European Journal of Radiology 106 (2018) 62–68

Contents lists available at ScienceDirect

European Journal of Radiology

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

Research article

Dynamic contrast enhanced perfusion CT imaging: A diagnostic biomarker tool for survival prediction of tumour response to antiangiogenetic treatment in patients with advanced HCC lesions

Davide Ippolito[a,b,*], Giulia Querques[a,b], Stefano Okolicsanyi[a,d], Cammillo Talei Franzesi[a,b], Anna Pecorelli[a,c], Sophie Lombardi[a,b], Eleonora Orsini[a,b], Mario Strazzabosco[a,d,e], Sandro Sironi[a,c]

[a] School of Medicine, University of Milano-Bicocca, Milan, Italy
[b] Department of Diagnostic Radiology, H. S. Gerardo, Monza MB, Italy
[c] Department of Diagnostic Radiology, H. Papa Giovanni XXIII, Piazza OMS 1, 24127, Bergamo BG, Italy
[d] Department of Surgery and Interdisciplinary Medicine, University of Milano-Bicocca, Milan, Italy
[e] Liver Center Section of Digestive Diseases, Yale University, New Haven, CT, USA

ARTICLE INFO

Keywords:
Computed Tomography
Perfusion imaging
Hepatocellular carcinoma
Survival rate
Antiangiogenic treatment

ABSTRACT

Purpose: To investigate whether perfusion-CT (p-CT) imaging could depict the inhibition of tumor neoangiogenesis induced by Sorafenib in advanced hepatocellular carcinoma (HCC), and whether it could be useful in predicting survival during treatment.

Materials and methods: Ninety-eight p-CT examinations were performed among 29 cirrhotic patients, with advanced HCC, before and every 2 months after Sorafenib administration, on a 256-slice MDCT scanner. Perfusion parameters were considered and statistically compared, at baseline and follow-up, between non-progressor (complete response, stable disease or partial response) and progressor (progressive disease) group. Kaplan-Meier analyses estimated the time-to-survival in overall population, after stratifying patients according to mRECIST.

Results: The group that responded to Sorafenib showed a significant reduction of values in HCC target lesions after anti-angiogenic therapy ($p < 0.01$), in comparison with progressor group that demonstrated an increase or no significant variation. When patients were stratified into mRECIST, higher survival rate was observed in the non-progressor group compared to the progressor (48.6% vs 28.6%), and statistically significant correlation ($p = 0.01$) was found between percentage variation of perfusion parameters, from baseline to follow-up, and overall survival rate.

Conclusion: Quantitative analysis of perfusion parameters, represents prognostic indicators useful in assessment of response to anti-angiogenic therapy, allowing for optimization of individualized treatment.

1. Introduction

Hepatocellular carcinoma (HCC) is a highly vascularized tumor, whose spread depends on its ability to recruit blood vessels by forming new vessels [1] and non-surgical locoregional treatment are increasingly used as alternative options to surgery, especially in patients with unresectable disease. In the past few years, with advances in knowledge of molecular regulatory mechanisms of cancer progression, targeted anti-neoplastic drugs have been rapidly developed. Sorafenib, an oral inhibitor of multiple kinases involved in tumor angiogenesis and cell proliferation [2], is the first approved molecular targeted therapy with a demonstrated significant survival benefit in patients with advanced HCC [3]. However some patients show no treatment effects or develop adverse reactions such as the hand foot skin reaction [3,4], that can reduce the quality of life leading to drug interruption or discontinuation [5]. Given the high cost, toxicity as well as choices of treatment options, there has been a growing interest to monitor the response at an early phase of treatment by measuring tumor viability and perfusion, which is an important requirement to any individualized treatment [6]. Traditionally, the European Association for the Study of the Liver (EASL) guidelines recommends that evaluation criteria for tumor progression or remission should incorporate serial tumor measurements of the changes in the maximum diameter of the viable tumor [7]. The modified Response Evaluation Criteria in Solid Tumors (mRECIST) are

* Corresponding author at: University of Milano-Bicocca, Department of Diagnostic Radiology, San Gerardo Hospital, Via Pergolesi 33, 20900, Monza MB, Italy.
E-mail address: davide.atena@tiscalinet.it (D. Ippolito).

https://doi.org/10.1016/j.ejrad.2018.07.012
Received 19 March 2018; Received in revised form 24 May 2018; Accepted 12 July 2018

currently the primary criteria for evaluating therapeutic efficacy in solid tumors [8]. However, use of mRECIST still poses a difficulty in measuring irregularly shaped HCC, since it requires unidirectional measurement of tumor size for overall evaluation of tumor burden. In this clinical setting, it would be beneficial to measure tumor permeability and perfusion, because vascular changes can happen long before there is any evidence of tumor volume variation on conventional imaging, and it could aid in the early selection of the most appropriate treatment. Currently quantitative functional imaging modalities, such as perfusion Computed Tomography (p-CT), have become more prominent in the management of HCC for staging, target definition, and early response detection of treatment efficacy, avoiding unnecessary treatment [9,10]. As a result, many Authors have reported that p-CT is a sensitive imaging biomarker for monitoring early antiangiogenic treatment effects as well as for predicting progression-free survival [11]. The aim of this study was to investigate whether p-CT imaging could depict the inhibition of tumor neoangiogenesis induced by Sorafenib in advanced HCC by quantifying the modifications of perfusion parameters and whether it could offer information related to the survival rate.

2. Materials and methods

2.1. Study population

From March 2012 to October 2016, a total of 43 consecutive patients with liver cirrhosis and intermediate-to-advanced HCC (Barcelona Clinic for Liver Cancer - BCLC - stage B and C) [12], eligible for treatment with Sorafenib and who underwent a standard multiphase CT scan coupled with a p-CT examination, were considered for inclusion in this study. Baseline inclusion criteria consisted of: 1) a diagnosis of HCC made according to the EASL criteria [12]; 2) Child-Pugh class A; 3) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; 4) no previous systemic treatment for HCC; 5) no contraindications to CT imaging. Exclusion criteria were determined by: 1) Child-Pugh class B and C; 2) previous administration of c-met inhibitors; 3) concomitant radiotherapy; 4) a history of/or concomitant other malignancies; 5) esophageal varices bleeding and/or coagulation disorders; 6) glomerular filtration rate be low 30 mL/min. Due to missing data, inacceptable toxicity or clinic decompensation, baseline p-CT study was not performed in 10 patients, and follow-up p-CT study was not performed in 4 patients. This resulted in a final study population of 29 patients, which included 25 men (range: 52–83 years) and 4 women (range: 72–83 years). Etiology of cirrhosis was of HCV infection in 12 cases, alcohol in 6 cases, combined HCV and alcohol in 4 cases, HBV infection in 4 cases, non-alcoholic steatohepatitis in 2 cases and cryptogenic in 1 case. Before Sorafenib administration, 17 patients were treated with transarterial chemoembolization (TACE) (13), hepatic resection (6), radiofrequency ablation (RFA) (4) and radioembolization (1). Institutional Review Board approved the study design and all patients provided written informed consent before being enrolled according to institutional guidelines.

2.2. Treatment protocol

According to current clinical guidelines, Sorafenib (Nexavar, Bayer Healthcare, Germany) was orally self-administered at the dose of 400 mg twice daily. Treatment continued until disease progression and/or clinic decompensation or unacceptable drug toxicity.

2.3. MDCT technique

In order to assess the effectiveness of systemic treatment and to evaluate the progression of the disease, according to international guidelines [12], all patients underwent an abdominal multiphasic MDCT examination and a p-CT study in the same setting, both at baseline and during follow-up with an interval time of 2 months for each examination, until patient's expiration. CT study was performed on a multi-detector 256-slice CT scanner (Brilliance, iCT, Philips Medical Systems, Eindhoven, The Netherlands). CT data were acquired before and after intravenous bolus injection of non-ionic iodinated contrast material (Xenetix 350; Guerbet, Aulnay, France); dose according to patient's weight, at a rate of 4.5 mL/s, using a 18-gauge catheter positioned into an antecubital vein. CT images were obtained in a cranio-caudal direction with a 2-mm collimation (pitch of 0.83) on the upper abdomen in the arterial and equilibrium phase, and from the hepatic dome to the pelvis in the portal venous phase. Bolus tracking technique was used to set individual acquisition times for the dynamic phases (i.e arterial, portal venous and delayed phase).

2.4. Perfusion-CT technique

To avoid influence of previously administered contrast medium, the p-CT study was performed about 45 min after the standard dynamic MDCT study [13,14]. After selecting the appropriate transverse level, single location cine CT (40 CT acquisitions; 16 slices/8 cm width) was performed during the intravenous bolus injection of additional 50 mL of non-ionic iodinated contrast agent (Xenetix 350; Guerbet, Aulnay, France) at a rate of 5 mL/s and 50 ml of saline with the following parameters: 100 kV, 100 mAs, 512 × 512 matrix, 5-mm slice thickness, 1.4-s acquisition time. CT data acquisition began after a 5 s delay from intravenous bolus injection. The length of standard multiphase CT acquisition protocol was about 5 min and the duration of pCT study was of about 1 min (considering both the 5 s delay and 56 s of acquisition in axial dynamic mode), for an overall acquisition time of 51 min for each patient, including the 45 min of suspension. To avoid motion artifacts a strap compressing the abdomen and limiting respiratory excursions was used.

2.5. Image analysis and quantification of perfusion parameters

Image analysis was performed by one experienced radiologist. Dynamic raw CT images were transferred to a workstation and a dedicated perfusion software (Functional Liver perfusion, Philips Intellispace Portal, Best, The Netherlands) automatically generated a quantitative map of liver perfusion displayed on a monitor by means of a color scale. The parametric map images were created by using the highest spatial resolution pixel-by-pixel calculation technique, and perfusion was assessed by a dedicated CT software based on maximum slope model [15]. The following perfusion parameters were obtained: hepatic perfusion (HP in mL/s per 100 g), which expresses the flow rate in the tissue region; time to peak (TTP, s), which is the time to reach the maximum value of contrast material concentration; arterial perfusion (AP, mL/s), which is the arterial fractional blood flow; hepatic perfusion index (HPI, %), which represents the percentage of total liver blood flow from arterial origin [AP/ (AP + Portal Perfusion]. The target lesion was represented by the one with the highest diameter (more than 10 mm), according to mRECIST [16]. For each study, a rounded, as large as possible, single ROI was placed in the target HCC lesion, on the color map, thus avoiding partial volume effects. For follow-up scans, we used references images from the baseline scan to identify the same location for p-CT acquisition and analysis. In patients with complete/partial response in whom the target lesion was not clearly recognized at MDCT study, ROIs were positioned in the area corresponding to the previously analyzed lesion.

2.6. Response evaluation criteria (mRECIST)

Patients were divided in two groups (non-progressors and progressors after two months of treatment) according to mRECIST [16]. Patients with stable disease (SD - any cases that do not qualify for either partial response or progressive disease), partial response (PR - at least