Non-invasive assessment of vascular changes in an animal model of breast cancer bone metastases after treatment with an integrin antagonist using DCE-MRI

D. Komljenovic[1], M. Merz[1], W. Semmler[1], and T. Bäuerle[1]
[1]Medical Physics in Radiology, DKFZ, Heidelberg, Germany

Introduction Breast cancer frequently metastasizes to the skeleton, resulting in predominantly osteolytic lesions causing pain and fracture. In bone metastases, αvβ3 integrin is significantly up-regulated on activated endothelial cells and recognized as an important factor in bone resorption. Furthermore, αvβ5 integrin is expressed on various breast cancer cells, including the human breast cancer cell line MDA-MB-231. In this study, we have investigated effects of the inhibition of αvβ3 and αvβ5 integrins in bone metastases by employing a small molecule antagonist of this integrin subclass. Further, our aim was to elucidate whether therapeutic effects, visualized and quantified using dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) and flat panel volumetric computed tomography (VCT), allow early prediction of treatment response in experimental breast cancer bone metastases.

Methods We examined 17 nude rats with hind leg bone metastases after injection of MDA-MB-231 human breast cancer cells. Rats of the treatment group (n=10) were injected with 75 mg/kg αvβ3 and αvβ5 antagonist (small molecule inhibitor) intraperitoneally 5 times per week for 4 weeks, starting at day 30 after tumor cell inoculation (p.i.). Treated rats were compared to untreated controls (n=7) at days 30, 35, 45 and 55 after tumor cell inoculation using a (i) flat panel-equipped VCT (VCT, Siemens) and (ii) clinical MRI scanner (1.5 T Symphony, Siemens) equipped with a home-built animal coil. For DCE MRI, 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 and perfusion) were determined in bone metastases according to the two-compartment model of Brix. Volumes of the osteolytic lesion and the soft tissue component of bone metastases as well as parameters A and k_{ep} were expressed as relative values compared to the initial values at day 30 p.i.. Results were statistically analyzed using the student T-test; p-values <0.05 were considered significant.

Results As assessed with VCT and MRI, mean relative values of the volume of the osteolytic lesion (OL) and the soft tissue component (STC) of bone metastases increased constantly in untreated controls until the end of the observation time (by 2.2, 5.2 and 14.1 fold compared to the initial lesion sizes for the OL (Fig 3) as well as by 2.3, 11.9 and 28.2 fold for the STC, at days 35, 45 and 55, respectively). Mean relative values in bone metastases of the treatment group, however, increased only by 1.6, 1.9 and 3.4 fold for the OL volume compared to initial values (Fig 3) as well as by 2.3, 6.5 and 8.6 fold for the STC (at days 35, 45 and 55, respectively). Significant differences between the groups were found at days 45 and 55 for the OL as well as at day 55 for the STC (see also Fig 1). For the relative mean values of the DCE MRI parameter *amplitude A*, a significant decrease was assessed in animals treated with the αvβ3 and αvβ5 inhibitor at days 35 (89% of initial value), 45 (91% of initial value) and 55 (86% of initial value) as compared to controls (day 35, 109%; day 45, 135% and day 55, 107% of initial values). DCE-MRI parameter k_{ep} revealed significant differences only at day 55 p.i. with significantly increased values in treated animals (83% of initial value) as compared to controls (42% of initial value), but not on days 35 (controls, 101% and treated animals, 100% of values at day 30 p.i.) and 45 (controls, 68% and treated animals, 81% of values at day 30 p.i.) (Fig 3, see also Fig 2).

Conclusion In nude rats bearing bone metastases a significant decrease in progression of both osteolytic lesions and soft tissue tumors was observed upon treatment with an αvβ3 and αvβ5 integrin inhibitor. Treatment response could be assessed by the use of DCE MRI-derived parameter *amplitude A* as early as 5 days after initiation of therapy, before significant differences of morphological features of bone metastases could be observed.

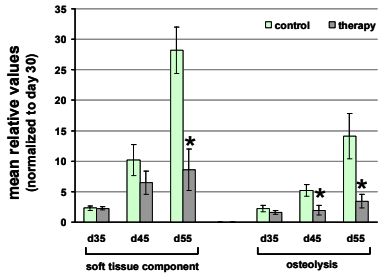

Figure 1 Comparison of the relative mean values of the tumor **soft tissue** volume (left) and the volume of the **osteolytic** changes (right) between treated rats and controls. (Error bars: standard errors, asterisks: p<0.05)

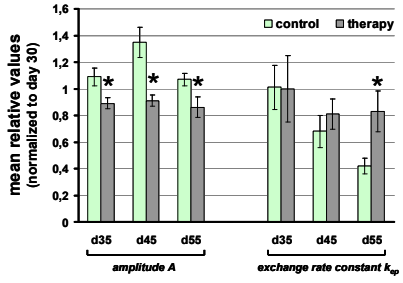

Figure 2 Relative mean values of *amplitude A* (left) and *exchange rate constant kep* (right) in treated rats compared to controls. (Error bars: standard errors, asterisks: p < 0.05)

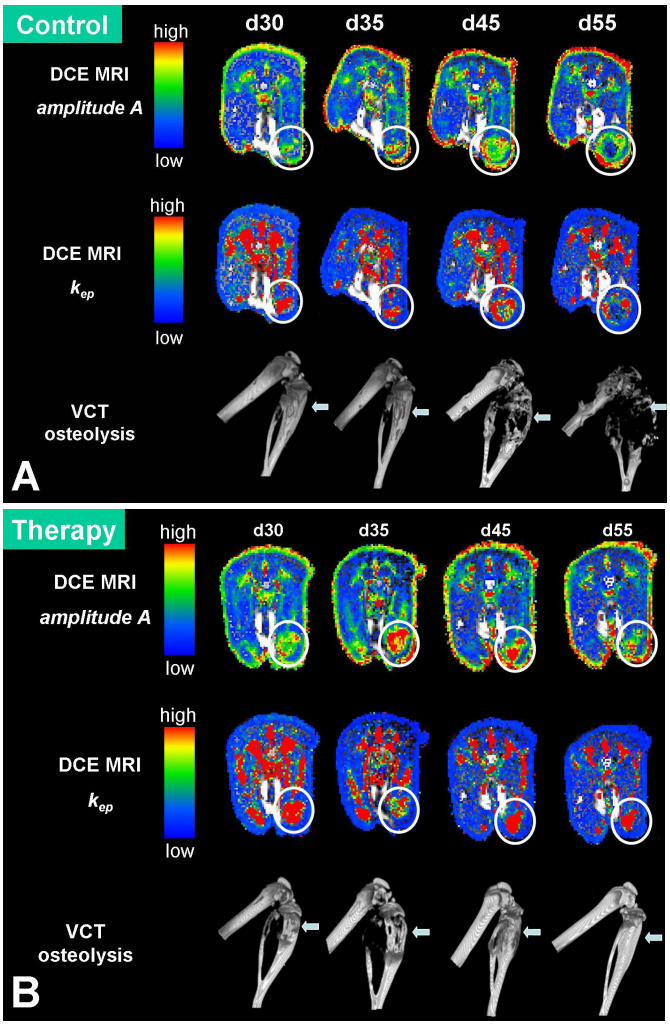

Figure 3 Comparison of osteolytic lesions and examined parameters *amplitude A* and *kep* at defined time points p.i. between untreated (A) and treated (B) animals.