ONCOLOGY

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Dynamic contrast-enhanced CT in patients treated with sorafenib and erlotinib for non-small cell lung cancer: a new method of monitoring treatment?

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Abstract *Objective* We investigated the feasibility of serial dynamic contrast-enhanced computed tomography (DCE-CT) in patients with advanced/metastatic non-small cell lung cancer (NSCLC) receiving anti-angiogenic (sorafenib) and anti-EGFR (erlotinib) treatment, and correlated tumour blood flow (BF) with treatment outcome. *Methods* DCE-CTs were performed at baseline and 3 and 6 weeks after starting treatment. Tumour BF, calculated with the maximum slope method, and percentage change were measured in 23 patients (14 male; median age 59 years). Tumour BF was compared at baseline and weeks 3 and 6; the relation with RECIST/Crabb response and progression-free survival (PFS) was assessed. *Results* Mean tumour perfusion decreased from 39.2 ml/100g/min at baseline to 15.1 ml/100g/min at week 3 ($p<0.001$) and 9.4 ml/100g/min at week 6 ($p<0.001$). Tumour perfusion was lower in RECIST and Crabb responders versus non-responders at week 3 (4.2 versus 17.7 ml/100g/min, $p=0.03$) and week 6 (0 versus 13.4 ml/100g/min, $p=0.04$). Patients with a decrease larger than the median at week 6 tended to have a longer PFS (7.1 versus 5.7 months, $p=0.06$). *Conclusion* Serial DCE-CTs are feasible in patients with NSCLC and demonstrated a significant decrease in tumour BF following sorafenib/erlotinib therapy. Early changes in tumour BF correlated with objective response and showed a trend towards longer PFS.

Keywords Dynamic contrast-enhanced CT · Erlotinib · Sorafenib · Non-small cell lung cancer · Tumour perfusion

Introduction

Angiogenesis, the formation of new blood vessels, is a key process in tumorigenesis [1]. Angiogenesis inhibitors have yielded promising results in oncology. They are considered largely cytostatic, inhibiting tumour growth and progression rather than causing tumour regression. Furthermore, anatomical changes lag behind functional changes and tumour shrinkage does not necessarily correlate with patient survival [2]. The standard anatomy-based response assessment using the Response Evaluation Criteria in Solid Tumors (RECIST), therefore seems inadequate for the early evaluation of the efficacy of these drugs [3, 4].

A logical approach to evaluating the effect of angiogenesis inhibitors is to assess their proposed direct target: the tumour vasculature. The current gold standard technique to determine tumour vascularity is measurement of microvessel density (MVD) on tissue samples [5]. However, this invasive method is unsuitable for serial measurements. Furthermore, only focal regions are assessed whereas tumour vasculature is heterogeneous. Non-invasive functional imaging techniques may be superior, providing information on whole tumour volumes. Traditionally dynamic contrast-enhanced magnetic

resonance imaging (DCE-MRI) has been used. However, its application in lung cancer is limited by a low spatial resolution. With the development of multi-detector CT and user-friendly perfusion software programs, the quantification of perfusion parameters using dynamic contrast-enhanced CT (DCE-CT) is increasingly being investigated in oncology.

Currently, there are limited data available concerning the application of DCE-CT for response monitoring of angiogenesis inhibitors. However, this does appear to be feasible and changes in tumour vascular parameters have been demonstrated [6–10]. In non-small cell lung cancer (NSCLC) whole tumour perfusion measured by DCE-CT has been shown to be reproducible [11, 12]. Perfusion parameters measured before surgery for lung cancer correlate with MVD in resected tumour specimens, implying a reliable assessment of tumour vascularity [13, 14]. No studies have, to our knowledge, assessed DCE-CT in monitoring response to angiogenesis inhibitors in NSCLC and how this correlates with patient outcome [15].

In the context of a phase II trial we prospectively evaluated the tumour blood flow (BF) measured by DCE-CT in patients with advanced or metastatic NSCLC treated with the multi-targeted tyrosine kinase angiogenesis inhibitor sorafenib and the anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib. Both have demonstrated anti-tumour efficacy in NSCLC [16–19]. The study aimed to investigate the feasibility of serial DCE-CTs in NSCLC patients receiving combined anti-angiogenic and anti-EGFR treatment, to determine the effect of sorafenib plus erlotinib on tumour BF and to relate tumour BF to treatment outcome.

Materials and methods

Patient selection

The study was conducted within a multi-centre phase II clinical trial of erlotinib and sorafenib in chemotherapy-naïve patients with inoperable, locally advanced/metastatic NSCLC (NCT00722969). Two out of the three participating centres took part in this side study. Approval was obtained from each centre's institutional review board. All patients provided written informed consent.

Between December 2007 and October 2008, 34 of the 50 patients in the phase II trial were prospectively enrolled onto this study. Inclusion criteria included Eastern Cooperative Oncology Group performance status 0–1, estimated life expectancy≥12 weeks and primary tumour size≥1 cm on CT. Patients with a known contrast medium allergy, the inability to hold their breath for long enough or the inability to obey breath-hold commands were ineligible.

Study design

Erlotinib (150 mg/day) and sorafenib (800 mg/day) were orally self-administered and continued until disease progres-

sion, unacceptable toxicity and/or withdrawal of consent. Dose reductions were allowed but did not occur within the first 3 weeks of treatment. Clinical assessments were scheduled every 3 weeks for the first 3 months then every 6 weeks. DCE-CT was performed at the same time as pre-treatment CTs and 3 and 6 weeks after starting treatment. Tumour anatomic size was evaluated at baseline, weeks 3 and 6 and then 6-weekly by standard contrast-enhanced CT of the thorax. Tumour anatomic response was assessed by change in size according to RECIST 1.0 and an alternative method incorporating tumour cavitation as proposed by Crabb et al. (a target lesion is measured by subtracting the longest diameter of a cavity [zero if no cavity present] from the longest diameter of the lesion) [20].

DCE-CT acquisition protocol

The DCE-CTs were obtained by using 64-slice multi-detector CT (MDCT) (Somatom Sensation, Siemens, Erlangen, Germany). An initial non-enhanced CT study (80 kV, 120 mAs , collimation 24×1.2 mm, pitch 1.15, rotation time 0.5 s, field of view 380 mm, slice width 5 mm, reconstruction increment 5 mm) was performed to determine the position of the primary tumour. The subsequent dynamic spiral CT series encompassed the whole primary tumour volume. A 50-ml intravenous bolus of a low-osmolar non-ionic contrast agent with an iodine concentration of 300 mg/ml (Ultravist-300 Iopromide; Schering A.G., Berlin, Germany) was injected over 6.25 s (8 ml/s), using an injection pump through an 18-gauge needle. After a start delay of 4 s, dynamic acquisition of image data was obtained over approximately 40 s, within one breath-hold period. CT parameters were 100 kV and 80 mAs at a slice collimation of 64×0.6 mm and a rotation time of 0.5 s. Temporal resolution was 4 s (1-s acquisition time; interscan delay 3 s). The images were reconstructed by using a slice thickness of 5 mm, with a reconstruction increment of 5 mm. Dynamic CTs were performed with a fixed lower tube current of 80 mAs to reduce radiation exposure. After this dynamic acquisition and following an additional 80-ml bolus of the same low-osmolar non-ionic contrast agent at an injection rate of 3 ml/s and a 30-s delay, a routine, post-contrast, spiral CT of the thorax (120 kV; 130 mAs with care dose automated exposure control) was obtained by using 5-mm-thick sections with a contiguous reconstruction algorithm. For a z-axis coverage of 5 cm (which is variable and depends on tumour size) the effective dose, expressed according to the International Commission on Radiological Protection recommendations, was 1.2 mSv for the non-enhanced CT and 4.4 mSv (10×0.44 mSv) for the dynamic CT protocol [21–23].

Post-processing analysis

Image registration (3D rigid-body) was performed with a commercially available 3D image fusion program (Vinci 2.36.0, Max-Planck Institute for Neurological Research,
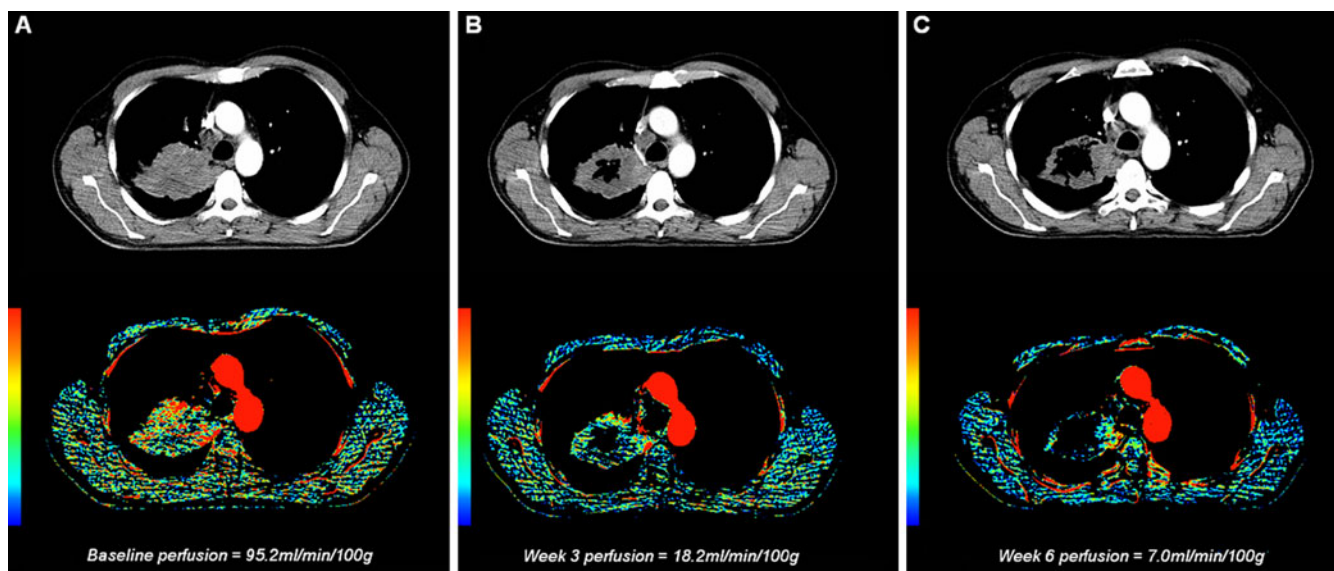
Fig. 1 An example of serial DCE-CT and perfusion parameter maps of the thorax (axial plane) of a study patient. **a** Tumour blood flow at baseline was 95.2 ml/100 g/min. **b** After 3 weeks of treatment tumour cavitation was present and the blood flow had decreased to 18.2 ml/100 g/min. **c** After 6 weeks there was more extensive tumour cavitation. Blood flow in the remaining peripheral tumour tissue had decreased to 7.0 ml/100 g/min

Cologne). For the quantification of tissue perfusion and for the creation of blood flow maps, the software program Basama Perfusion 3.0.7.1 (Kanazawa, Ishikawa, Japan) was used [24, 25]. This program uses the maximum slope method, calculating perfusion as the maximum slope of the tumour time–density curve divided by the peak arterial enhancement [26]:

$$\frac{F}{V} = \frac{\frac{d}{dt}[c(t)]\max}{a(t)\max}$$

Table 1 Patient characteristics and outcome

Characteristic		Patients included in original clinical trial (n=50)		Patients included in perfusion study (n=34)		Patients included in perfusion analysis (n=23)	
		No. of patients	%	No. of patients	%	No. of patients	%
Sex	Female	22	44	14	41	9	39
	Male	28	56	20	59	14	61
Age, years	Median	60		60		59	
	Range	41–78		41–78		41–78	
Ethnicity	Caucasian	45	90	30	88	20	87
	Black	2	4	2	6	2	9
	Asian	3	6	2	6	1	4
ECOG PS	0	30	60	19	56	15	65
	1	20	40	15	44	8	35
Tumour histology	Adenocarcinoma	36	72	26	77	17	74
	Squamous	5	10	3	2	9	9
	Large cell	6	12	2	6	2	9
	NSCLC NOS	3	6	3	9	2	9
Tumour stage[a]	IIIB	13	26	11	32	5	22
	IV	37	74	23	68	18	78
RECIST 1.0	Responder[b]	14	28	12	35	6	26
	Non-responder[c]	31	62	17	50	15	66
	Not evaluable	5	10	5	15	2	9
Median PFS, months		4.6		5.6		5.9	
Median OS, months		12.0		12.4		12.4	

Abbreviations: *ECOG PS* Eastern Cooperative Oncology Group performance status, *BAC* bronchioloalveolar carcinoma, *NOS* not otherwise specified, *EGFR* epidermal growth factor receptor, *RECIST* Response Evaluation Criteria in Solid Tumors version 1.0 [39], *PFS* progression-free survival, *OS* overall survival

[a] Tumour stage according to the 6th edition of TNM Classification of Malignant Tumours [40]

[b] Responder = patient with complete response or partial response

[c] Non-responder = patient with stable disease or progressive disease

where F is blood flow, V is blood volume, $c(t)$ is the contrast density in the tissues and $a(t)$ is the contrast density in the feeding artery (aorta). Regions of interest (ROIs) were drawn within the aorta and within the tumour (as large as possible to minimise noise but excluding large cavitations and extensive areas of necrosis [density< 5 HU]) (see Fig. 1). Tumour ROIs were defined in all slices that covered the tumour and the tumour BF was calculated as follows:

$$\frac{\sum_{\text{all slices}}(tumour\ ROI\ density\ (in\ HU)\ \times\ surface\ area\ (in\ mm^2)_{\text{slice x}})}{\sum_{\text{all slices}}tumour\ ROI\ surface\ areas\ (in\ mm^2)}$$

Blood flow is expressed in millilitres per 100g of tumour tissue per minute (ml/100 g/min). Imaging analysis was performed by an experienced radiologist blinded to the clinical outcome.

Statistical analysis

Baseline (pre-treatment) tumour BF was compared with tumour BF after 3 and 6 weeks of treatment using the non-parametric Wilcoxon signed-rank test. Tumour BF and percentage change in tumour BF were compared between responders (defined as those achieving an objective complete or partial response [PR] according to the RECIST and Crabb methods) versus non-responders (defined as those having stable disease [SD] or progressive disease [PD]) using the Mann–Whitney test. Log-rank statistics were used to test associations with progression-free survival (PFS) and overall survival (OS). Two-tailed $p<0.05$ was considered statistically significant.

Results

The study protocol was easily integrated into the clinical routine. No side effects were seen and all patients tolerated the dynamic CT well. The clinical characteristics of the 34 patients included did not differ from the entire study population of the clinical trial (Table 1). Thirty patients had at least two DCE-CTs. Reasons for less than two CT being performed were: logistical problems ($n=2$); discontinuation of study medication ($n=1$) and withdrawal of consent ($n=1$). Seven patients were excluded from the perfusion analysis. Reasons for exclusion were: inclusion errors (tumour too small [$n=3$]; tumour not evaluable due to post-obstructive atelectasis and a large pleural effusion [$n=1$]); beam-hardening artefact due to the close proximity of the tumour to a major blood vessel ($n=2$); and technical imaging error ($n=1$). Of the 23 patients included in the analysis 19 had tumour BF measurements at all three time points. There were 14 male and 9 female patients with a median age of 59 years (range 41–

78 years). Five patients had stage IIIB and 18 stage IV (Table 1). After a median follow-up of 10.9 months (95% CI 9.2–12.7) 12 patients remain alive of whom 9 are progression-free. Median PFS was 5.9 months (95% CI 5.4–6.4) and median OS 12.4 months (95% CI 10.3–14.6), which is similar to the total clinical trial patient population (PFS 4.6 months and OS 12.0 months) (Table 1).

Anatomical response evaluation

Mean tumour size decreased from 5.6 cm (range 1.9–14.0 cm) at baseline to 4.8 cm (range 1.6–11.0 cm) at week 3 and 4.6 cm (range 1.4–10.1 cm) at week 6. The mean change in size was −13% (range −45 to +5%) and −19% (range −38 to 0%) respectively. The RECIST response was unavailable for 2 out of the 23 patients: one patient discontinued treatment before the week 6 response CT and one patient was not evaluable for
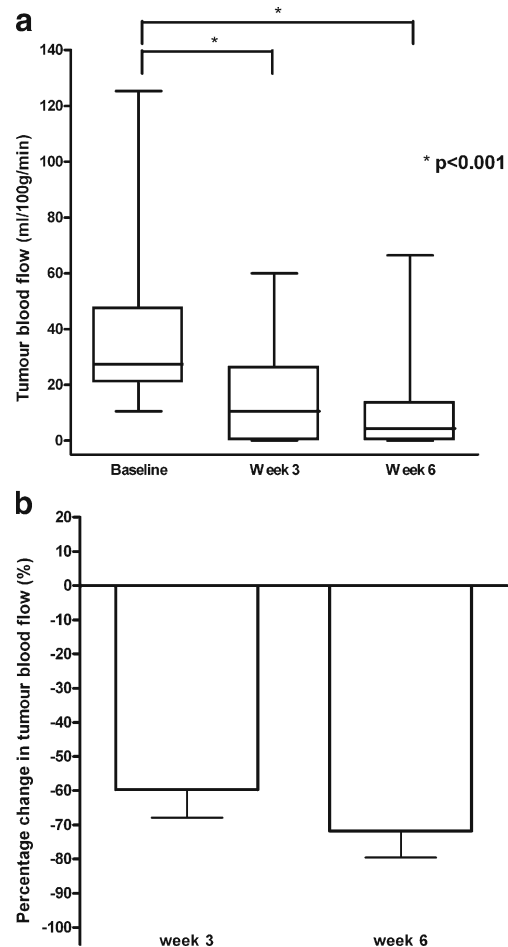
Fig. 2 Box plots showing **a** tumour blood flow at baseline and 3 and 6 weeks after starting treatment and **b** percentage tumour change after 3 and 6 weeks of treatment. Tumour blood flow decreased significantly after 3 and 6 weeks ($p<0.001$)

response because of the development of a large cavity superimposed with infection. Of the evaluable patients, 6 had PR and 15 SD as their best objective primary tumour response according to RECIST (Table 1). Nine patients developed extensive cavitations during treatment. No tumour cavitation was observed at baseline. According to the Crabb criteria 11 patients had PR and 10 SD.

Tumour blood flow

There was a wide variation in baseline BF, ranging from 10.5 to 125.0 ml/100 g/min but mean BF values did not differ between the two centres. Mean baseline BF was 39.2±29.9 ml/100 g/min. After starting treatment, BF decreased in all but one patient after 3 weeks (this patient showed a subsequent decrease in BF at week 6) and all except one patient after 6 weeks (this patient had an initial decrease at week 3) compared with baseline. An example is shown in Fig. 1. The mean perfusion decreased significantly to 15.1± 16.5 ml/100 g/min (range 0 to 60.0 ml/100 g/min; $p<$ 0.001) at week 3 with a mean decrease of 60±37% (range −100 to +7%) and to 9.4±15.4 ml/100 g/min (range 0 to 66.4 ml/100 g/min; $p<0.001$) at week 6 with a mean decrease of 72±35% (range −100 to +18%) compared with baseline (Fig. 2). As a result of

extensive necrosis and/or cavitation of the primary tumour, BF was not measurable in seven patients at week 3 and nine patients at week 6, and was recorded as being zero. Baseline BF was lower in patients who developed extensive cavitations (31.2±21.0 ml/100 g/min) compared with those who did not (50.0±35.2 ml/100 g/min), $p=0.012$.

Tumour blood flow and anatomical response evaluation

Baseline BF was not significantly different in responders versus non-responders according to both the RECIST (mean 28.3±12.3 ml/min/100 g versus 34.3±21.3 ml/100 g/min, $p=0.79$) and the Crabb methods (mean 27.1± 10.8 ml/100 g/min versus 38.6±24.5 ml/100 g/min, $p=$ 0.38) (Fig. 3).

After 3 weeks of treatment RECIST responders had a significantly lower tumour BF than non-responders (mean 4.2±7.8 ml/100 g/min versus 17.7±13.4 ml/100 g/min, $p=0.03$; Fig. 3 a). SD was the best tumour response in the patient with an increase in tumour BF at week 3. After 6 weeks all RECIST responders had necrosis and/or extensive cavitation of the primary tumour with a BF value set to zero. Three additional patients, considered to be RECIST non-responders, had necrosis and/or tumour cavitation with no measurable BF. BF in responders was

Fig. 3 Box plots showing tumour blood flow according to **a** RECIST tumour response and **b** tumour response according to Crabb. Responders (*unshaded blocks*) had significantly lower blood flow after 3 and 6 weeks of treatment compared with non-responders (*shaded blocks*) according to both response methods
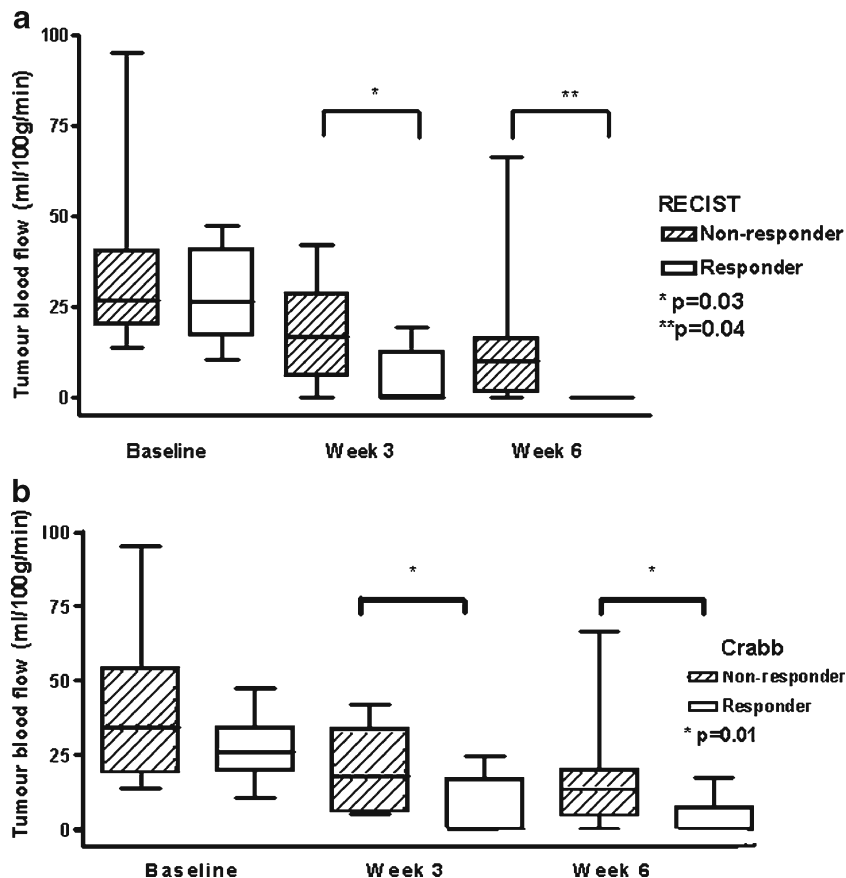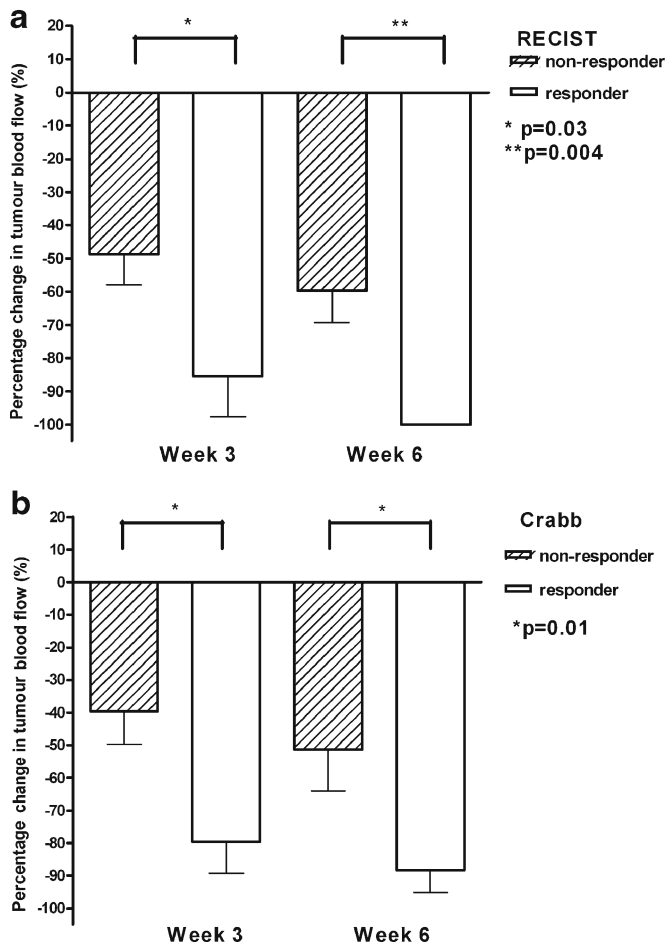
Fig. 4 Bar chart showing percentage change in tumour blood flow according to **a** RECIST tumour response and **b** tumour response according to Crabb. Responders (*unshaded blocks*) had a significantly larger decrease in blood flow after 3 and 6 weeks of treatment compared with non-responders (*shaded blocks*) according to both response methods

also significantly lower than in non-responders at week 6 (mean 0 ± 0 versus 13.4 ± 16.9 ml/100 g/min, $p = 0.04$; Fig. 3a). SD was the best tumour response in the patient with an increase in BF at week 6.

When incorporating the Crabb criteria into the objective response assessment all but one out of the seven patients in whom BF was not measurable after 3 weeks and all but one out of the nine patients in whom the BF was not measurable at week 6 were considered responders. BF after 3 and 6 weeks of treatment were lower in responders than in non-responders (mean 6.5 ± 9.5 ml/100 g/min versus 20.8 ± 13.2 ml/100 g/min, $p = 0.01$ and mean 3.2 ± 5.9 ml/100 g/min versus 17.3 ± 19.8 ml/100 g/min, $p = 0.01$ respectively; Fig. 3b). Again, SD was the best tumour response in the two patients with an increase in tumour BF at weeks 3 and 6.

Regarding the percentage change in BF, RECIST responders demonstrated a significantly larger decrease in BF after 3 weeks (mean $-85 \pm 30\%$ versus $-49 \pm 34\%$, $p = 0.03$) and 6 weeks of treatment (mean $-100 \pm 0\%$

versus $-60 \pm 36\%$, $p = 0.004$) (Fig. 4a). This was similarly seen in Crabb responders versus non-responders at weeks 3 ($-80 \pm 30\%$ versus $-40 \pm 32\%$, $p = 0.01$) and 6 ($-88 \pm 22\%$ versus -51 ± 38 %, $p = 0.01$; Fig. 4b).

Tumour blood flow and progression-free/overall survival

There was no association between pre-treatment absolute BF values relative to the median and PFS. Patients with a decrease larger than the median decrease of 91% at week 6 showed a trend towards a longer PFS than those with a smaller decrease (7.1 months [95% CI 5.1–9.0] versus 5.7 [95% CI 0–14.2], $p = 0.06$; Fig. 5). This was not apparent at week 3. Neither absolute change nor change in BF relative to the median was associated with OS.

Discussion

This is, to our knowledge, the first study to assess tumour perfusion measured by DCE-CT in patients with NSCLC receiving anti-angiogenic and anti-EGFR therapy. We found serial DCE-CTs to be feasible, well tolerated and easily integrated into the routine clinical practice with perfusion measurements possible in most patients. Tumour cavitation, beam-hardening artefacts and small tumour size were the main reasons why perfusion could not be reliably measured. The last two
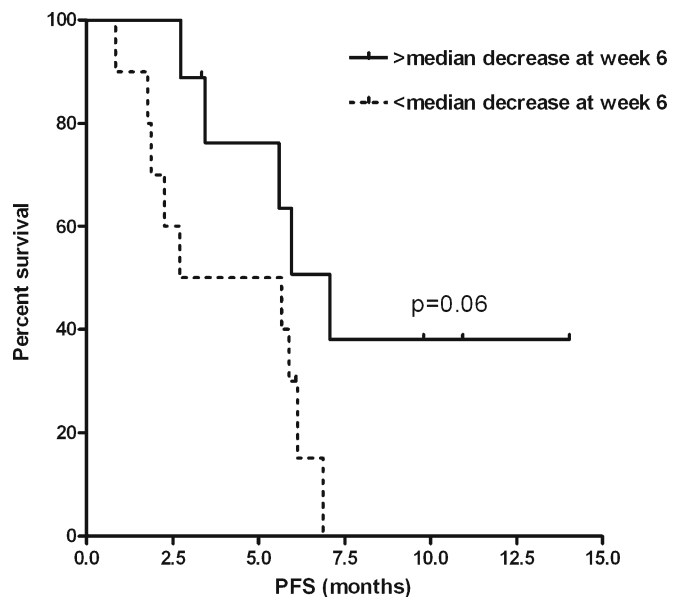
Fig. 5 Kaplan–Meier curve of progression-free survival (PFS). Patients with a decrease in tumour blood flow larger than the median decrease at week 6 (*solid line*) tended to have a longer PFS versus patients with a change in blood flow smaller than the median decrease at week 6 (*dashed line*) ($p = 0.06$)

of these factors are known to prohibit perfusion measurements [27, 28].

Tumour cavitation frequently occurs in patients receiving angiogenesis inhibitors [20]. We found that baseline tumour BF was lower in patients who developed extensive cavitations compared with those who did not. In some cases cavitations posed a challenge for BF measurements. On the one hand, when the cavitation was limited, BF in the remaining tumour volume could be quantified. However, perfusion is not distributed homogeneously throughout tumours [27, 29]. Measuring average BF in the remaining peripheral tumour volume may overestimate BF and thus, in part, explain the wide variation in BF seen. On the other hand, in some patients cavitation was so extensive that insufficient tumour tissue remained to enable a reliable measurement of BF and this was recorded as zero. Although, we assigned a value of zero in these patients it is clear that BF was not truly absent, but simply not measurable by DCE-CT.

Although the sample size is small and there was a wide variation in absolute BF levels, tumour BF decreased in all but one patient after 3 and 6 weeks of treatment with sorafenib and erlotinib. Additionally, the mean BF of the whole group decreased significantly following 3 and 6 weeks of treatment. This may reflect the proposed anti-angiogenic mechanism of action of sorafenib. Bevacizumab, a monoclonal antibody angiogenesis inhibitor, has similarly been shown to reduce tumour perfusion in colorectal cancer [7, 10, 30]. For NSCLC, a reduction in tumour blood volume is reported after administration of combretastatin, a vascular disrupting agent, in patients who had an increase in tumour permeability following radiotherapy and after treatment with N-nitro-L-arginine, a nitric oxide synthesis (NOS) inhibitor [29, 31].

On the other hand, other studies have also shown changes in tumour vascular parameters in patients with NSCLC receiving "non-vascular targeting" therapies. Kiessling et al. describe a reduction in tumour perfusion in a patient after two cycles of chemotherapy [27]. Wang et al. found a significant decrease in blood flow and volume in patients responding to (chemo)radiotherapy [32]. The decrease in tumour BF in our study may thus reflect a general therapy effect.

Currently standard response assessment by RECIST is based on anatomical measurements with response defined as a decrease in tumour size greater than 30%. However, anatomical changes lag behind functional changes and responses based on anatomical assessments may become apparent after prolonged treatment duration. We demonstrated a significant difference in tumour perfusion in objective (anatomical) responders compared with non-responders after only 3 weeks of treatment, with responders having lower BF levels than non-responders. This is partly explained by the development of extensive cavitations in responders as discussed above. More importantly, however, a larger decline in BF after 6 weeks of treatment was associated with a trend towards a longer PFS. To our knowledge, only one other study has investigated the correlation between the anti-vascular effect of treatment and outcome in NSCLC. Although there were no significant changes in the whole group, responders to (chemo)radiotherapy had a significant decrease in tumour blood flow and volume, and patients with a decrease in permeability–surface area product had a longer PFS and OS [32].

Despite the encouraging results of our study, a number of unresolved issues remain regarding DCE-CT. The optimal timing of response assessment of anti-angiogenic therapy is unknown. Jain's concept of a transient normalisation of tumour vasculature and improved tumour BF with anti-angiogenic treatment, followed by vascular pruning and a reduction in tumour blood flow, is estimated to occur within the first week of anti-angiogenic therapy [7, 33, 34]. We performed our first follow-up DCE-CT after 3 weeks of treatment and therefore most likely beyond this normalisation period. Another question concerns the reproducibility of whole tumour perfusion measurements [11]. We plan to determine the reproducibility of our perfusion measurements in a follow-up study. Additionally, the magnitude of change in tumour perfusion which is clinically relevant and the optimal temporal resolution of DCE-CT for the calculation of tumour vascular parameters remain unknown. In stroke and colorectal patients acquisition intervals of more than 1 s and more than 3 s, respectively, influence perfusion measurements [35–37]. We used a temporal resolution of 4 s because a higher temporal resolution would not have permitted whole tumour measurements.

Limitations of DCE-CT are the current lack of standardised protocols [38], the requirement of breath holding during image acquisition to prevent motion artefact and beam-hardening artefacts of tumours located close to large central blood vessels giving potentially false positive results. However, compared with other imaging techniques used to assess tumour perfusion, DCE-CT is cheap, simple, widely available, has high spatial resolution and can be integrated into existing CT protocols.

In conclusion, serial DCE-CTs appear to be feasible in patients with NSCLC. Using this technique we demonstrated a decrease in tumour blood flow following sorafenib and erlotinib therapy. Moreover, early changes in blood flow were predictive of objective response and tended to indicate a longer progression-free survival. Further studies are needed but our data suggest that tumour perfusion may be valuable in the early response monitoring of anti-angiogenic agents, with larger reductions reflecting greater treatment efficacy. Early response methods will enable earlier discontinuation of ineffective treatment, thereby limiting unnecessary side effects and enabling earlier switching to other, potentially effective, therapy.

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