Direct comparison of macromolecular contrast agent Vistarem with Dotarem for detecting drug effects on tumor vasculature by DCE MRI

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Introduction

The vascular permeability of tumors is currently assessed in the clinic by approved dynamic contrast-enhanced (DCE) MRI using small molecular Gadolinium chelates such as Dotarem. These contrast agents (CA) are, however, less than ideal since the rate limiting step of CA extravasation may be either vascular permeability or blood perfusion in the immature tumor blood vessels. Assessment of vascular permeability with lesser influence of perfusion variations can be achieved by using macromolecular contrast agents. Although such macromolecular CA's are successfully applied in DCE MRI studies, to our knowledge no direct head-to-head comparison between low molecular and macromolecular CA has been performed. The aim of this study was to compare the macromolecular CA Vistarem versus Dotarem (both Guerbet, Paris France) in various tumor models.

Material and Methods

DCE-MRI: Vascular permeability was measured by DCE inversion recovery (IR) TrueFISP at 4.7 T. CA's (Dotarem 0.1 mmol Gd/kg BW; Vistarem 0.028 mmol Gd/kg BW) were infused by a spectrometer controlled pump. DCE MRI was performed using Dotarem followed after ~3 h by Vistarem in the same animals.

Post-processing: Vascular permeability (K^{trans}) was quantified using a two compartment kinetic model according to Tofts (1).

Tumor models: (i) Orthotopic, syngeneic BN472 mammary tumor in Brown Norway rats. (ii) Orthotopic, syngeneic B16 melanoma metastases in C57/BL6 mice.

Treatment: Vehicle or an efficacious schedule of PTK787/ZK222584 (PTK/ZK is co-developed by Novartis and Schering AG, Berlin).

Results

Baseline transfer constant K^{trans} was approximately three times lower for Vistarem than for Dotarem ($2.9x10^{-4}$ s^{-1} vs. $8.2x10^{-4}$ s^{-1}).

The decline in the transfer constant K^{trans} was not significantly different in the PTK/ZK-treated group compared to the vehicle-treated control group in either tumor model (Fig. 1: B16 melanoma metastases, Fig. 2: BN472 breast tumor) when measured with the Gd chelate Dotarem. However, when measured with macromolecular Vistarem in the same animals at the same time points a more pronounced decline of K^{trans} was observed. Furthermore, PTK/ZK treatment resulted in a clearly stronger K^{trans} decline than in the control groups.

A decline of K^{trans} in vehicle-treated animals was observed as well, although to a lower degree, which may reflect the rapid growth of the tumors out-growing their blood supply. A more than 30% reduction of tumor blood volume during the treatment period (data not shown) supports this assumption.

Discussion

This study demonstrated that real treatment effect on vascular permeability K^{trans} can be missed with small molecular Gd chelates. This may be explained by the fact, that PTK/ZK increased perfusion parallel to the reduction of K^{trans} which as net effect resulted in no K^{trans} change (2). With the macromolecular contrast agent Vistarem the influence of perfusion change could be reduced to such an extent that the permeability reduction became experimentally assessable. The shift of the rate limiting step of K^{trans} from perfusion to permeability is of less importance with other drug classes such as anti vascular drugs, where these two parameters alter in parallel (3).

Conclusion

DCE MRI using macromolecular contrast agents results in higher K^{trans} dynamic range due to anti-angiogenic treatment and they should preferably be used to profile this drug class.

References

1. Tofts PS, et al., *Magn. Reson. Med.*1991;17(2):357-67
2. L. Lee, et al., *Cancer Chemotherapy and Pharmacology* 2006 (In Press)
3. West CM., Price P. *Anti-Cancer Drugs.* 2004; 15:179-87

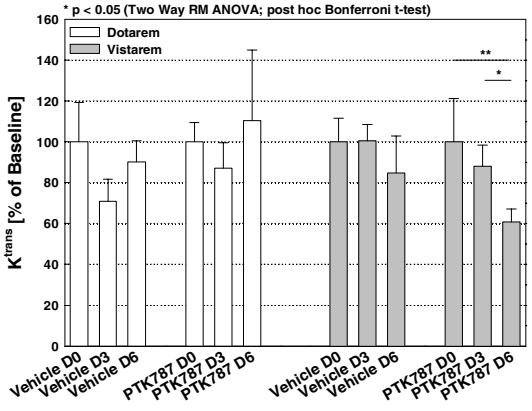

Figure 1 K^{trans} in B16 melanoma metastases before, 3, and 6 days after onset of

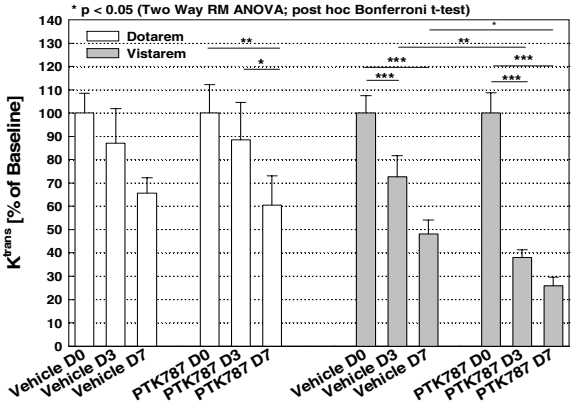

Figure 2 K^{trans} in BN472 breast tumors before, 3, and 7 days after onset of treatment