Dynamic contrast enhanced MRI of solid tumors treated with NGR-TNF, a novel vascular targeting agent

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Introduction: Targeted delivery to the tumor of picogram doses of TNF-α can be achieved by coupling TNF-α with CNGRC (NGR-TNF), a peptide that targets tumor neovasculature. NGR-TNF can improve response to chemotherapy (1) by altering tumor vasculature and tumor microenvironment. To assess NGR-TNF efficacy, the direct effect of NGR-TNF on these tumor characteristics should be evaluated, rather than measuring its effect on tumor growth. Moreover, to avoid exposure to a treatment which may cause side-effects it would be desirable to evaluate NGR-TNF efficacy at an early stage of the treatment. The aim of this study was to asses NGR-TNF efficacy with dynamic contrast enhanced MRI (DCE-MRI) during a phase I trial with NGR-TNF in an early stage of the treatment.

Patients and Methods: Cancer patients in sufficient condition for whom no standard systemic therapy was available, were included in a phase I trial with NGR-TNF. NGR-TNF was administered once every 3 weeks by a 20 min intravenous infusion to cohorts of 3-6 pts. Dose escalation was performed with a doubling of the dose until grade 2 toxicity was observed; thereafter a modified Fibonacci schedule was used. All patients gave written informed consent and the study was approved by the local ethical committee. DCE-MRI was performed in cycle 1 at baseline and two hours after start of the infusion of NGR-TNF on a 1.5 T Siemens MR system. After conventional T1- and T2-weighted imaging, 15 ml 0.5M Gadolinium-DTPA was administered intravenously in 6 seconds by a Spectris^{TM} 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 primary tumor or metastases was monitored. To obtain a normalization function bolus passage in a carotid artery (for tumors/metastases in the head and neck region) or in large vessels in the spleen (for liver metastases) was measured. Sequence parameters were: TR 50 ms, TE 4.4 ms, α 45°, 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. To obtain maps for k_{ep} and K^{trans} we adapted the analysis for DCE-MRI data as described by Rijpkema et al. and Van Laarhoven et al. (2,3) This method for data-acquisition and analysis has shown to be reproducible. (2,3) From each map, the mean k_{ep} and K^{trans} of the whole tumor/metastasis was calculated. Also, for each tumor/metastasis a threshold value (TV) was calculated from the formula TV = < M> ± 1.96*SD, where < M> and SD are the mean k_{ep} or K^{trans} and the standard deviation values at baseline. At the two time points, the percentage of pixels that were below and above this threshold was determined. The statistical significance ($p < 0.05$) of differences between the percentage of pixels below or above TV at baseline and follow-up was determined by means of a two-tailed paired t-test. (4,5)

Results and Discussion: Twenty-one patients underwent a DCE-MRI at baseline and two hours after NGR-TNF infusion with a dose range of 0.2 to 8.4 μg/m^2. Nineteen patients had livermetastases of different primary tumors; two patients at lymph node metastases of head and neck cancer. Baseline values of k_{ep} and K^{trans} at baseline showed a large interpatient variability (fig. 1). After treatment with doses of NGR-TNF <1.3 μg/m^2 both increases (no. 2, 9, 11) and decreases (no. 5, 10) were observed in k_{ep} and K^{trans}.in individual patients. These changes were larger than the coefficient of repeatability which we determined in a previous study. (3) At dose-levels ≥1.3 μg/m^2 only decreases (no. 26, 32, 37) were observed which were larger than the coefficient of repeatability. Although on average for the whole population the mean k_{ep} and K^{trans} were not significantly different at baseline and follow-up, at dose-levels ≥1.3 μg/m^2 the mean k_{ep} and K^{trans} significantly decreased ($p < 0.05$). For the whole population the number of pixels with a value of k_{ep} and K^{trans} below TV significantly ($p<0.05$) increased (fig. 2), whereas the number of pixels with a value of k_{ep} and K^{trans} above TV did not significantly change. These results suggest an anti-vascular effect of NGR-TNF.

Fig 1. Mean k_{ep} at baseline and two hours after NGR-TNF infusion for all patients.

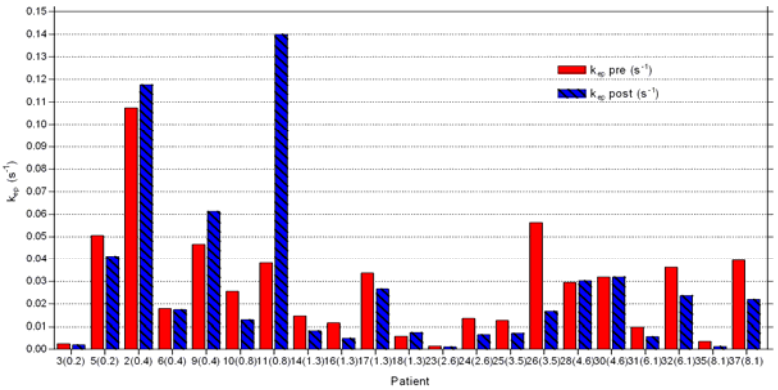
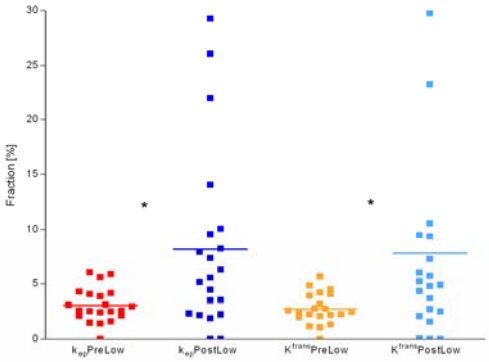


Fig 2. Number of pixels with a value of k_{ep} and K^{trans} below TV. (See Patients and Methods.)



Conclusion: DCE-MRI performed two hours after NGR-TNF infusion showed a significant decrease in k_{ep} and K^{trans}, suggesting anti-vascular effect of NGR-TNF.

Literature: 1) Curnis, F., et al. J Clin Invest, 2002;110:475-482; 2) Rijpkema, M., et al. J.Magn Reson.Imaging 2001;14:457-63; 3) van Laarhoven, H., et al., J.Magn Reson.Imaging 2003;18:315-20; 4) Kauppinen, R., NMR Biomed, 2002;15:6-17; 5) Duvvuri, U., et al. Cancer Res, 2001;61:7747-53.