Contrast-enhanced ultrasonography for evaluating antiangiogenic treatment in hepatocellular carcinoma. A long way from research to clinical practice

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related deaths. At the time of diagnosis, most patients have advanced stage disease AND co-existent chronic liver disease [1,2].

Therapeutic modalities for patients with advanced stage HCC were very limited until results from the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial were published. In this trial sorafenib demonstrated a significant improvement in overall survival (OS) (median OS increased from 7.9 months to 10.7 months) and in median time to radiologic progression (from 2.8 months to 5.5 months) despite a disappointing 2% response rate (RR) as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) which use the change in tumor size as response parameter [2]. In clinical practice, the absence of any clear sign of therapeutic efficacy can be a problem, especially in patients who develop toxic adverse effects.

These discrepancies and other difficulties in assessing response to loco regional treatments for HCC (percutaneous tumor ablation or transarterial chemoembolization) have determined experts to reconsider the evaluation criteria. In 2000 a panel of experts from the European Association for Study of the Liver (EASL) suggested that the estimation of the reduction in viable tumor area using contrast-enhanced imaging should be the optimal method to assess treatment response [3]. Based on these recommendation in 2010 an adaptation of RECIST, termed modified RECIST (mRECIST), was designed specifically for HCC [3].

According to mRECIST the target lesion is no longer the whole lesion but only the contrast-enhanced portion of the hepatic lesion at the arterial phase of a dynamic imaging technique computed tomography (CT) scan or magnetic resonance image.

Contrast-enhanced ultrasound using second generation contrast agents (CEUS) is used nowadays to accurately measure not only the tumor size but also the contrast agent uptake, giving information on tumor vascularity [4]. It is now possible to quantitatively assess tumor perfusion by analyzing the linear raw data received by the US scanner or to analyze the quasi-logarithmic compressed data displayed on the video screen [4,5].

Using the first approach specific perfusion parameters may be calculated (peak intensity, latency time, time to peak intensity, maximal intensity value a.o). The utility of these technique for determining early responses (as early as 3 days after treatment start) to targeted agents in various solid tumors has recently been demonstrated [4,5]. However, parametric CEUS requires optimal, standardized and fully reproducible imaging conditions using the same scanning plan. This technique has been used extensively for research purposes in the last 10-15 years but seems to be less suitable for every day clinical practice.

Using CEUS and mRECIST criteria it is possible to assess the extent of necrosis induced by sorafenib in HCC and to calculate the response type. In one recently published paper using contrast-enhanced CT as imaging method it was demonstrated that mRECIST criteria are more reliable than RECIST in establishing the correct response type after treatment. Patients who achieved a response (complete and partial) according to mRECIST had a longer overall survival (OS) than nonresponding
patients with stable disease (SD) or progressive disease (PD) (median OS, 18 months and 8 months, respectively; p= 0.013) [2].

In this issue of Medical Ultrasonography Moschouris et al [6] present an interesting paper on the use of US, CEUS and mRECIST criteria to assess the efficacy of sorafenib in intermediate and advanced hepatocellular carcinoma. This is the first published experience using CEUS and mRECIST in the evaluation of treatment response in patients with HCC after sorafenib.

The authors also describe for the first time the cystic changes of HCC nodules in US, changes that were mostly found in tumors with extensive necrosis after sorafenib. As in the work of Edeline et al using CT, the authors demonstrate the superiority of mRECIST criteria in evaluating the response after sorafenib in intermediate and advanced HCC. The responders (those with complete and partial response) according to mRECIST had significantly longer mean OS compared to the non-responders (21.5 vs. 12.2 months, p=0.018). Due to the relatively small number of patients the statistical significance was reduced (p=0.065) after adjustment for BCLC staging system (Barcelona Clinic Liver Cancer) and Child’s class.

These findings strongly support the use of CEUS and mRECIST in evaluating the treatment with sorafenib in patients with HCC in clinical practice.

The CEUS mRECIST evaluation of viable tissue changes after sorafenib (or other antiangiogenic drugs) although simple and practical has some limitations. The assessment of the extent of enhanced areas (which represent the still viable tissue) should be performed in the same plane before and after the treatment which is not so easy in everyday clinical practice. A second limitation refers to cases where the enhancement (before and/or after treatment) is discontinuous or multinodular. In those particular situations a simple 2D measurement of the enhancing areas may misinterpret the volumetric extent of remained enhanced areas. The use of three-dimensional CEUS, which is now available on some systems, may overcome the above mentioned limitations, thus offering a global and almost exact assessment of changes after antiangiogenic treatments [7].

In the near future it seems possible to assess the efficacy of various antiangiogenic treatments both in early phases using parametric, quantitative CEUS and in time using 3D CEUS.

Reference