Vascular effects of the vascular targeting agent NGR-hTNF in patients with advanced solid cancer: a dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) study

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Introduction: Vascular targeted TNF, NGR-hTNF, has antivascular properties. In a recent phase I study, it was not possible to select an optimal biological dose of NGR-hTNF from DCE-MRI measurements.(1) This study aims to examine the reasons for this. We hypothesized that the following factors could play a role: 1) insufficient reproducibility of the DCE-MRI method; 2) lack of specific targeting of tumor vasculature by NGR-hTNF; 3) lack of sufficient tumor neovascularization to enable NGR-hTNF efficacy; 4) non-vascular effects of NGR-hTNF interfering with the anti-vascular effects.

Patients and Methods: DCE-MRI, CT, clinical and laboratory data of patients treated in the phase I dose escalation study of NGR-hTNF in patients with advanced solid cancer were analyzed. The utility of DCE-MRI imaging as a predictive biomarker for clinical response and determination of optimal biological dose was an objective for this study. The results of the phase I study were published separately.(1) NGR-hTNF was administered intravenously once every 3 weeks in 20-60 minutes in cohorts of 3-6 patients. DCE-MRI was performed baseline and two hours after start of the first administration of NGR-hTNF in all patients with either primary or metastatic tumors in the liver (n=26) or the head and neck region (n=5). A 1.5 T Siemens MR system was used. After conventional T1- and T2-weighted imaging, 15 ml 0.5M Gadolinium-DTPA was administered intravenously in 6 seconds by a Spectris MR injection system. Using a T1-weighted fast low-angle shot (FLASH) sequence with a time resolution of 2 seconds Gd-DTPA uptake in the tissue was monitored. An arterial input factor (AIF) was determined in a carotid artery (for the head and neck region) or in the spleen (for the liver). Sequence parameters were: TR 50 ms, TE 4.4 ms, α 45º, slice thickness 7mm, 4-6 slices, FoV 512x416. DCE-MRI data were acquired for 90 seconds. For follow-up scans slice positions were matched with the first session using anatomical hallmarks as a reference. We obtained maps for kep and Ktrans as described previously.(2) From each map, the mean kep and Ktrans of the whole tumor/metastasis. To assess tumor heterogeneity, histogram analyses were performed. For the first hypothesis, reproducibility measurements were performed in five additional patients with liver metastases without systemic treatment. The method of Bland Altman was used to determine repeatability coefficients.(3) The reproducibility in the metastases. Our results suggests that this was caused by a combination of the following factors: (i) less adequate reproducibility in healthy liver tissue due to more than expected heterogeneity in vascular response, (ii) more than expected changes in healthy liver tissue which influences the amount of contrast between metastases and healthy liver tissue (iii) difference in the effect of NGR-hTNF between tumors related to tumor size and (iv) the development of soluble TNFα receptors.

Results and discussion: Reproducibility was tested in the 5 additional patients with liver metastases. A mean kep of 0.059 s⁻¹ and mean Ktrans of 0.046 s⁻¹ was found in metastases with a reproducibility coefficient of 0.013 s⁻¹ for kep and 0.055 s⁻¹ for Ktrans. For healthy liver tissue a mean kep value of 0.088 s⁻¹ was found with a reproducibility coefficient of 0.030 s⁻¹, and mean Ktrans was 0.058 s⁻¹ with a repeatability coefficient of 0.024 s⁻¹. In both metastases (n=31) and healthy liver tissue (n=26) of patients treated with NGR-TNF, no significant changes were found in mean absolute values of kep (p>0.1) and Ktrans (p>0.1). Despite this, the changes in mean kep values exceeded the repeatability coefficient in metastases in 6 patients and in healthy liver tissue in 9 patients (fig. A). The fraction of pixels with kep values below the lower threshold (TV kep) significantly increased ( kep=0.002) for metastases. This is in contrast with an increase in fraction of pixels above TV kep in healthy liver tissue (p=0.03) (fig. B, C). Therefore, NGR-hTNF seems less tumor specific than expected, although this did not result in a correlation between DCE-MRI parameters of healthy liver tissue and liver function. Mean values of delta kep and Ktrans were not correlated with longest tumor diameters of the liver metastases and metastases in the head and neck region. The change in percentage of pixels with Ktrans values below TV kep was inversely associated with the longest diameters of the tumors (r²=-0.171, p=0.021) but not significantly correlated to the change in pixels with kep values below the TV kep (p=0.067). Therefore, the effect of NGR-hTNF seems higher in smaller tumors with less mature vessels. At low dose (<1.3 mg/m²) the levels of sTNF-R1 and sTNF-R1I were scattered around zero and increased in a dose proportional manner (r²=0.53, p=0.0014 and r²=0.61, p=0.003, respectively), with an apparent plateau observed at ≥25 mg/m². There was no relation between sTNF-R1 and sTNF-R1I and DCE-MRI parameters. No increase of anti-hNGR-hTNF antibodies was observed.

Conclusions: The failure of the applied DCE-MRI approach to determine an optimal biological dose of NGR-hTNF was not due to inadequate reproducibility in the metastases. Our results suggests that this was caused by a combination of the following factors: (i) less adequate reproducibility in healthy liver tissue due to more than expected heterogeneity in vascular response, (ii) more than expected changes in healthy liver tissue which influences the amount of contrast between metastases and healthy liver tissue (iii) difference in the effect of NGR-hTNF between tumors related to tumor size and (iv) the development of soluble TNFα receptors.