In Vivo Monitoring of the Effect of Repeated Administration of Combretastatin A-4-Phosphate by Diffusion-Weighted Magnetic Resonance Imaging.

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Introduction:

Vascular targeting agents selectively damage the intratumoral immature blood vessels. A single dose of these compounds only rarely induces complete tumor death, but the agents can be helpful in a repeat protocol or in combination with other treatment modalities. The purpose of the present study was to evaluate the antitumoral effects of the vascular targeting agent combretastatin A-4-phosphate (CA-4-P) after repeated drug administrations, using diffusion-weighted magnetic resonance imaging (DW-MRI).

Material and Methods:

Rhabdomyosarcoma (R1) tumors were implanted subcutaneously in 13 male WAG/Rij rats (one in each flank, n=26) and left to grow for two weeks, resulting in baseline volumes of 3.6±1.3 cm³. Six rats (n=12 tumors) received 3 intraperitoneal injections of Combretastatin A-4 phosphate (CA-4-P, OXiGENE, Watertown, MA; 25mg/kg body weight), spread 9 days apart. MR scans were performed on these rats before and at 6 hours and 2 days after each treatment. For histopathological validation of the treatment-induced changes after a single treatment, 4 animals were sacrificed. The remaining 3 rats (n=6 tumors) were used as a control group and followed for the whole time period. The MR examinations were performed on a clinical 1.5T system (SONATAVision, Siemens, Erlangen, Germany) using a 4-channel wrist coil. Conventional T1- and T2-weighted spin-echo sequences, covering the entire tumor volumes, were used for morphology.

For functional evaluation, a diffusion-weighted echo-planar sequence with b-values of 0, 50, 100, 150, 200, 250, 300, 500, 750 and 1000 s/mm² was used, again covering the entire tumor volume. The apparent diffusion coefficient (ADC) map using all these b-values was calculated automatically by the system (ADCavg). Afterwards, volumes of interest (VOI) were delineated covering the entire tumor, the center and the periphery for each tumor. The amount of necrosis in the tumors was estimated by measuring the in-plane ratio of necrotic diameter vs. total diameter of the tumor on the ADC map in the two perpendicular main directions of 3 central tumor slices.

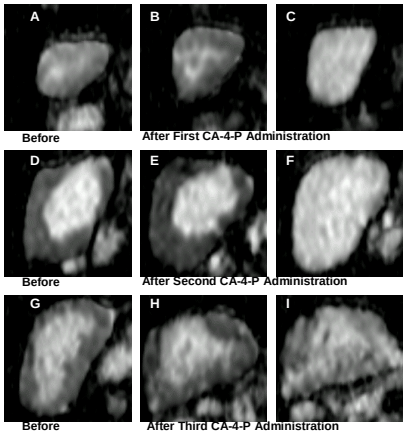

Fig. 1: ADC maps of the central slice during the follow-up period. Before (A, D, G), 6 hours after (B, E, H) and 2 days after (C, F, I) the three respective CA-4-P administrations.

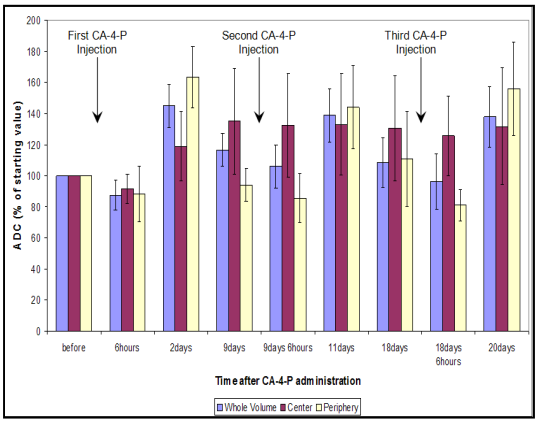

Fig. 2: Relative (compared to baseline) ADC values during the follow-up period for the whole tumor volume, center and periphery.

Results:

An example of a tumor in this repeated treatment schedule is given in Fig 1. A decrease in ADC in the periphery is seen at 6 hours, followed by a strong increase in ADC at the 2 day time point after each CA-4-P administration. The area of necrosis does not change much during the first 6 hours, but is strongly increased at the 2 day time point. The separate delineations of tumor center and periphery (Fig. 2) indicate that the major changes occur only in the periphery, which shows identical changes as the whole tumor delineation with decreases immediately after each CA-4-P administration followed by a strong increase to the 2 day time point. The tumor centers only showed an effect after the first treatment, but no substantial changes after the second and third administration. Fig 3 shows the necrotic vs. total diameter ratio of the treated rats compared to the untreated rats. The untreated rats show a steady increase in necrotic fraction due to spontaneous necrosis induction, whereas the treated rats always experience massive necrosis induction after each CA-4-P administration, which is then followed by strong regrowth from the surviving periphery.

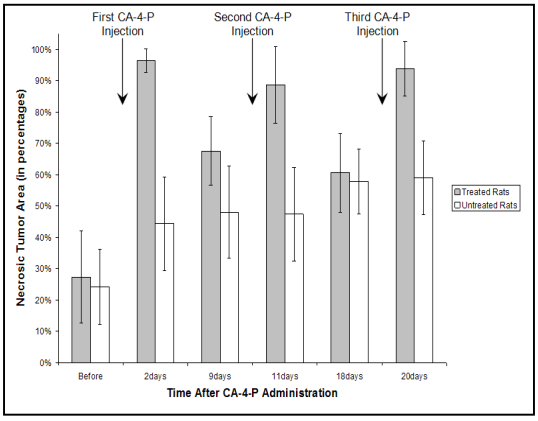

Fig. 3: Ratio of necrotic vs. total diameter of the tumors of treated rats vs. control rats.

Discussion:

In the current rat tumor model with the chosen time points, repeated CA-4-P administration seems to induce similar effects: similar results were obtained up to two days after each drug administration, supporting the absence of drug-induced resistance during such a treatment course.