 months of sorafenib exposure in the majority of patients (fig. 2e). Considerable pancreatic shrinkage was observed already after a cumulative sorafenib dose of <100 g (fig. 2d). Although there is a considerable variation in the pancreas volumes before the onset of treatment (fig. 2c), the volume reduction by sorafenib was statistically significant in the whole cohort of patients (fig. 2a). It has been discussed that pancreatic exocrine insufficiency could contribute to sorafenib-induced diarrhea [11]. Accordingly, Hescot et al. [6] found steatorrhea in 1 of the 2 HCC patients who could be successfully treated with pancreatic enzyme replacement. Due to the lack of data on stool elastase or steatorrhea in our retrospective analysis, we cannot comment on this aspect of sorafenib-induced diarrhea. However, since the early onset of diarrhea (at a median of 89 days) was paralleled by an early pancreatic volume loss after at least 90–120 days of sorafenib treatment, shrinkage-induced exocrine pancreatic insufficiency might indeed contribute to sorafenib-induced diarrhea. In our cohort, we could not detect a significant correlation between pancreatic volume loss and sorafenib-induced diarrhea, which might, however, be biased by the preemptive therapy with loperamide. In contrast, the extent of pancreatic volume loss correlated with a late onset of HFSR. This observation might be explained by the fact that patients with a late onset of HFSR (due to consequent prophylaxis by ointments) did not need an early sorafenib dose reduction, leading to a higher cumulative sorafenib dose, which in turn correlated with pancreatic volume reduction (fig. 2d). Accordingly, we calculated a median cumulative sorafenib dose of 88 versus 146 g in patients with early (<50 days) and late (>50 days) HFSR, respectively. However, since only 8 patients of our cohort developed HFSR (4 with early HFSR), a scrutinized or even multivariate analysis of the interdependence of HFSR and pancreatic atrophy is impossible.

The antiangiogenic properties of sorafenib might account for a reduced microvasculature in both tumor and normal tissue, leading to the atrophy of the pancreas [6], muscle [12], and thyroid gland [13], and possibly also to frequent side effects like diarrhea and HFRS. Thus, a higher frequency and grade of antiangiogenic side effects might be associated with a stronger antitumor effect by and a higher survival benefit from sorafenib treatment. Accordingly, the occurrence of diarrhea [4, 5] and/or early HFSR [3, 14–16] and the presence of adverse events in general [17] have been reported to be associated with a favorable outcome in HCC and renal cell cancer patients under sorafenib. However, in our cohort with an overall survival ranging from 233 to 940 days (table 1), pancreatic volume reduction was not associated with a longer survival time.

The previously discussed issues already illustrate the limitations of our hypothesis-generating study: the retrospective nature of our analysis limits the generalization of its statements. In 2 patients, the last CT scan prior to sorafenib treatment was performed 92 and 207 days before the onset of sorafenib, respectively. In these patients, significant changes of pancreatic volumes before sorafenib treatment were ruled out by additional MRI scans that had been performed within 90 days before sorafenib treatment. For a better comparability of volumetric measurements, MRI data were not included in our analysis. All other patients had baseline CT scans within 90 days before sorafenib treatment. Furthermore, data regarding steatorrhea or lipase levels are lacking. A large prospective observational study is needed to clarify these intriguing issues.

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Disclosure Statement

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