Quantification of dynamic contrast-enhanced ultrasound in HCC: prediction of response to a new combination therapy of sorafenib and panobinostat in advanced hepatocellular carcinoma

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SUMMARY

Here, we report the case of a patient, who showed an antitumour response to a new combination therapy of sorafenib and the histone deacetylase inhibitor panobinostat (LBH-589). D-CEUS (Dynamic contrast-enhanced ultrasonography) was able to predict response to the new therapy regime and may be an interesting tool in the early evaluation of response to therapy. It might be especially useful to differentiate between responders and non-responders of new-targeted pharmaceuticals like multikinase inhibitors in hepatocellular carcinomas.

BACKGROUND

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide with an incidence of 2–8% per year in patients with chronic hepatitis B/C and established cirrhosis. Therapeutic strategies for advanced HCC have been enhanced through the introduction of multikinase inhibitors targeting angiogenesis of the tumour. Until now, strategies and imaging modalities for the differentiation of good response or poor response have not been well established.

CASE PRESENTATION

In this case, as described in detail previously,¹ a patient was first histologically diagnosed with moderately differentiated (G2) multilocal hepatocellular carcinoma, in September 2009, with metastasis in vertebral body, back muscles and the thyroid gland. The patient presented with liver cirrhosis (Child-Pugh A). Stage C—advanced stage—was considered according to the Barcelona Clinic Liver Cancer staging system.²

INVESTIGATIONS

MR whole body imaging was performed at the start of therapy. MRI of liver and abdomen was also performed after 1 month. Imaging studies were completed after 5 and 7 months for interpretation of response to therapy. D-CEUS (Dynamic contrast-enhanced ultrasonography) investigations were timed prior to the start of sorafenib (day 3) and after 3 months (78 days) and 5 months (138 days) of therapy. To complete D-CEUS investigations, a secondary video analysis of examinations with Qontrast software (Esaote S. p. A., Italy) was performed. Area of necrosis was calculated with Java-based image-processing program called ImageJ, developed at the National Institutes of

Health, Bethesda, MD, USA (available at <http://rsb.info.nih.gov/ij/>).

Initial MRI imaging showed mixed response to single therapy with sorafenib after 1 month according to pretreatment imaging in September. After 5 months, contrast-enhanced MRI showed increasing necrosis and with liquid transformation of the liver tumours and metastasis in comparison with previous imaging. At this time, results were radiologically interpreted as response to therapy. The greatest lesion in liver parenchyma was 11 cm × 9 cm at the beginning and 9 cm × 7 cm after 5 months (figure 1). For example, a metastasis in the vertebral body was measured from 2.1 cm × 2.4 cm to 2.1 cm × 2.2 cm after 5 months. Necrosis in MRI was calculated to be 14%, 40% and 59% in the greatest diameter of the greatest lesion (figure 2A). Contemporaneously performed D-CEUS and secondary video quantification of time-intensity curves showed increasing necrosis and ascending time to peak (TTP) and mean transit time (MTT). TTP was 8.83 s in September 2009, 12.32 s after 3 months and 15.25 s after 5 months of therapy (figure 2B) (MTT: 11.04 s—17.48 s—26.60 s) (figure 2C). Necrosis in D-CEUS was approximately calculated to be 70% in the greatest diameter. Last MRI (5 months after start of treatment) showed no new upcoming lesions in liver parenchyma, shrinking osseous and autochthonic spine musculature metastasis.

Necrosis of both imaging methods ($r=0.9344$) as well as necrosis of D-CEUS and TTP ($r=0.9478$, data not shown), and necrosis calculated in MRI and TTP ($r=0.9992$, $p=0.0253$, figure 2D) showed good correlation.

TREATMENT

Treatment was started with sorafenib (dose of 200 mg 2–0–2). An additional therapy of histone deacetylase (HDAC) inhibitor LBH-589 (panobinostat) was initiated at the end of the second month. The patient received three cycles of sorafenib/LBH-589 consisting of 2 weeks combination of sorafenib/LBH-589 and 1 week sorafenib alone. Doses were set to 800 mg sorafenib daily (2–0–2) and 20 mg LBH-589 twice a week (day 1 and 4). This trial was approved by the local ethics committee and is registered at clinical trials.gov (NCT00823290); the patient signed informed consent.

OUTCOME AND FOLLOW-UP

After 9 months, the patient stopped therapy because of side effects especially experiencing loss of appetite.

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Figure 1 Imaging studies from baseline (top), 3 months (middle) and 5 months (bottom). Pictures from the left to the right: MRI showing liquid transformation, D-CEUS (dynamic contrast-enhanced ultrasonography) imaging indicating potential areas of necrosis and, quantification of D-CEUS with false-colour rendering of maximum intensity levels and time-intensity curves.

Sorafenib was continued as single treatment regime according to HCC practice guidelines.² The patient died 8 months after initiation of final therapy.

DISCUSSION

HCC is ranked as the sixth most common cancer and the third most common cause of cancer-related death.³ More than

Figure 2 Values of the imaging quantification: (A) necrosis calculated in MRI; (B) time-to-peak intensity analysed with secondary video quantification of CEUS (contrast-enhanced ultrasonography) (in relation to basic value); (C) mean-transit-time analysed with secondary video quantification of CEUS (in relation to basic value); (D) correlation of necrosis in MRI with time-to-peak values.

600 000 people die as a consequence of HCC each year.⁴ Options for late stage treatment are limited because patients often present when symptoms are worsening in case of a progressive disease. This mainly limits their chances of survival, for example, surgical resection, a potentially curative modality, is no longer appropriate.⁵ Therefore, chemotherapeutic strategies have become more important; especially, inhibitors of angiogenesis have shown significant antitumour efficiency in HCC as well as in other cancer entities. Several studies have shown that these therapeutics can help improve patients' progression-free or overall survival.^{6–7} Up to now, current RECIST (Response evaluation criteria in solid tumours) criteria are used to describe the effects, respectively, the response to therapy. They mainly focus on tumour size reduction and implement the use of cross-sectional imaging techniques such as CT and MRI.⁸ Nevertheless, in using these criteria, one major problem might remain: specific therapeutics produce necrotic areas without a significant reduction in tumour size. In this case, RECIST criteria will not provide suitable answers and advice for the physician for further proceedings in therapy. Kudo *et al*⁹ made an approach to specify this question and established RECICL (response evaluation criteria in cancer of the liver) criteria in order to implement evaluation criteria for alternative treatments in HCC to answer the question of response to therapy more accurately. They put an emphasis on necrotic areas, which might describe effects of an inhibition of angiogenesis more precisely than a simple reduction in diameter. Multikinase inhibitors like sorafenib change the vascular profiles of tumour tissues and therefore, lead to necrosis. Jain¹⁰ also described these effects on vasculature and signalling pathways. He established a morphological concept, named 'normalisation' of the tumour vasculature, and proposed different steps of vascular alterations during antiangiogenic treatments.

CEUS has recently been proofed to let us gain access to the interpretation of changes occurring in microvasculature. These findings have been used to answer questions of effectiveness and response to therapy.^{11–12} Therefore, CEUS secondary video quantification has been used to produce time intensity curves, including different interpretable parameters like TTP, MTT or AUC (area under the curve), which have been correlated with clinical parameters.¹³

In our case, D-CEUS and MRI simultaneously showed increasing necrotising areas interpreted as a partial response according to RECICL criteria (necrotising effect between 50% and <100%).⁹ Quantification of D-CEUS video data showed corresponding rises in TTP and MTT, whereas a response in MRI was only definitely evident after 5 months. In contrast, simultaneously increasing TTP values and MTT values indicated a response to therapy already within the first month. Since we performed measurements only in the remaining vital tissue areas, and not in areas of necrosis, the observed effects on TTP and MTT probably are due to early vascular changes during antiangiogenic treatment.

Additional studies confirm these findings and have proven CEUS as a powerful tool to evaluate early response and monitor therapy more precisely and faster than radiological investigation, according to RECIST criteria, could do now. It has also been shown that measurements accurately predict response within the first month.^{11–14} Especially, TTP seems to be a stable, reproducible parameter for secondary video quantification.¹⁵ TTP could easily be used in clinical settings, especially because it includes several advantages including the usability of shorter video sequences in comparison with other parameters like MTT or AUC. This guarantees better feasibility for clinical investigators

and less storage demand for medical data processing and documentation. CEUS secondary video quantification of TTP can therefore be used to produce user-independent results for important clinical questions.

This approach for the measurement of dynamic parameters illustrates the promising power of CEUS monitoring effects of therapy very precisely over time. In fact, D-CEUS is very sensitive to visualisation of microcirculation and changes in tumour microvasculature under new therapeutic concepts. These promising results suggest a reasonable hope that it could help in moving forward the point of time for evaluation of early response to therapy further than the present imaging concepts can do at the moment. Thus, the use of D-CEUS could enable physicians to improve therapeutic options and finally improve the treatment of human disease. Further studies are needed to confirm the possible value of secondary video quantification of D-CEUS in clinical routine.

Learning points

- ▶ New combination of molecular-targeted therapies could have synergistic effects with significant antitumour effect without showing radiological response.
- ▶ Assessing early response and monitoring of therapy is a challenge for future developments.
- ▶ Dynamic contrast-enhanced ultrasonography might be a promising tool used in follow-up of patients treated with antiangiogenic pharmaceuticals.
- ▶ Dynamic assessment might overcome obstacles of common RECIST (Response evaluation criteria in solid tumours). Time-to-peak is a promising marker of early response and follow-up of treatment.
- ▶ Moving forward the point of therapy evaluation would improve patients' chances and options in therapy while saving resources in healthcare systems.

Competing interests None.

Patient consent Obtained.

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