Dynamic contrast enhanced MRI of solid tumors and healthy tissue during treatment with NGR-TNF, a novel vascular targeting agent

H. W. van Laarhoven[1], J. A. van Asten[2], I. Desar[1], G. P. Rizzardi[3], C. Bordignon[3], C. Punt[1], C. van Herpen[1], and A. Heerschap[2]

[1]Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Molmed, Milan, Italy

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. To assess NGR-TNF efficacy, the direct effect of NGR-TNF on vasculature should be evaluated, rather than measuring its effect on tumor growth. Since NGR-TNF specifically targets tumor vasculature it is expected that the effect of NGR-TNF on healthy tissue is minimal. The aim of this study was to asses the effect of NGR-TNF on solid tumors and healthy liver tissue using dynamic contrast enhanced MRI (DCE-MRI) during a phase I trial with NGR-TNF.

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 or 1 hour 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 tissue was monitored. To obtain a normalization function bolus passage in a carotid artery (for the head and neck region) or in large vessels in the spleen (for the liver) 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. We obtained maps for k_{ep} and K^{trans} as described previously. (1) This method for data-acquisition and analysis has shown to be reproducible. (1) From each map, the mean k_{ep} and K^{trans} of the whole tumor/metastasis and in case of liver metastases an ROI containg healthy tissue (ROI_{ht}) was calculated. The statistical significance ($p < 0.05$) of difference between the mean k_{ep} and K^{trans} at baseline and follow-up was determined by means of a two-tailed paired t-test.

Results and Discussion: Twenty-five patients underwent a DCE-MRI at baseline and two hours after NGR-TNF infusion with a dose range of 0.2 to 45.0 μg/m^2. Twenty-two patients had liver metastases of different primary tumors; three patients at lymph node metastases in the head and neck region. Baseline values of k_{ep} and K^{trans} of the tumors at baseline showed a large interpatient variability. After treatment with doses of NGR-TNF <1.3 μg/m^2 both increases and decreases were observed in k_{ep} and K^{trans} in individual patients which were larger than the coefficient of repeatability which we determined in a previous study (fig. 1). (1) At dose-levels ≥1.3 μg/m^2 the majority of patients showed a significant decrease in k_{ep} and K^{trans} compared to baseline (fig. 1). 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 (.019 vs .012 for k_{ep} s^{-1}; .012 vs .079 for K^{trans} a.u. s^{-1}; $p < 0.01$). In healthy liver tissue both significant increases and decreases in k_{ep} and K^{trans} in individual patients were observed, however without a consistent relation with dose levels. No effect of NGR-TNF on liver function (transaminases, alkaline phosphase, γ-glutamyl-transferase) was observed. On average the mean k_{ep} and $K^{trans}$of healthy liver tissue were not significantly different at baseline and follow-up, neither for the whole population (mean .101 vs .102 for k_{ep} s^{-1}; .077 vs .067 for K^{trans} a.u. s^{-1}) nor at dose-levels ≥1.3 μg/m^2 population (mean .108 vs .111 for k_{ep} s^{-1}; .079 vs .070 for K^{trans} a.u. s^{-1}). These results suggest a tumor-specific anti-vascular effect of NGR-TNF.

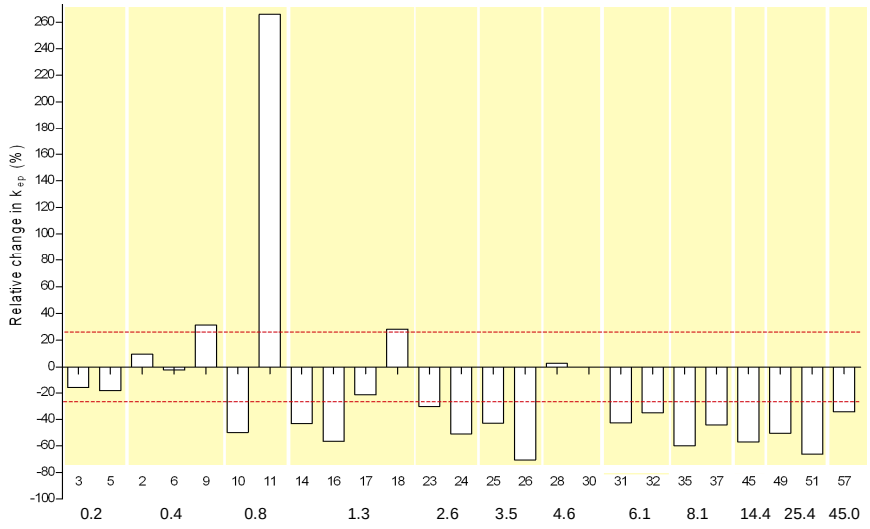

Fig 1. Difference in mean k_{ep} of solid tumors at baseline and two hours after NGR-TNF infusion for all patients. The red dotted line indicates the reproducibility.

Conclusion: DCE-MRI performed two hours after NGR-TNF infusion showed a significant decrease in k_{ep} and K^{trans} in solid tumors but not in healthy tissue, suggesting a tumor-specific anti-vascular effect of NGR-TNF.

Literature: 1) van Laarhoven, H., et al., J.Magn Reson.Imaging 2003;18:315-20.