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Towards new tools for refined management of patients with advanced hepatocellular carcinoma under systemic therapy: Some enthusiasm with a word of caution

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In the present issue of the *Journal of Hepatology*, Dr. Zocco and coworkers from Rome, Italy, showed original data on a much debated and burning issue: is it possible to early predict response to antiangiogenic treatment in hepatocellular carcinoma (HCC) prior to the first standard assessment at approximately two months [1]?

Clearly this issue is important for any tumor. Indeed a molecular characterization prior to therapy commencement has already become part of clinical practice for some tumors, in order to tailor the pharmacological therapy to the aim of limiting the occurrence of non or poor responders. This is not yet in place for HCC, where the single standard agent for advanced cases or cases unsuitable for locoregional treatments is the antiangiogenic drug sorafenib.

Nonetheless, even having one single agent, the question of whether it is possible to predict the response to sorafenib before its start is important. Unfortunately, this question has received a negative answer so far, since no marker has been identified yet [2] and no patient is selected for treatment based on the expectations of response. The next question is, therefore, whether it would be at least possible to have an early on-treatment information about the outcome and most importantly about which patient is going to rapidly progress notwithstanding sorafenib. In fact, whoever will achieve stable disease or response will continue the systemic therapy, hence even an earlier information about a later beneficial outcome will not change the strategy, but may only add costs. Conversely, the possibility to identify at an early time point (within the first 15 days after treatment start) those patients who will subsequently show tumor progression already at the first imaging assessment (usually at 6–10 weeks after treatment start, corresponding to no benefit from systemic therapy) would be of crucial importance. Such information could theoretically anticipate the stop of treatment and accordingly could enable the enrolment in second line treatment trials, before the patient's general conditions or liver dysfunctions have deteriorated to a level no more matching the enrolment criteria. An early stop of ineffective treatment would also contribute to save money and avoid the persistence of possible side effects.

Clearly any such decision, to anticipatedly stop treatment, is an important issue. Thus the tool for the decision should be specific enough to avoid false positive cases of inefficacy.

The article by Zocco *et al.* [1] proposes the use of dynamic contrast enhanced ultrasound (CEUS) of tumor perfusion at two weeks after sorafenib start as a tool to identify those patients who will be categorized as progressors already at two months when assessed by the mRECIST criteria, as currently recommended [3,4]. The use of CEUS to this aim is not new, as it has been studied in other tumors, and particularly in gastrointestinal stromal tumors (GIST), treated with antiangiogenics. In this setting, the use of CEUS to monitor treatment response to GIST has been already endorsed by the European Society of Medical Oncology [5] and was shown to provide useful information in other tumors treated with antiangiogenics, such as renal cell carcinoma [6]. Some preliminary data were also reported for HCC, but either not under the standard of treatment [7] or with very limited number of patients [8] or using different contrast parameters and assessment timing [9].

CEUS is advantageous in this setting, thanks to its low cost and easy repeatability and is very well accepted by patients.

The study by Zocco *et al.* [1] has some strong points. Patients were enrolled according to the usual clinical indications to start sorafenib, with not excessively restrictive criteria, even though the number of patients with no extravascular spread nor macrovascular invasion, but only with symptomatic tumor was relatively high, thus it will reflect the clinical practice. Only three patients (7%) could not be included due to unsuitable ultrasound target, thus there was not an additional reason for superselection.

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Abbreviations: HCC, hepatocellular carcinoma; CEUS, Contrast Enhanced Ultrasound; GIST, gastrointestinal stromal tumor.

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The timing at two weeks for reassessment is reasonable. Later time points, such as at one month, would not provide a significant advantage over standard reassessment, despite they were used by two preliminary studies [8,9]. Conversely, earlier time points, not investigated herein, up to a few days after treatment start, could be of interest and deserve specific investigations. The authors correctly separated progressors (who are the target of the study) from non-progressors at the standard time of two months.

Very interestingly, the CEUS parameters showing most reliable predictive value are two variables related to the blood volume in the investigated area [10,11]. At variance, time-to-peak which is related to blood flow [10,11] was not significantly associated with progression, as well as mean transit time. Such data tend to suggest that indeed CEUS is able to identify a decrease in tumor blood volume. The fact that the former two parameters appear to be reliable to the aim of predicting response is based on the finding that responders showed negative values up to the threshold of third interquartile (decrease in enhancement level) whereas progressors had positive values. According to the results of the study, however, progressors were considered those subjects showing an increase of such values by >10% at two weeks of treatment in comparison to baseline. Selecting higher threshold would theoretically make the identification of progressors more specific, but would decrease the overall accuracy, as reported by the authors, since some progressors would be considered as responders. However, in order to avoid stopping therapy in dubious responders, a suggestion could be to initially adopt a more conservative approach, selecting a higher threshold than the most accurate (change >10%).

The fact that progressors were separated from non-progressor by such a narrow range (change >10%, corresponding to slightly more than the mean coefficients of variations) justifies the need for automated and computerized calculations of signal intensity [11], preventing the possibility to adopt a strategy only based on visual impression. The limited coefficient of variations of CEUS quantification and the reliability of the results may have derived from the use of a methodology based on quantification of pre-compressed, raw signal data and not linearized video data [12]. This is only speculative, but just mentioning that there are different methodologies for contrast quantification, based on different proprietaries softwares implies a word of caution in using the results directly in the clinical practice, especially when the technology is not identical to the one used in this article [1]. Another study on a more limited patient population, using a different equipment and quantification software, consistently showed the Area Under the Curve of enhancement to be the most useful parameter, which is reassuring, but the best cut-off was quite different [8]. Very importantly, the operators need to be adequately trained in CEUS quantification (which involves a specific and reliable choice of the scanning plane and acquisition settings and contrast injection modality, so that subsequent scans over time could be reproduced) and the equipments or softwares should be preliminary tested and validated.

Conflict of interest

Fabio Piscaglia has received fees from Bayer, Bracco, Esaote, GE, Siemens; Christoph F. Dietrich has received fees from Abbott (Abvie), Bracco, Essex, Falk, GE, Hitachi, Merck, Novartis, Sanofi-Aventis, Pentax, Roche, Shire, Siemens, Toshiba. The other authors have nothing to disclose.

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