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Long-term therapy with sorafenib is associated with pancreatic atrophy

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ABSTRACT

Background: Although the short-term adverse effects of sorafenib are well known, few data exist on long-term toxicity. The objective of the present study was to investigate the prevalence of pancreatic atrophy among a cohort of patients with hepatocellular carcinoma (HCC) who were treated with sorafenib for ≥2 y.

Methods: Between March 2007 and December 2013, 31 patients with HCC who were treated with sorafenib for ≥2 y were identified. The effect of pancreatic atrophy and enhancement on incidence of adverse events, tumor response, and overall survival (OS) were assessed.

Results: Thirty-one patients with HCC were treated with sorafenib for ≥2 y and met inclusion criteria; 11 patients (35.5%) were Barcelona-clinic liver cancer stage B, whereas 20 patients (64.5%) were Barcelona-clinic liver cancer stage C. Median duration of treatment with sorafenib was 35.2 mo. Pancreatic atrophy and a decrease in pancreatic enhancement occurred in 24 patients (77.4%) and 15 patients (48.4%), respectively. On the basis of the modified response evaluation criteria in solid tumors, four patients (12.9%) had a complete response, 10 patients (32.3%) had a partial response, and 17 patients (54.8%) had stable disease. Patients treated with sorafenib with pancreatic atrophy had a median OS of 49.4 mo (95% confidence interval, 41.2–57.5 mo) compared with 31.2 mo (95% confidence interval, 25.7–36.7 mo) among patients who did not develop pancreatic atrophy ($P = 0.009$). In contrast, survival was not associated with decreased *versus* normal enhancement of the pancreas (OS, 47.7 mo *versus* 41.7 mo, respectively; $P = 0.739$).

Conclusions: Pancreatic atrophy occurred in many HCC patients after 2 y of treatment with sorafenib. Patients who experienced pancreatic atrophy had a better tumor response and OS.

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related mortality in the world [1]. Treatments for HCC may include surgical resection, transplantation, ablation, chemoembolization, stereotactic body radiation therapy, and chemotherapy [2]. Although these options have improved over the past 30 y, the prognosis of patients with HCC is still poor [3]. In fact, up to 60%–70% of patients with HCC present with intermediate- to advanced-stage disease at the time of diagnosis [4]. Patients with advanced, unresectable, or metastatic HCC have a median survival that may be as short as 3–6 mo [3].

Sorafenib is an oral inhibitor of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors and the Raf pathway, which decreases tumor cell growth and inhibits angiogenesis in tumors [5]. Initially approved for renal-cell carcinoma [6], sorafenib has subsequently been demonstrated to have activity against several different malignancies including lung cancer [7], thyroid cancer [8], and soft tissue sarcomas [9].

Sorafenib has similarly been shown to improve overall survival (OS) among patients with advanced HCC. In the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial, sorafenib therapy resulted in an OS of 10.7 mo compared with 7.9 mo for patients who received placebo [10]. A similar relative survival benefit associated with sorafenib was found in the subsequent Asia–Pacific trial (hazard ratio, 0.68) [11]. To date, sorafenib is the only approved targeted agent for the treatment of HCC. Sorafenib can be associated with well-known short-term adverse effects including hand–foot skin reaction (HFSR), diarrhea, and fatigue, which typically occur within the first two cycles of treatment and can be moderate to severe [6]. Because of the poor prognosis of advanced HCC, few studies have been published on the long-term toxicity of sorafenib in patients with HCC.

Recently, Hescot *et al.* [12] reported on two patients who were noted to have irreversible pancreatic atrophy after long-term treatment with sorafenib. Although intriguing, no other study has confirmed a possible sorafenib-related effect on the pancreas. As such, the objective of the present study was to investigate the prevalence of pancreatic atrophy among a cohort of patients with HCC who were treated with sorafenib for long term. In addition, we sought to investigate the possible relationship between pancreatic atrophy, other adverse effects, and overall sorafenib efficacy.

2. Methods

2.1. Study population

Patients with a diagnosis of unresectable and untransplantable HCC who were treated with sorafenib at Sun Yat-Sen University Cancer Center between March 2007 and December 2013 were identified. The diagnosis of HCC was based on either histology, or a hypervascular lesion on cross-sectional imaging and an alpha-fetoprotein level of ≥200 ng/mL [13]. Only patients who had been treated with sorafenib for a prolonged period of time, defined as ≥2 y, were included in the study cohort. Additionally, only patients who had computed tomography (CT) scan and Digital Imaging and Communications in Medicine image data at least every 3 mo throughout the treatment course were included in the study. The institutional review board of Sun Yat-Sen University Cancer Center approved the study, and the consent of the patients was obtained.

2.2. Measurements

Patients were followed regularly with blood and radiological tests. In addition, patients' tumor response was routinely evaluated with spiral contrast-enhanced CT every 2–3 mo. CT imaging was performed using a 16-section scanner (Philips Brilliance TM, Eindhoven, The Netherlands) or 64-section scanners (Toshiba Aquilion, Tokyo, Japan; GE Healthcare, Charfont St Giles, England). The CT parameters included a detector field of view, 35 cm × 35 cm; pitch, 1 mm; peak, 120 KVp; mAs, 150; section thickness, 5 mm; no section overlap. Multidetector CT was performed before the administration of contrast medium and during the hepatic arterial, hepatic venous, and delayed phases. All patients received 1.5 mL/kg total body weight of an intravenous nonionic contrast medium. The contrast medium was administered using a mechanical power injector at a rate of 2.5–3.5 mL/s through an intravenous catheter inserted into an arm vein, followed by a flush of 25 mL of saline administered at the arm injection rate. Hepatic arterial phase and venous phase scanning were started automatically at 25 and 50 s, respectively, after the trigger threshold (150 HU) was reached at the level of the suprarenal abdominal aorta. The delayed phase was started 120 s after the start of contrast material injection.

All images were stored and handled by the postprocessing workstation software (GE Healthcare Advantage workstation, version AW4.5). Volumes of the pancreas were calculated by a volumetric computed tomographic measurement system. Both the volume and the density of pancreas were measured at three time points: (1) before the initial dose of sorafenib, (2) 1 y after the initiation of sorafenib therapy, and (3) 2 y after the initiation of sorafenib. At each time point, density was measured at the head, body, and tail of pancreas, respectively, and an overall average pancreatic density was calculated. In addition, density before contrast (DBC) and density after contrast (DAC) of pancreas were also calculated. Finally, the difference in density (DD) values after contrast (DD = DAC − DBC) was calculated; the DD reflected a relative degree of pancreatic enhancement at each time point measured. Two experienced radiologists performed all measurements independently, and the mean of measurement was taken as the final pancreatic density and volume measurement for the purpose of analyses. Pancreatic atrophy was defined as a 10% decrease in pancreatic volume, whereas decreased pancreatic enhancement was categorized as a 10% decrease in DD.

Adverse events (AEs) were recorded according to the National Cancer Institute Common Toxicity Criteria (CTCAE v3.0) [14].