Assessment of drug-induced vessel remodeling in experimental bone metastases by DCE MRI

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Introduction Bone is among the most frequent locations of metastasis in breast cancer patients. Expression of integrins αvβ3 and αvβ5 confers on breast cancer cells a higher metastatic potential to bone and is known to a play pivotal role in angiogenesis during the development of bone metastasis. The aim of this study was to investigate effects of the inhibition of αvβ3/αvβ5 integrins on the vasculature in a nude rat model of site-specific breast cancer bone metastases using dynamic contrast-enhanced MRI (DCE MRI).

Methods We examined 44 nude rats after inoculation with MDA-MB-231 breast cancer cells in the superficial epigastric artery to induce site-specific bone metastases. Of these animals, n=17 rats were treated with a high dose (HD; 75 mg/kg) and n=15 rats with a low dose (LD; 25 mg/kg) of an αvβ3 and αvβ5 antagonist (small molecule inhibitor) intraperitoneally 5 times per week for 4 weeks, between days 1 and 30 after tumor cell inoculation, respectively. Treated animals were compared to n=15 untreated control rats. Magnetic resonance imaging (1.5 T Symphony, Siemens) using a home-built animal coil and flat-panel volumetric computed tomography (VCT, Siemens) were employed to assess volumes of soft tissue tumors and osteolytic lesions of bone metastases at day 30 after cancer cell inoculation. For DCE MRI, a T1w saturation recovery turbo FLASH sequence was used while infusing 0.1mmol/kg Gd-DTPA, whereas the volume of the soft tissue component of bone metastases was determined from T2w images. DCE MRI-acquired parameters amplitude A (associated with blood volume) and exchange rate constant k_{ep} (associated with vessel permeability) were determined in bone metastases according to the two-compartment model of Brix. Volumes of the osteolytic lesions and the soft tissue components of bone metastases as well as parameters A and k_{ep} were expressed as treatment over control values in percent (T/C%). At the end of the observation period mean positive area fractions of SMA (smoth muscle actin) and collagen IV as well as mean vessel diameters were determined in representative animals of all groups by immunhistological analysis. Results were statistically analyzed using the Wilcoxon rank sum test; p-values <0.05 were considered significant.

Results As assessed with MRI and VCT, mean volumes of the soft tissue tumors (LD, 26 T/C%; HD, 33 T/C%; p<0.01, respectively) and the osteolytic lesions (LD, 16 T/C%; HD, 13 T/C%; p<0.01, respectively) were significantly decreased after treatment with the inhibitor of αvβ3 and αvβ5 integrins in comparison to controls (Fig.1, Fig.2). Furthermore, decreased values for the amplitude A in bone metastases were assessed by DCE-MRI in treated rats as compared to controls (LD, 83 T/C%; HD, 80 T/C%; p<0.05, respectively). DCE MRI parameter k_{ep} revealed significant differences at day 30 with significantly increased values in LD treated animals (LD, 136 T/C%, p<0.05) as compared to controls (Fig.2, Fig. 3). Immunhistology analysis revealed significantly decreased mean vessel diameters and SMA/collagen IV ratios in skeletal lesions after integrin inhibition. Results from DCE MRI and immunohistology are compatible with a decrease in blood volume due to smaller and partly nonfunctional blood vessels and increased vessel permeability due to the increased number of immature vessels upon treatment with the integrin inhibitor.

Conclusion In experimental bone metastases inhibition of αvβ3 and αvβ5 integrins resulted in a significant decrease of both osteolytic lesions and soft tissue tumors of bone metastases. The mechanism of action of the integrin inhibitor could be characterized non-invasively by DCE MRI revealing drug-induced vessel remodeling in experimental breast cancer bone metastases.

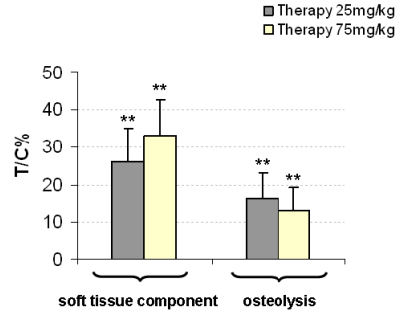

Figure 1 T/C% values of the volumes for the soft tissue tumors (left) and the osteolytic lesions of bone metastases (right) at day 30 after tumor cell inoculation. Grey columns, treatment with 25 mg/kg of the integrin inhibitor daily; yellow columns, treatment with 75 mg/kg of the integrin inhibitor daily. Error bars, standard error; **: p<0.01.

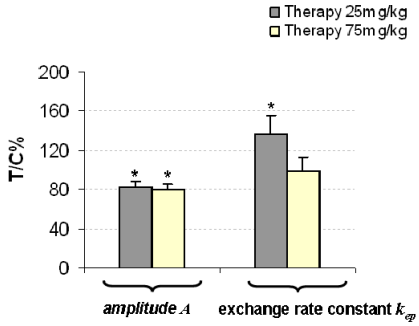

Figure 3 T/C% values of the amplitude A (left) and the the exchange rate constant k_{ep} in bone metastases (right) at day 30 after tumor cell inoculation. Grey columns, treatment with 25 mg/kg of the integrin inhibitor daily; yellow columns, treatment with 75 mg/kg of the integrin inhibitor daily. Error bars, standard error: *: p<0.05.

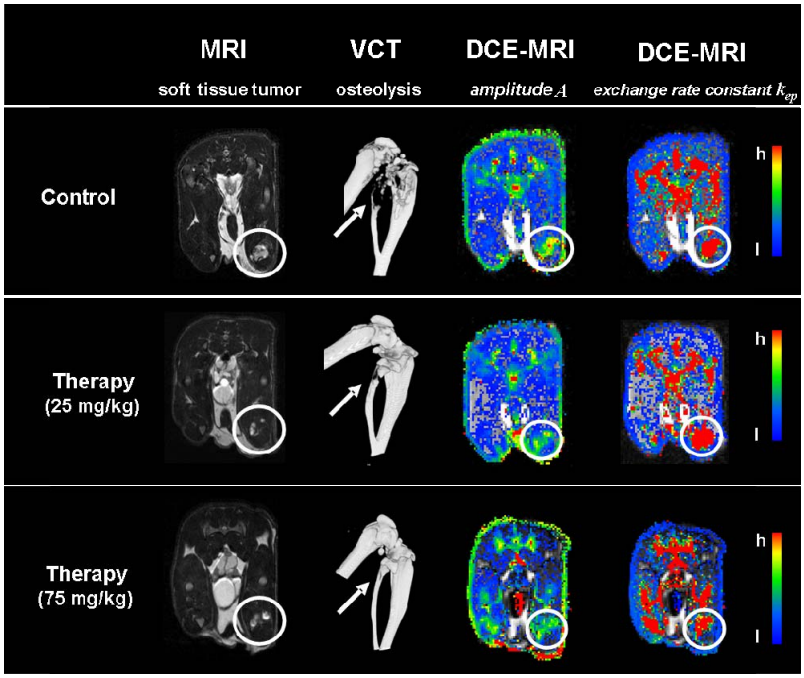

Figure 2 Soft tissue tumors (white circles) as imaged by T2w MRI and osteolytic lesions (arrows) as imaged by VCT of controls and treated rats (25 mg/kg and 75 mg/kg of the integrin inhibitor). Color-coded maps for amplitude A and exchange rate constant k_{ep} ranging from red (high values, h) to blue (low values, l) in bone metastases (white circles) of controls and treated rats (25 mg/kg and 75 mg/kg of the integrin inhibitor). All presented animals were imaged at day 30 after tumor cell inoculation.