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Research article

Hepatocellular carcinoma treated with sorafenib: Arterial tumor perfusion in dynamic contrast-enhanced CT as early imaging biomarkers for survival

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ABSTRACT

Objectives: To investigate whether hepatic perfusion CT yields early imaging biomarkers predictive of the prognosis of hepatocellular carcinoma (HCC) patients treated with sorafenib.

Methods: We evaluated 36 HCC patients who underwent hepatic perfusion CT before- and one week after sorafenib therapy. We measured arterial and portal perfusion in the hepatic tumor and liver parenchyma [(AP)(PP)$_{tumor}$], [(AP)(PP)$_{liver}$]. The perfusion ratio was calculated by dividing the post- by the pre-sorafenib value. The effect of each value on the overall survival rate was analyzed with the Cox proportional hazards model; statistically significant parameters were subjected to receiver operating characteristic analysis based on median survival after sorafenib administration to determine the overall survival rate with the Kaplan-Meier method.

Results: Pre-AP$_{tumor}$ was significantly associated with the overall survival rate (hazard ratio (HR) and 95% confidence interval (CI), 0.16 and 0.02-0.84, p = 0.03). The AP$_{tumor}$ ratio tended to be associated with the overall survival rate (HR and 95% CI, 2.94 and 0.94-7.88, p = 0.06). The overall survival rate was higher in patients with pre-AP$_{tumor}$ > 71.7 mL/min/100 mL, and with AP$_{tumor}$ ratio ≦ 1.1 (p < 0.01 and 0.03, respectively, in Kaplan-Meier method with log-rank).

Conclusion: Hepatic perfusion CT yields early imaging biomarkers for predicting overall survival in HCC patients treated with sorafenib.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide [1]. Sorafenib, the oral multikinase inhibitor that inhibits excessive angiogenesis of abnormal arteries seen in advanced HCC, prolongs the overall survival of patients with advanced HCC [2,3]. However, some patients suffered severe adverse effects or had a very short survival [4]. In addition, no drugs have clearly shown a survival benefit in second-line treatment after sorafenib failure in advanced HCC [5–7]. Thus, the ability to predict the early therapeutic response is very important for the identification of patients who may/may not benefit from sorafenib therapy.

Tumor markers and imaging modalities are used for the diagnosis and response assessment of patients with HCC. However, the utility of tumor markers, especially for the early evaluation of the therapeutic effect of sorafenib, remains controversial [8,9]. Computed tomography (CT)– and magnetic resonance imaging (MRI) findings apply modified Response Evaluation Criteria in Solid tumors (mRECIST), taking into account a decrease in enhancing tumor and tumor necrosis, to evaluate the HCC response to antiangiogenic drugs including sorafenib [9,10].

Abbreviations: HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; mRECIST, modified response evaluation criteria in solid tumors; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; ECOG PS, eastern cooperative oncology group performance status; ROI, region of interest; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; FOV, field of view; Auto-mA, automatic tube current modulation; CTDI$_{vol}$, computed tomographic dose index; DLP, dose-length product; SSDE, size-specific dose estimate; AIDR3D, adaptive iterative dose reduction-three-dimensional; AP, arterial perfusion; PP, portal perfusion; ROC, receiver operating characteristic; DCE-US, dynamic contrast-enhanced ultrasound

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However, sorafenib-elicited disease stabilization may result in tumor shrinkage and/or an induction of intralesional necrosis that may not lead to a marked decrease in the tumor size [3,11]. Consequently, the early evaluation of the therapeutic effects of sorafenib based on mRECIST is not sufficient.

Perfusion CT facilitates the quantification of organ perfusion in absolute units at high spatial resolution [12]. Quantitative evaluation of hepatic perfusion on CT images has been reported as a more sensitive imaging biomarker than the tumor size and tumor density for monitoring the anti-angiogenic treatment effects in HCC [13,14]. Based on an earlier study [15] that evaluated the therapeutic effects of sorafenib on perfusion CT images we investigated whether hepatic perfusion CT performed before- and one week after the start of sorafenib administration yields early imaging biomarkers for the survival of HCC patients.

2. Materials and methods

This prospective study was approved by the Human Ethics Review Committee of our institute and a signed consent form was obtained from all study subjects.

2.1. Study population

Patients with advanced HCC who had undergone hepatic perfusion CT before and one week after the start of sorafenib administration at our institution were included in this study. They were considered ineligible for surgery, liver transplantation, repeat locoregional therapy, repeat transarterial chemoembolization (TACE), or repeat hepatic arterial infusion chemotherapy (HAIC). The inclusion criteria for sorafenib treatment were an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2 or less, Child-Pugh liver function class A or B, adequate hematologic function (platelet count $\geqq 5 \times 10^4$/μL, hemoglobin $\geqq 8.5$ g/dL), adequate hepatic function (albumin $\geqq 2.8$ g/dL, total bilirubin $\leqq 3$ mg/dL, and alanine aminotransferase and aspartate aminotransferase $\leqq 5$ times the upper limit of the normal range), and adequate renal function (serum creatinine $\leqq 1.5$ times the upper limit of the normal range) according to the SHARP and GIDEON study [3,16]. The inclusion criteria for hepatic perfusion CT were an age over 20 years, no contraindication for iodinated contrast medium, no renal failure (estimated glomerular filtration rate < 45 mL/min/1.73 m^2), and no severe thyroid disease.

Based on these criteria we enrolled 53 consecutive HCC patients between October 2012 and July 2015. 15 patients were excluded because perfusion of tumor could not be obtained because of difficulty of setting region-of-interest (ROI) on the accurate tumor location due to its small size (n = 2, the tumors measured less than 1 cm) and absence of intrahepatic lesion (n = 13, all of whom manifested extrahepatic metastases). Two were subsequently excluded because the hepatic perfusion CT parameters differed from our protocol (only half dose of contrast material was administered intravenously due to extravasation), or because the administration of sorafenib was stopped after 2 days due to side effects that included worsening liver function and numbness in a limb. Thus, the final study population consisted of 36 patients (Fig. 1). The clinical characteristics of the 36 included patients are summarized in Table 1. Tumor staging was based on the Barcelona Clinic Liver Cancer (BCLC) staging system [17].

2.2. Sorafenib treatment regimens

All patients commenced standard sorafenib treatment (400 mg × 2/day). In patients with adverse drug reactions, treatment was interrupted or the sorafenib dose was changed to 400 mg × 1/day. Sorafenib administration continued until the patient died, experienced adverse effects that necessitated its discontinuation, manifested a deterioration in the ECOG PS score to 4, exhibited worsening liver function, or withdrew consent for further treatment with the drug. The liver function criterion for drug discontinuation was total bilirubin > 3 mg/dL 4 weeks after treatment cessation.

2.3. Tumor markers

To assess the treatment response we recorded the concentration of the serum tumor markers α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) before (pre-AFP, pre-DCP) and one month after (post-AFP, post-DCP) the start of sorafenib. We calculated the AFP (DCP) ratio using the equation AFP (DCP) ratio = post-AFP (DCP)/pre-AFP (DCP). The threshold for the AFP- and DCP ratio was defined as 1.0 and 3.0, respectively [9]. These threshold values were used for categorization of patients.

2.4. Hepatic perfusion CT

2.4.1. CT studies

All examinations were performed on a 320-detector row CT scanner (Aquilion ONE; Toshiba Medical Systems, Ohtawara, Japan). The settings were 0.5-mm thickness, 320 slices, 512 × 512 matrices, scanning field of view (FOV) 32.0–42.8 cm, craniocaudal coverage 16 cm, 80 kV, automatic tube current modulation (auto-mA), 0.5 s/rotation. Slices for hepatic CT perfusion were selected from pre-contrast abdominal helical scans and included as much as possible of the liver. Iohexol (Daiichi-Sankyo Seiyaku, Tokyo, Japan) or Iomeprol (Eizai, Tokyo, Japan) with an iodine concentration of 300 mgI/mL, or Iopamidol (Bayer Yakuhin, Osaka, Japan, iodine concentration 370 mgI/mL) was administered using a power injector (Dual Shot, Nemoto Kyorindo, Tokyo, Japan) and a 20-gauge catheter inserted into an antecubital vein. The contrast material dose for all patients was 200 mgI/kg body weight. The injection duration was 8 s in all patients, and the delivery of contrast material was followed by flushing with 30 mL of physiologic saline administered at the same injection rate. We acquired 25 dynamic scans after contrast material injection. The patients were instructed to breathe quietly during scanning. A bath towel was wrapped tightly around the subcostal abdominal wall to minimize respiratory liver motion. The timing of the first dynamic scan was determined by test injection of contrast material diluted with physiologic saline (contrast medium concentration 30%); the total volume was equal to the volume delivered for real dynamic scanning. Monitoring was at the L1 vertebral body level; an ROI cursor was placed in the abdominal aorta. Real-time low-dose (80 kV, 30 mA) serial monitoring studies began 8 s after the start of contrast injection. The aortic peak time was defined as the time to peak abdominal aortic enhancement from the start of contrast material injection; the timing for the first dynamic scan was set at aortic peak time minus 4 s. The first 10 scans were performed every 2 s; they were followed by 6 scans every 3 s, and 4 scans every 4 s.

To assess radiation exposure, the computed tomographic dose index ($CTDI_{vol}$) and the dose-length product (DLP) displayed on the scanner console were recorded for each patient. The size-specific dose estimate (SSDE), an index in which the CTDI is corrected by the body habitus, was also calculated by using the CTDI [18,19]. Size-dependent conversion factors were obtained from AAPM Report 204 [20]; they were based on the sum of the antero-posterior and lateral dimensions at the mid-liver level of each patient.

2.4.2. Image analysis

The CT images were reconstructed on the scanner console by applying the adaptive iterative dose reduction three-dimensional (AIDR3D; Toshiba Medical Systems, Ohtawara, Japan), a hybrid-type iterative image reconstruction method. The reconstructed CT images were transferred to a workstation; a software program (Body Perfusion; Toshiba Medical Systems, Ohtawara, Japan) was used for analysis. This software program automatically corrects the spatially non-consistent position of each organ among the 25 dynamic images with non-rigid