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Review

To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: Pilot study using dynamic contrast-enhanced Doppler ultrasound ☆

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ABSTRACT

Introduction: The objective of this study was to evaluate dynamic contrast-enhanced Doppler ultrasound (DCE-US) with perfusion software (Vascular Recognition Imaging) and contrast agent injection as a predictor of tumour response, progression-free survival (PFS) and overall survival (OS).

Patients and methods: Thirty patients with a metastatic renal cell carcinoma (RCC) already enrolled in a double-blind randomised study were evaluated. Examinations were performed at baseline, and after 3 and 6 weeks on sorafenib or a placebo in patients with tumour targets that were accessible to DCE-US.

Results: A total of 85 examinations were performed, 30 at baseline, 28 at 3 weeks and 27 at 6 weeks. The combination of a decrease in contrast uptake exceeding 10% and stability or a decrease in tumour volume allowed us to discriminate seven good responders and 20 poor responders at 3 weeks. There was a statistically significant difference in PFS ($p = 10^{-4}$) and OS ($p = 10^{-4}$) between good and poor responders.

Conclusion: DCE-US is a new noninvasive imaging technique which might be an effective tool for evaluating antiangiogenic drugs in renal cancer.

1. Introduction

Sorafenib (BAY43-9006) was originally identified through its inhibitory effects on Raf-1 (c-Raf IC 50 = 2 nM.), a serine/threonine kinase and member of the Raf/MEK/ERK signalling pathway.[1] Addition, biochemical and cellular mechanistic assays demonstrated further activity against B-Raf (B-raf wild type IC50 = 25 nM, B-raf mutant = 38 nM) and several receptor

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tyrosine kinases, including VEGFR-2, PDGFR, Fit-3 and c-KIT2.[2] Sorafenib significantly inhibited neovascularisation in breast and colon xenograft models, and showed potent dose-dependent tumour regression in various xenograft models[1] including two human colon cancers, pancreatic and human breast cancer.[2]

Different phase I and II studies have demonstrated the efficacy of this new agent in refractory solid tumours.[3–5] Ahmad and colleagues in a series of 41 patients with renal cell carcinoma (RCC) demonstrated stable disease in 30% and tumour shrinkage of >25% in 40%.[6]

The activity of sorafenib in renal cell carcinoma (RCC) has been demonstrated in a phase II trial with disease control in 70% of 202 patients at 12 weeks.[33] A double-blind randomised phase III study was initiated in November 2003 in RCC comparing sorafenib, 400 mg bid or a matching placebo (orally) in patients who had failed first-line treatment, and 905 patients had been enrolled. Highly significant improvement in PFS has recently been reported.[34]

Solid tumour survival and distant dissemination largely depend on two angiogenic growth factors, bFGF and VEGF, which have been shown to differentially activate Raf. Targeted delivery of a mutant form of Raf-1 to tumour blood vessels inhibited angiogenesis and was also shown to lead to regression of established tumours.[7] Doppler ultrasonography (DCE-US) is the technique usually used at our institute to assess the size and echostructure of abdominal tumours as well as tumour neovascularisation.[35] DCE-US imaging of tumour vascularisation could therefore be an excellent tool for predicting the efficacy of antiangiogenic drugs such as sorafenib in the clinic.

Morphological and functional imaging modalities such as contrast-enhanced magnetic resonance imaging (MRI), computed tomography (CT scan) or positron emission tomography (PET scan) must be used to evaluate tumour response to antiangiogenic treatment. Both morphological and functional data are provided by Doppler ultrasonography (DCE-US) with contrast agent injection.[8] The size of tumours can be accurately measured and the percentage of contrast uptake, a yardstick of tumour vascularity, can be evaluated with this technique.[9]

The objective of this study was to evaluate whether DCE-US using perfusion software (Vascular Recognition Imaging) and contrast agent, could be used to correlate changes in tumour vasculature with tumour response, progression-free survival (PFS) and overall survival (OS).

We thus compared the changes from baseline in patterns of tumour vascularisation detected during treatment, in an attempt to predict clinical outcomes.

2. Materials and methods

2.1. Patients

Thirty patients, 12 women and 18 men (mean age: 56.2 ± 8.7 SD) with ultrasonographically evaluable metastatic RCC were enrolled in this parallel study during the above-mentioned large phase III study. Examinations were performed at baseline, and after 3 and 6 weeks on sorafenib or a placebo in patients with tumour targets that were accessible to DCE-US. Specialised sonographers were blinded to treatment group assignment. Metastatic RCC were in the liver (patients [pts] $n = 8$), homolateral adrenal gland (pts $n = 3$), abdominal lymph nodes [diffuse] (pts $n = 8$), controlateral kidney (pts $n = 2$), pancreas (pts $n = 1$), local relapse (pts $n = 3$), liver and controlateral kidney (patient [pt] $n = 1$), liver and pancreas (pt $n = 1$), abdominal lymph nodes and homolateral adrenal gland (pt $n = 1$), homolateral adrenal gland and pancreas (pt $n = 1$) and finely pancreas and controlateral kidney (pt $n = 1$). The protocol was approved by our local Ethics Committee and our Institutional Review Board.

2.2. Materials

An Aplio sonograph (Toshiba Medical®, Puteaux, France) was used with a 4.4 MHz C37 convex array equipped with Dynamic Flow (DF) perfusion software which, thanks to wide-band Doppler technology, provides imaging of flow with excellent spatial resolution, a rapid imaging rate and suppression of the blooming effect. A new software, VRI (Vascular Recognition Imaging) was used. VRI couples harmonic imaging with pulse subtraction and DF after injection of Sonovue contrast agent (Bracco S.P.A.®, Milano, Italy) which consists of sulphur hexafluoride-filled microbubbles (stable encapsulated gas: perfluorocarbon). This contrast agent diffused strictly in intravascular tissues without diffusion in interstitial tissues. This sonographic method is original because B-mode imaging of tissue and of different coloured microbubbles thanks to 'Advanced Dynamic Flow' (ADF), can be visualised simultaneously but independently.

Two emission processes were used at a low Mechanical Index ($0.05 < MI < 0.2$) to avoid destroying contrast agent microbubbles and combined as follows: (i) emission/reception with a fundamental frequency for imaging tissue in grey scale; (ii) an emission/reception sequence involving the harmonic response of bubbles (ADF) for differentiated detection of moving and static microbubbles. This technique allows: (i) conservation of anatomical marks before and during an examination with contrast agent; (ii) differential analysis of microvessels with information on flow direction (red/blue) and perfusion (green); (iii) individualised or simultaneous imaging depiction of data related to tissue or microbubbles.

2.3. Methods

A total of 85 DCE-US examinations were performed in two steps :

1. The *morphological study* was performed in B mode. The three diameters of each lesion were measured with electronic calipers and the tumour volume was computed as depth × length × width/2 (mm^3).
2. The *dynamic study* was performed after injection of 4.8 ml of Sonovue at a concentration of 8 μl/ml (intravenous bolus injection) according to Bracco's specifications. Signal enhancement of intratumour neovessels was evaluated visually in real time and the dynamic sequence was recorded on a digital tape. We selected one to two lesions per patient (Table 1). The criteria for lesion selection were: minor necrosis and lesions with a good acoustic window. Qualitative and quantitative evaluations were performed:

Table 1 – Description of the location and the number of lesions in the study population (30 pts)

TARGETS	PATIENTS	ONE LESION ANALYSED	TWO LESIONS ANALYSED
Abdominal lymph nodes	8	2	6
Controlateral kidney	2	2	
Homolateral adrenal gland	3	3	
Liver	8	5	3
Local relapse	3	3	
Pancreas	1		1
Controlateral kidney and liver	1		1
Liver and pancreas	1		1
Abdominal lymph nodes and homolateral adrenal gland	1		1
Homolateral adrenal gland and pancreas	1		1
Pancreas and controlateral kidney	1		1
TOTAL	**30**	**15**	**15**

- *Qualitative analysis*: the percentage of contrast uptake throughout the lesion was evaluated by the specialised sonographers conducting the examination and validated by two specialised sonographers.
- *Quantitative analysis*: quantification of mean contrast uptake by digital analysis of images was performed in the following manner: (i) the tumour was outlined using Adobe Photoshop which automatically discriminates colours distinguishing two zones in two different tonalities; (ii) the image was analysed with the Matrox Inspector software, which quantifies image pixels, allowing one to discriminate the tonalities and to evaluate the percentage of perfused tissue.

Morphological and dynamic parameters were combined to define response. A good response was defined as:

1. *a decrease in contrast uptake exceeding 10%*
2. *stability or a decrease in tumour volume*

Results were compared to CT scan studies at 6 weeks for response. PFS and OS were analysed after unblinding. Statistical analyses were performed with NCSS 2005 software (Number Cruncher Statistical Systems, Kaysville, Utah). The level of significance was set at $p < 0.05$ for all tests. Variables were expressed as a mean ± SD or median, and tested with the Wilcoxon Rank-Sun test when suited. Survival curves were calculated with the Klapan-Meier method and compared with the Log-rank test.

3. Results

Thirty patients were enrolled and a total of 85 examinations were performed: 30 at baseline, 28 at 3 weeks (two patients had stopped the treatment before 3 weeks) and 27 at 6 weeks (one patient had stopped the treatment before 6 weeks). Among the 27 patients who were fully assessable, nine were treated with sorafenib and 18 received the placebo. The difference in PFS between these two groups of patients (median: 18 weeks placebo group and 40 sorafenib group) was statistically significant ($p = 0.04$) (Fig. 1).

The volume of all ultrasonographically-measured tumours varied from 1–1146.6 cm^3. A mean decrease of 32% in tumour vascularisation was observed in 10 out of 28 patients at 3 weeks and in 10 out of 28 patients at 6 weeks. Changes in tumour vascularisation observed in patients at 3 weeks were always consistent in the same patient at 6 weeks with a stable decrease at 3 weeks.

The combination of a decrease in contrast uptake exceeding 10% and stability or a decrease in tumour volume allowed us to select seven good responders and 20 poor responders at 3 weeks. Results were not significantly modified between 3 and 6 weeks.

In the group of good responders, mean contrast uptake was 92% before treatment and decreased to 60% at 3 weeks. The mean volume was 115 cm^3 before treatment, 107 cm^3 at 3 weeks and 104 cm^3 at 6 weeks for the good responders (Fig. 2). In the group of poor responders, mean contrast uptake was 77% before treatment and increased to 82% at 3 weeks. In the group of poor responders, the mean volume was 73 cm^3 before treatment, 98 cm^3 at 3 weeks and 134 cm^3 at 6 weeks (Fig. 3).

There was a statistically significant difference in PFS ($p = 10^{-4}$) and in OS ($p = 10^{-4}$) between good and poor responders (Figs. 4 and 5).

We also analysed the different lesion sites and sizes between good and poor responders and no statistical difference was found. In the same patients all the lesions were concordant: i.e. responding and non responding lesions were not found in the same patient.

Among the nine patients who received sorafenib, five were poor responders and four were good responders. The median PFS was 24 weeks for poor responders ($n = 5$) and 57 weeks for good responders ($n = 4$). The median OS was 33 weeks for poor responders and 57 weeks for good responders. DCE-US therefore allowed us to select patients with longer PFS (PFS > 32 weeks) and longer OS (OS > 47 weeks) (Fig. 6).

Among the 18 patients who received the placebo, 15 patients were poor responders and three were good responders. The median PFS was 16 weeks for poor responders ($n = 15$) and 36 weeks for good responders ($n = 3$) ($p = 0.01$). The median OS was 36 weeks for poor responders ($n = 15$) and 51 weeks for good responders ($n = 3$). DCE-US therefore

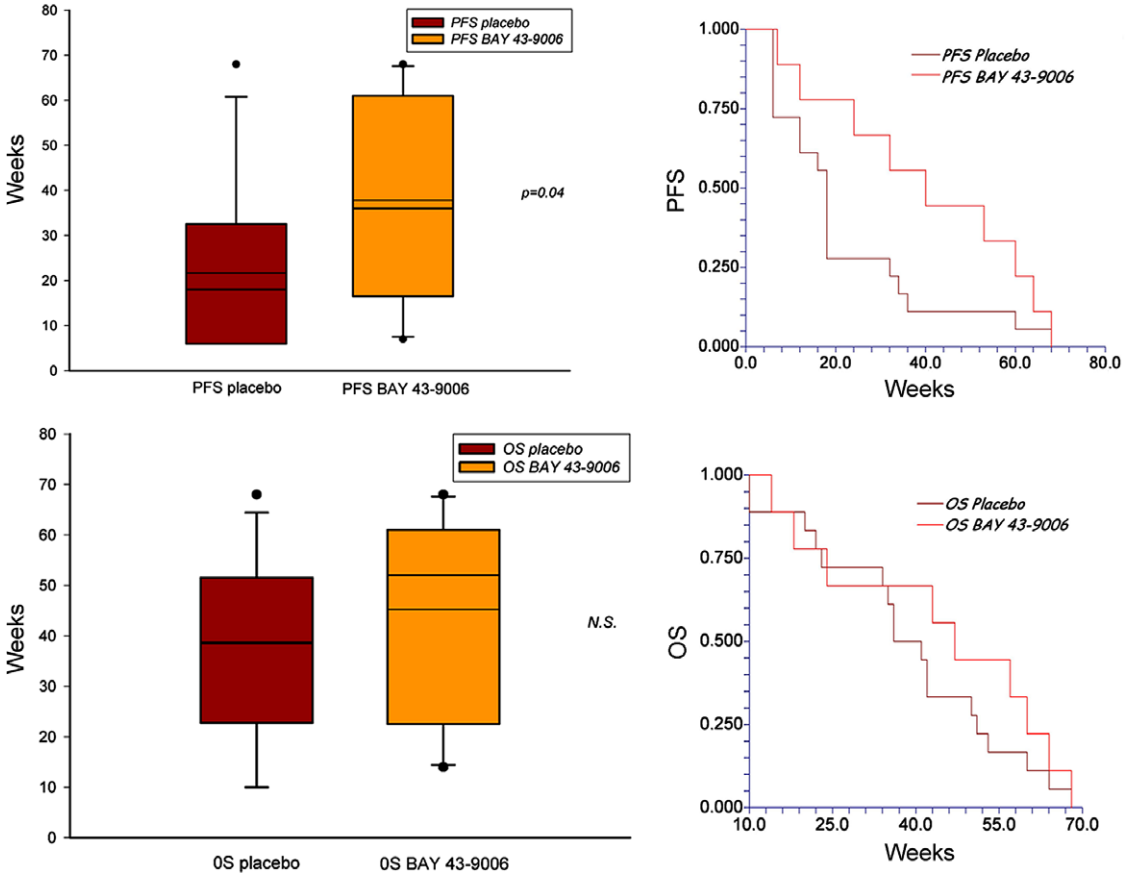

Fig. 1 – Comparison of PFS and OS between the patients receiving sorafenib and the placebo with survival curves.

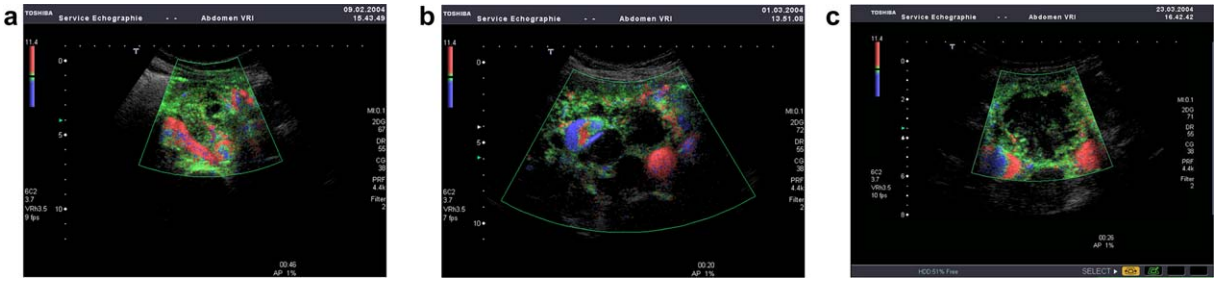

Fig. 2 – Abdominal lymph node from an RCC in a 37 year-old woman (good responder) treated with sorafenib. (a) DCE-US before treatment shows contrast uptake throughout the tumour estimated at 81%; (b) DCE-US after 3 weeks of treatment shows contrast uptake throughout the tumour estimated at 48%; (c) DCE-US after 6 weeks of treatment shows contrast uptake throughout the tumour estimated at 31%.

allowed us to select patients with longer PFS and OS in the placebo group. The three good responders who received the placebo exhibited a decreased contrast uptake, a stable tumour volume with a necrotic centre.

4. Discussion

The results of this study demonstrate the value of evaluating tumour vascularity with DCE-US with perfusion software (VRI) and contrast agent injection.

Since 1999, high-frequency Doppler ultrasonography has been capable of detecting neovascularisation in animal tumour models[10,11] and in human tumours.[12,13] Contrast-enhanced ultrasonography has been used to optimise the detection of angiogenesis.[14] This technique has benefited from major technological improvements such as digitisation and electronically-driven ultrasound signal processing, as well as the multiplication of transducer channels allowing enhanced resolution and greater sensitivity for micro-vessel detection.[15] Imaging of slow flow has also improved as a result of technical innovations.[16] The use of contrast agents in ultrasonography allows vessel signal enhancement and even the detection of neo-vessels as tiny as 40 microns in diameter.[14,15]

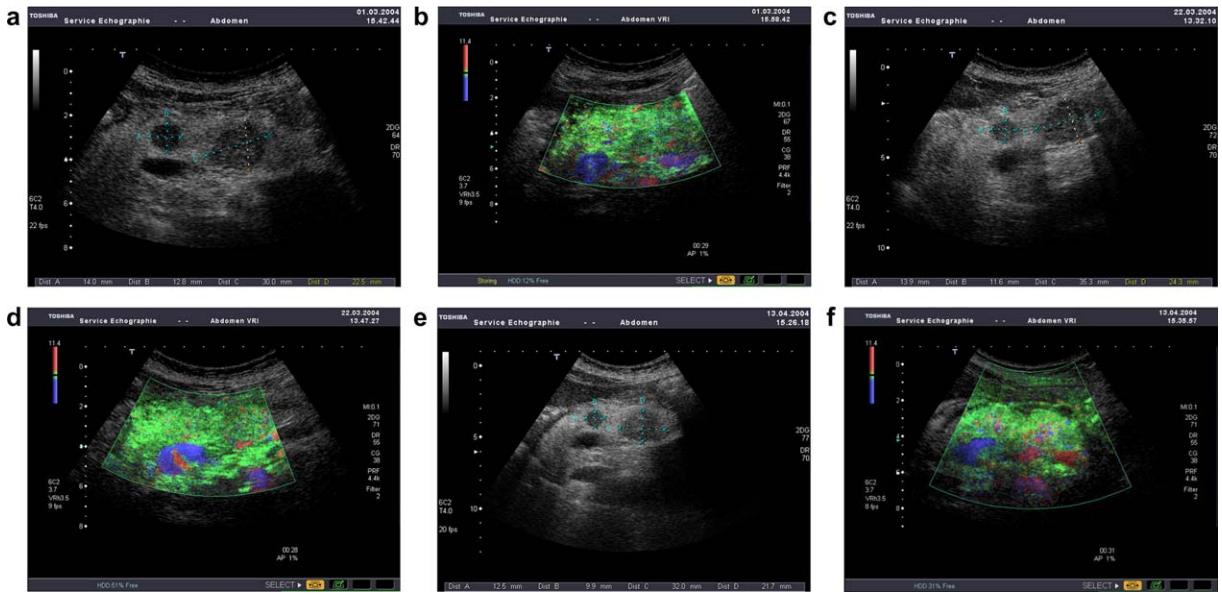

Fig. 3 – Pancreatic metastasis from an RCC in a 57 year-old woman (poor responder) treated with sorafenib. (a) US imaging before treatment: the two lesions measured 14 × 13 mm and 30 × 23 mm; (b) DCE-US before treatment shows contrast uptake throughout the tumour estimated at 100%; (c) US imaging after 3 weeks of treatment: the two lesions measured 14 × 12 and 35 × 24 mm; (d) DCE-US after 3 weeks of treatment shows contrast uptake throughout the tumour estimated at 100%; (e) US imaging after 6 weeks of treatment: no change in tumour size; (f) DCE-US after 6 weeks of treatment shows contrast uptake throughout the tumour estimated at 100%.

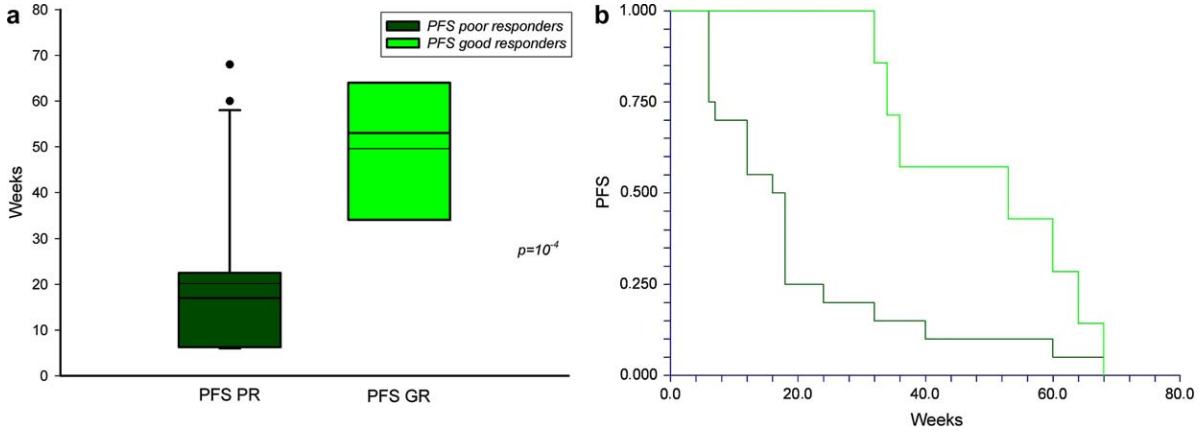

Fig. 4 – Comparison of PFS (median: 17 weeks poor responders and 53 good responders) between good and poor responder patients with ultrasonography discrimination criteria with survival curves.

World Health Organization criteria[17] or RECIST (response evaluation criteria in solid tumour) criteria[18] are not appropriate for the evaluation of targeted therapy because tumour necrosis is often obtained before a decrease in tumour volume can be detected.[19]

The study of tumour neovascularisation is now a major objective in imaging research so that the efficacy of new antiangiogenic treatments [20] and the metastatic potential of tumours[21,22] can be evaluated early. Contrast agent injection allowed us to optimise the detection of microvascularisation and to confirm the absence of residual neovessels. This 'parenchymography' (parenchymal vascularization) exposes any viable residual tumour inside the induced necrosis.[9] New agents such as Sonovue® (BR1, Bracco, Italy) are effective at a low Mechanical Index and prolong the duration of enhancement. Several passages are possible with this agent (up to six injections can be administered) as well as more effective vascularisation studies.[23]

The major advantage of DCE-US, with perfusion software (Vascular Recognition Imaging) and contrast agent injection, for the evaluation of new anti-tumour treatments is that the examination is inexpensive and is always rapidly feasible and repeatable without adverse effects. In addition, we previously showed that this technique is not operator dependent.[24]

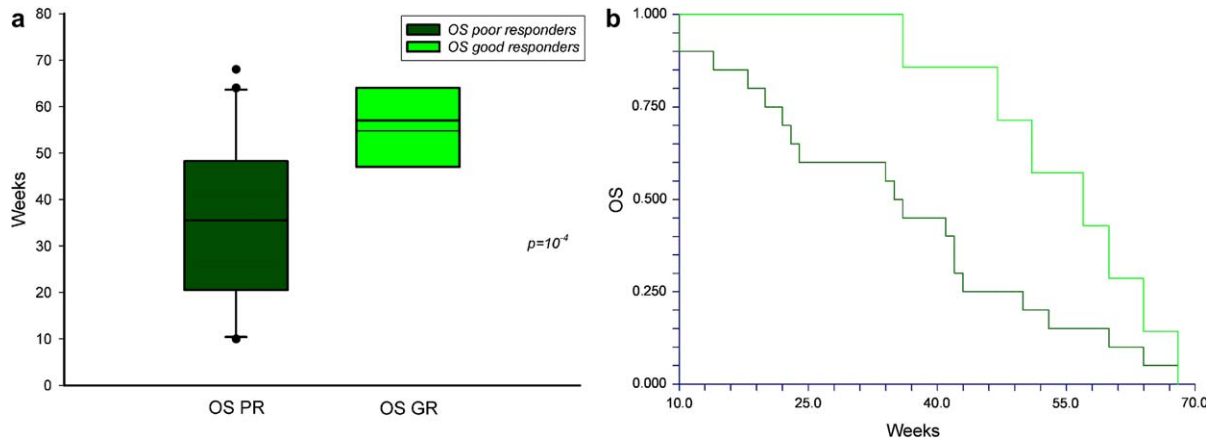

Fig. 5 – Comparison of OS (median: 36 weeks poor responders and 57 good responders) between good and poor responders with ultrasonography discrimination criteria with survival curves.

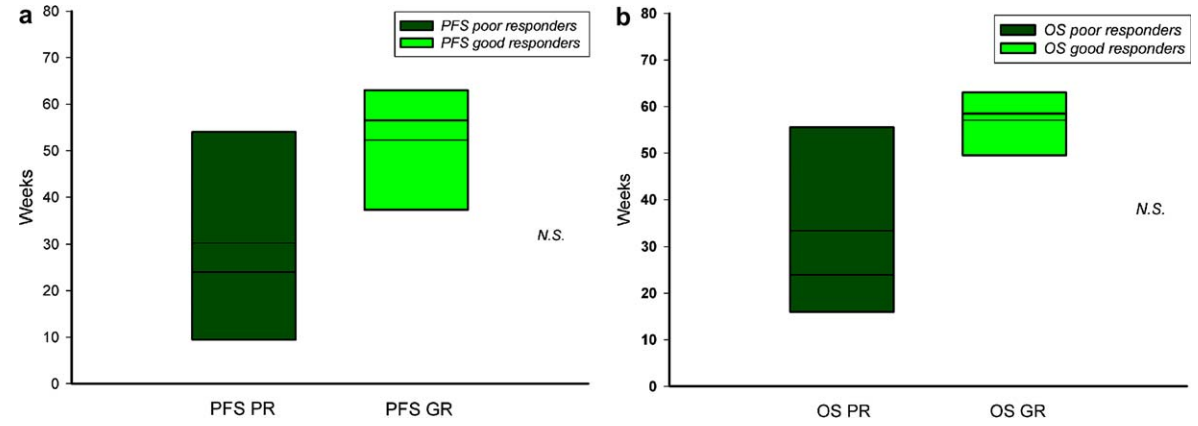

Fig. 6 – Comparison of PFS and OS between good and poor responders with ultrasonography discrimination criteria in patients treated with sorafenib.

The availability of new software packages for objective signal quantification as a function of time would reduce limits such as operator dependence and would enable us to differentiate tumour tissue kinetics from that of inflammatory areas.

Sorafenib is a novel anti-tumour treatment that has demonstrated significant inhibition of neovascularisation in xenograft models of human cancers.[1,2] Several authors have demonstrated the efficacy of this new drug in refractory solid tumours in phase I and II studies.[3–5]

New ultrasonography techniques, such as contrast-enhanced US and tissue harmonic imaging, have improved the sensitivity and resolution of conventional ultrasonography. These new techniques are capable of monitoring antiangiogenic therapy.[9,25] For example, the effect of thalidomide, an antiangiogenetic drug, has been evaluated with new ultrasonography techniques in hepatocellular carcinoma[26] and in renal cell carcinoma.[27,28]

Since 2004, several teams have proposed novel trial designs and endpoints to evaluate new agents in RCC. Time to progression is a novel endpoint proposed by Rini and colleagues and the impact is that patients with better PFS and OS can be identified. In addition, this technique was able to select responders to treatment. Another methodological aspect concerns the number of targets evaluated. Schwartz and colleagues' results obtained using a mathematical model showed that it is preferable to choose fewer targets as this lowers the risk of errors.[29] We chose one to two targets per patient.

A number of studies have demonstrated that angiogenesis is a major prognostic factor in cancers. Fukata and colleagues underscored the importance of angiogenesis in the development of metastatic RCC. Mice with increased intratumour microvessel density and expression of angiogenic genes (bFGF,VEGF, IL-8, MMP-9, MMP-2) had a worse metastasis-free survival curve than controls. In addition, Fukata and colleagues demonstrated a correlation between intratumour microvessel density and the expression of angiogenic genes.[30]

The same authors analysed prognostic factors for survival in patients with RCC. In that study they reported promising results with the new agent and the important role played by angiogenesis in the prognosis.[31,32]

5. Conclusion

DCE-US is a new simple noninvasive imaging technique allowing accurate evaluation of tumour vascularisation. Overall, the combination of a decrease in contrast uptake

exceeding 10% with stability or a decrease in tumour volume significantly predicted PFS and OS in this population of RCC patients. In addition, these criteria seem capable of selecting patients who will benefit from treatment with sorafenib. Imaging approaches such as DCE-US may advance the identification of new predictors of efficacy for targeted agents such as sorafenib in RCC. Further studies with a greater number of patients are required to validate whether techniques used in this study can be used prospectively to predict patient response to sorafenib.

Conflict of interest statement

None declared.

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