European Journal of Radiology 82 (2013) 327–334

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Quantitative therapy response assessment by volumetric iodine-uptake measurement: Initial experience in patients with advanced hepatocellular carcinoma treated with sorafenib

Xu Dai[a,b], Heinz-Peter Schlemmer[b], Bernhard Schmidt[c], Karolin Höh[d], Ke Xu[a], Tom M. Ganten[d], Maria-Katharina Ganten[b,*]

[a] Department of Radiology, The First Affiliated Hospital of China Medical University, 155 Nanjingbei Street, Shenyang, 110001, China
[b] Department of Radiology, Deutsches Krebsforschungszentrum, Im Neuenheimer, Feld 280, 69120 Heidelberg, Germany
[c] Siemens AG, Healthcare Sector, Siemensstr. 1, 91301 Forchheim, Germany
[d] Department of Gastroenterology, Internal Medicine IV, University of Heidelberg, Im, Neuenheimer Feld 410, 69120 Heidelberg, Germany

ARTICLE INFO

Article history:
Received 15 May 2012
Received in revised form 21 October 2012
Accepted 7 November 2012

Keywords:
CT density
DECT
Hepatocellular carcinoma
Response evaluation
Sorafenib
Volumetric iodine-uptake

ABSTRACT

To investigate the volumetric iodine-uptake (VIU) changes by dual-energy CT (DECT) in assessing the response to sorafenib treated hepatocellular carcinoma (HCC) patients, compared with AASLD (American Association for the Study of Liver Diseases) and Choi criteria.

Materials and methods: Fifteen patients with HCC receiving sorafenib, monitored with contrast-enhanced DECT scans at baseline and a minimum of one follow-up (8–12 weeks) were retrospectively evaluated. 30 target lesions in total were analyzed for tumor response according to VIU and adapted Choi criteria and compared with the standard AASLD.

Results: According to AASLD criteria, 67% target lesions showed disease control: partial response (PR) in 3% and stable disease (SD) in 63%. 33% lesions progressed (PD). Disease control rate presented by VIU (60%) was similar to AASLD (67%) and Choi (63%) ($P > 0.05$). For disease control group, change in mean VIU was from 149.5 ± 338.3 mg to 108.5 ± 284.1 mg (decreased $19.1 \pm 42.9\%$); and for progressive disease group, change in mean VIU was from 163.7 ± 346.7 mg to 263.9 ± 537.2 mg (increased $230.5 \pm 253.1\%$). Compared to AASLD (PR, 3%), VIU and Choi presented more PR (33% and 30%, respectively) in disease control group ($P < 0.05$). VIU has moderate consistency with both AASLD (kappa = 0.714; $P < 0.005$) and Choi (kappa = 0.648; $P < 0.005$), while VIU showed a better consistency and correlation with AASLD (kappa = 0.714; $P < 0.005$; $r = 0.666$, $P < 0.005$) than Choi with AASLD (kappa = 0.634, $P < 0.005$; $r = 0.102$, $P = 0.296$).

Conclusion: VIU measurements by DECT can evaluate the disease control consistent with the current standard AASLD. Measurements are semi-automatic and therefore easy and robust to apply. As VIU reflects vital tumor burden in HCC, it is likely to be an optimal tumor response biomarker in HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the third common cause of cancer related death worldwide, and at the time of diagnosis, most patients are in advanced stages [1]. Therapeutic modalities for patients with advanced stage HCC have been limited until the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial was reported [2] in 2008.

Sorafenib is a multikinase inhibitor that simultaneously inhibits certain targeted tyrosine kinases, thereby inhibiting tumor proliferation and abrogates neoangiogenesis. It is expected to mainly control and stabilize tumor growth, rather than to shrink lesions [3]. Some recent studies describe early necrosis in hepatic tumors treated with sorafenib [4]. However, since the therapeutic mechanism of sorafenib is different from the conventional chemotherapy, the anatomic response assessment criteria currently in use might be inadequate. In the SHARP study for example, the sorafenib treatment prolonged the clinical progression time apparently compared with the placebo group, while the response rate (CR and PR) was

* Corresponding author at: Department of Radiology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany. Tel.: +49 6221 422493; fax: +49 6221 422462.
E-mail addresses: daixudex@vip.sina.com (X. Dai), h.schlemmer@dkfz-heidelberg.de (H.-P. Schlemmer), bernhard.schmidt@siemens.com (B. Schmidt), Karolin.hoeh@med.uni-heidelberg.de (K. Höh), kexu@vip.sina.com (K. Xu), tom.ganten@med.uni-heidelberg.de (T.M. Ganten), m.ganten@dkfz-heidelberg.de (M.-K. Ganten).

0720-048X/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejrad.2012.11.013

as disappointing as 2% by the assessment criteria of Response Evaluation Criteria in Solid Tumor (RECIST) which are based on size measurement [2].

RECIST relies on the sum of the greatest diameters of target lesions [5]. It is an anatomic size measurement, which is easy to apply in a clinical setting, and is more appropriate to measure cytotoxic effects of chemotherapy. However RECIST fails to show therapy-induced intratumoral changes in response to sorafenib [2,6]. HCC is a heterogeneous and often multifocal tumor, whose growth rates may vary among lesions. And even within the same tumor nodule, there are varying degrees of differentiation, which makes macroscopic growth patterns hard to interpret, underlining the importance of function-based evaluation methods [1,7].

Therefore, both the European Association for the Study of the Liver (EASL) [8] and the American Association for the Study of Liver diseases (AASLD) [9,10] recommended that the assessment of tumor response should incorporate the reduction in viable tumor burden, defined by the area (EASL) or diameter (AASLD) measurement of contrast enhancing tumor on arterial phase imaging to assess the tumor response. Until now, AASLD diameter measurement of viable tumor is widely used in clinic and considered as the standard assessment of treatment efficiency in patients receiving antiangiogenic therapy [11], however it has some limitations as measurement in one single transversal selected slice which may be easily affected by the artificially selected variations, therefore reproducible measurements are very observer dependent [12].

Recently, Choi et al. have proposed the measurement of CT density as a potential indicator of gastrointestinal stromal tumor (GIST) response in patients undergoing targeted therapy [13]. This method had also been applied to other tumor entities, such as the targeted therapy response assessment of HCC [14]. Conversely, a substantial change in tumor density at CT often occurs during targeted therapy. In antiangiogenesis targeted therapy, decreased tumor density of responding area on CT pathologically correlates with the development of tumor necrosis on histopathology, which is derived from the disruption of neoangiogenesis. Tumor necrosis often occurs later than the neovessel disruption and the following blood perfusion reduction. Therefore, decreased CT density changes may not be detected sensitively in the early stage of response. In rare cases, however, HCC response may result in increased density because of the intratumoral hemorrhage, which is a rare effect observed during sorafenib therapy [15], thus result mislead tumor density measurements and failed Choi response assessement. Therefore, ideally, new parameter directly related with neovascularisation should be acquired to assess the density differences related to contrast medium accumulation, or, those related to vital and vascularized tumor tissue.

Dynamic contrast-enhanced CT perfusion has been explored as potential new method for assessing response of tumor vascularization to antiangiogenic therapy [6,14]. However in clinic practice the promotion of CT perfusion is prohibited regarding the limitations (e.g. limited coverage of all tumor sites, unstandardized postprocessing, radiation dose) [16].

Dual-energy CT (DECT) is a promising technique used to obtain material specific images. It allows selective quantification and visualization of iodine-related density differences [16,17] and improves the ability to detect contrast agent and to distinguish high-density substances created by iodine from those created by hemorrhage. The iodine map generated by DECT encodes the iodine distribution in each individual CT voxel and subsequently is used to subtract the iodine from the image, which permits selective quantification of iodine-related attenuation (IRA, measured in Hounsfield unit, HU) and volumetric iodine-uptake (VIU, measured in mg) in specified sample tissue based on this material-specific feature [16,17]. Furthermore, as the amount of iodinated contrast medium in tissue depends on its degree of vascularization, the amount of VIU by DECT may be considered as representative of blood perfusion and vascularization in the tumor.

One preliminary study [16] had shown that IRA in DECT might be a more robust response parameter than CT density of Choi for it is not influenced by intratumoral hemorrhage. IRA in DECT measured by HU reflects the mean iodine density of the whole volume, it neglects the impact of volume on tumor response assessment. However, the VIU reflects the total amount of iodine in the whole tumor, which is the product of iodine density and tumor volume. We assumed the VIU may reflect the blood perfusion changes in the vital tumor burden more directly and sensitively. First of all proof of principle studies are requested as to demonstrate the feasibility of VIU measurements in solid tumors.

Therefore, the purpose of this pilot study was to investigate the VIU changes by DECT in assessing the therapy response in advanced HCC patients treated with sorafenib, compared to the other two vital tumor burden measurements criteria, the current standard AASLD, and Choi.

2. Materials and methods

2.1. Patients demographics

We retrospectively analyzed data from all advanced HCC patients who received sorafenib treatment and monitoring by DECT in our institution between September 2010 and January 2012. Baseline contrast enhanced DECT scan was obtained up to one month before sorafenib treatment and at least one follow-up scan in 8–12 weeks under sorafenib treatment. Informed consent was obtained from all patients; the study was approved by our institutional review board.

The inclusion and exclusion criterias of patient's selection were as following:

- histologically proven or clinically diagnosed [10] inoperable (due to size, localization etc.) HCC;
- hepatic function Child–Pugh Class A or B;
- presence of a measurable target lesion showing intratumoral arterial enhancement in contrast enhanced DECT [9]. The measurable diameter should be at least 1 cm and the lesion should be suitable for repeated measurements;
- exclusion:prior systemic treatment; possible prior transarterial chemoembolizatoion (TACE), or radiofrequence abladation (RFA) had to be stopped more than 3 months before the initiation of sorafenib therapy; prior treatment with TACE was only permitted if patients had new lesions or apparent recurrence out of the embolized area;

In total, 41 HCC patients were examed in our institution with DECT at least one time in this period, including 24 patients treated with sorafinib. At last 15 patients (13 men and 2 women) with 30 measurable target lesions (median 2 lesions/patient, range 1–5) were included in this study, the excluded 9 patients without following up DECT exams. The patients characteristics are displayed in Table 1.

2.2. Sorafenib treatment

Patients self-administered sorafenib (Bayer Healthcare, Leverkusen, Germany) orally at a starting dose of 400 mg twice daily and treatment was adapted according to the standard recommendations.