

Comparison of parameters of Dynamic Contrast Enhanced (DCE-)MRI and Contrast Enhanced UltraSound (CEUS) applied in a clinical pharmacological study

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Introduction

Tumor survival and growth is critically dependent on blood supply among others. Thus tumor vasculature presents an ideal target for cancer therapy and numerous antivascular strategies are currently under investigation. DCE-MRI (Dynamic contrast-enhanced magnetic resonance imaging) is a non-invasive technique that is capable to measure tumor haemodynamics [1,2]. It is therefore suitable for monitoring vascular targeted therapies which are expected to produce vascular effects within the tumor. Contrast enhanced ultrasound (CEUS) is discussed as an alternative to DCE-MRI in some applications. Whereas DCE-MRI has been used in drug studies for a couple of years and standards were published [3], CEUS is a relative new technique [4] and standards have to be developed. In the current study patients were examined with DCE-MRI and CEUS and results were compared.

Method

The current investigation was performed within an open-label study including patients exhibiting a large variation in tumor size, entity and previous anticancer treatments. Pharmacokinetic parameters of a cationic liposomal formulation of paclitaxel (EndoTAG™-1) and its effect on tumor vascularisation were under investigation. DCE-MRI and CEUS were performed once before start of treatment (day 1) and then at day 4, 15 and 29 during treatment.

MRI data were acquired using a 1.5 T system (Magnetom-Sonata, Siemens Medical Solutions, Germany). For DCE-MRI an inversion recovery TrueFISP sequence [5] was used in a time series covering the period before, during and after contrast agent (CA) injection. The CA (Magnevist, Bayer-Schering Pharma, Germany) was injected using a power injector (MEDRAD, Inc. USA). A software package, developed under MATLAB (<http://www.mathworks.com>), was used for data analysis. Initial area under concentration curve ($iAUC_{60}$) and the transfer constant (K^{trans}) [6] were obtained for Region of Interests (ROI) enclosing a metastasis in the liver.

CEUS scans (duration 60s) were performed after manual injection of an ultrasound contrast agent containing microbubbles (SonoVue, Bracco Inc., Italy). Video clips of contrast enhancement were recorded using a Logiq 9 ultrasound machine (General Electric Co., USA). Contrast enhancement in regions of interest (ROI), a circle of 20 mm diameter within the reference tumor lesion, was plotted as time-intensity curves (TIC) and modelled using a saturation kinetic model. The rate constant k and the maximal contrast enhancement ΔC_{max} of the ROIs were documented.

For 14 patients reference lesions in the liver have been examined with DCE-MRI and CEUS. The relative change of the size of the reference lesion and of the perfusion parameters have been compared between the two modalities.

Results

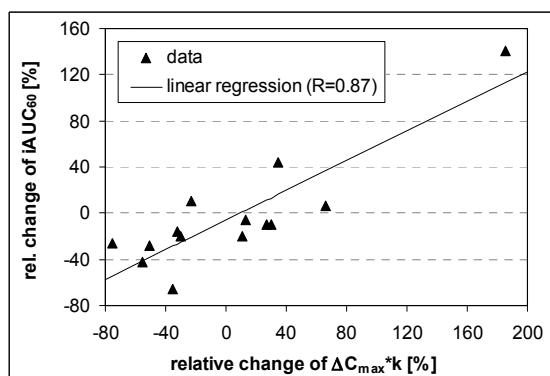
The relative change of the size of the reference lesion at day 29 compared to screening measured by MRI was compared to the changes determined with CEUS. If linear regression is performed the resulting straight line is very near to $y=x$, which would be expected, if the two different modalities measure exact the same changes. The correlation coefficient is 0.74, which is caused by the spread of the data points. Further the correlation between the CEUS parameters ΔC_{max} and k and the DCE-MRI parameters K^{trans} and $iAUC_{60}$ were checked. The highest correlation of $R=0.87$ was found between the relative change of the product of $\Delta C_{max} * k$ and the relative change of $iAUC_{60}$ at day 29 compared to screening (see Figure).

Discussion

It has to be mentioned that MRI and ultrasound imaging were performed and analysed at different sites. By technical reasons the slice orientation of the scans were not the same for both imaging modalities and the reference lesion examined was not identical for all patients at both modalities. Nevertheless, the response to the therapy should concern all lesions of an individual patient, even though not all of them in exact the same extent.

Since the contrast agent of CEUS is intravascular but that one used for DCE-MRI passes fast to the extravascular space, comparing DCE-MRI and CEUS is not straight forward. But with suitable assumptions it can be shown that the product of the CEUS rate constant k and the maximal enhancement ΔC_{max} will be proportional to local blood flow [7]. The DCE-MRI parameter K^{trans} and $iAUC_{60}$ are also expected to depend on blood flow [3]. In agreement with this considerations a good correlation between the relative change of $\Delta C_{max} * k$ and of $iAUC_{60}$ was found in the current study. The smaller correlation to the transfer constant could be due to the fact that the determination of $iAUC_{60}$ is more robust than that of K^{trans} . For a more detailed analysis of the correlation between DCE-MRI and CEUS further investigations have to be performed.

[1] Hylton N., J Clin Oncol 24: 3293 (2006) [2] Goh V. et al., Lancet Oncol 8: 245 (2007) [3] Tofts P.S. et al., JMRI 10: 223 (1999) [4] Lamuraglia M. et al., Crit Rev Oncol Hematol 73: 202 (2010) [5] Scheffler K., MRM 49: 781 (2003) [6] Tofts P.S., JMRI 7: 91 (1997) [7] Wei K. et al., Circulation 97: 473 (1998)



Relative change of $iAUC_{60}$ at day 29 compared to the screening versus the change of $C_{max} * k$ for all 14 patients.