Assessment of early vascular targeting-induced changes with contrast-enhanced sonography as a predictive parameter for induced necrosis formation on diffusion MRI.

V. Vandecaveye[1], F. De Keyzer[1], W. Landuyt[2], H. Bosmans[1], F. Chen[1], X. Sun[1], Y. Ni[1], M. Thys[1], R. Hermans[1]

[1]Radiology, University Hospitals Leuven, Leuven, Belgium, [2]Experimental Radiobiology/LEO, Katholieke Universiteit Leuven, Leuven, Belgium

PURPOSE

Vascular targeting agents induce a near-immediate perfusion decrease in the targeted tumor, which can be examined using contrast-enhanced sonography (CES). However, the amount of treatment-induced necrosis formation, which is the desired endpoint for this kind of therapy, can not be accurately determined by CES. The purpose of this study was therefore to assess the early vascular changes after administration of a vascular targeting agent by CES and to correlate this to the treatment-induced necrosis measured by diffusion-weighted magnetic resonance imaging (DW-MRI).

MATERIALS AND METHODS

Five WAG/Rij rats underwent subcutaneous implantation of R1 rhabdomyosarcomas on both flanks (n=10). After 2 weeks, baseline CES and DW-MRI examinations were performed, after which an intraperitoneal injection of 25 mg/kg of Combretastatin A-4-phosphate (CA-4-P ; OXiGENE Inc., Watertown, MA, USA) was administered. Three hours post-injection, the CES examination was repeated to assess the early treatment-induced perfusion changes. At 3 days after the administration, both CES and DW-MRI examinations were performed to examine possible revascularization and necrosis induction.

For CES a clinical ultrasound system was used (ALOKA, Tokyo, Japan), with standard transverse slices during and after an injection of the contrast agent Sonovue (Bracco, Milan, Italy). The MR scans were performed on a clinical 1.5T MR unit (SONATA, Siemens, Erlangen, Germany), using a 4-channel wrist coil. The DW-MRI used an echoplanar sequence with a large range of b-values (0-1000 s/mm²), and the apparent diffusion coefficient (ADC) was specifically calculated from the high b-values (b>500s/mm^2) for differentiation between necrotic and viable tissue. Correlation with histopathology at each time point was obtained using a separate batch of rats.

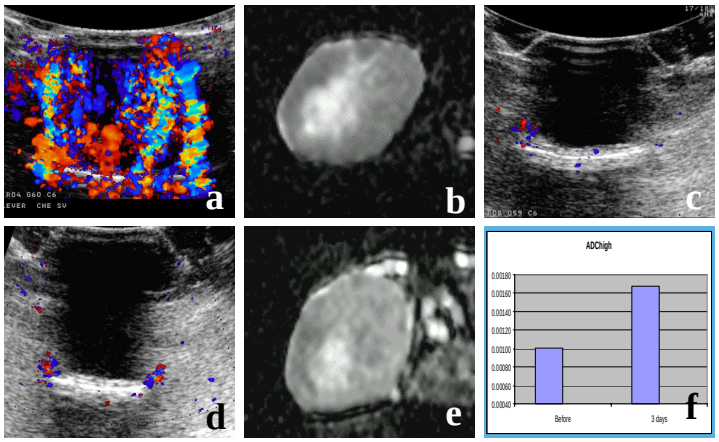

Fig. 1. Random example of a tumor with strong treatment-induced effects. Baseline CES (a) and DW-MRI (b), CES 3h post-injection (c) and CES (d) and DW-MRI (e) 3 days after therapy. ADC values show a strong increase in this timeframe (f).

RESULTS

The induced necrosis, demonstrated by DW-MRI, correlated with the necrosis depicted on histology. Six tumors showed complete loss of perfusion already at 3 hours after CA-4-P administration and did not show increase of flow at three days. These tumors showed a large increase of necrotic tumor area on the DW-MRI scan, leaving only a thin viable rim (Example, see Fig. 1). Limited persistent flow in the feeding artery and the intratumoral vessels was seen in three tumors at three hours post treatment; they showed strong peripheral (re)vascularization after three days. A thick viable peripheral rim was visible on the DW-MRI images with only limited enlargement of the central necrotic area (Example, see Fig. 2). However, one tumor also showed limited remaining flow in the feeding vessel and no intratumoral flow at three hours post treatment; this tumor showed moderate peripheral (re)vascularization in parallel with limited additional necrosis three days later.

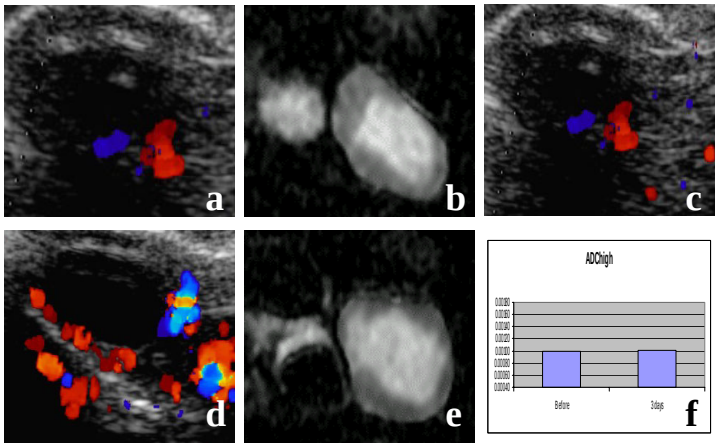

Fig. 2. Random example of a tumor with minimal treatment-induced effects. Baseline CES (a) and DW-MRI (b), CES 3h post-injection (c) and CES (d) and DW-MRI (e) 3 days after therapy. ADC values do not show substantial increase (f).

CONCLUSION

The early vascular changes after CA-4-P administration as assessed by CES show a strong correlation to the amount of treatment-induced necrosis, measured by DW-MRI, and might therefore be used as a predictive parameter for therapy outcome in this tumor model.