

Two Vascular Disrupting Agents at a Clinically Equivalent Dose on Rodent Liver Tumors: Comparison of Therapeutic Outcomes with Multiple MRI Biomarkers

H. Wang¹, J. Li¹, F. Chen¹, F. De Keyzer¹, J. Yu¹, Y. Feng¹, Y. Jiang¹, G. Marchal¹, and Y. Ni¹

¹Department of Radiology, Catholic University of Leuven, Leuven, Vlaams Brabant, Belgium

Objectives: To compare tumoricidal outcomes after intravenous administration of 2 lead vascular targeting agents (VDAs), namely Combretastatin A-4-phosphate (CA4P) and ZD6126 at a clinically equivalent dose in rodent liver tumors by using multiparametric magnetic resonance imaging (MRI) biomarkers in correlation with postmortem microangiography and histopathology.

Materials and Methods: Forty rhabdomyosarcomas of 8-14 mm in diameter were obtained 16 days after implantation into right liver lobe of rats and randomly assigned into group of CA4P (n=15), ZD6126 (n=15) or control (n=10). Using a 1.5T Siemens Symphony magnet and a 4-channel wrist coil, T2-weighted imaging (T2WI), pre-contrast T1-weighted imaging (T1WI) and contrast-enhanced T1WI (CE-T1WI), diffusion-weighted imaging (DWI, b=500, 750, 1000s/mm²), and T1-weighted dynamic contrast-enhanced MRI (DCE-MRI) were acquired at pre-treatment baseline, 1, 6, 24, 48, and 120h after iv injection of CA4P or ZD6126 at 10mg/kg or equivalent volume of vehicle, respectively. In vivo multiple MRI biomarkers including tumor volume derived from T2WI, enhancement ratio from T1WI and CE-T1WI, apparent diffusion coefficient (ADC) value from DWI, volume transfer constant per unit volume of tissue, K, from DCE-MRI-derived and necrosis ratio from CE-T1WI, were correlated with ex vivo tumoral microangiography and histopathological findings.

Results: Both VDAs significantly inhibited tumor growth compared to controls, while the volume of tumors with CA4P was significantly smaller than with ZD6126 at 120h (P<0.05) (Figs. 1, 2). The vascular shutdown effect was evident on CE-T1WI from 1h, but more prominent at 6 and 24h. However, enhanced rim occurred in the periphery at 48h after ZD6126 treatment, while later with CA4P only at 120h, indicating neovascularization (Figs. 1, 2, D, D'). K and enhancement ratio quantitatively reflected the vascular shutdown from 1 to 24h for ZD6126, and from 1 to 48h for CA4P, and the peripheral recurrence of tumor (P<0.05). At 5d, necrosis ratio with CA4P was significantly higher than with ZD6126 (P<0.05) (Figs. 1, 2, C'). ADC map enabled distinction between necrotic and viable tumors (Figs. 1, 2, C'). Both VDAs selectively targeted at tumoral vessels while normal liver was not affected. MR imaging biomarkers were verified by postmortem microangiographic and histopathological techniques (Figs. 1, 2, E, F).

Conclusions: Multiple MRI biomarkers allowed morphological and functional monitoring of VDA-related vascular shutdown, tumoral necrosis, and peripheral resistance of liver tumors in rats. Clinically equivalent dose of CA4P has longer vascular shutdown effect until 48h than of ZD6126 until 24h, thus leading to significantly different tumor growth delay at 120h after treatment.

References

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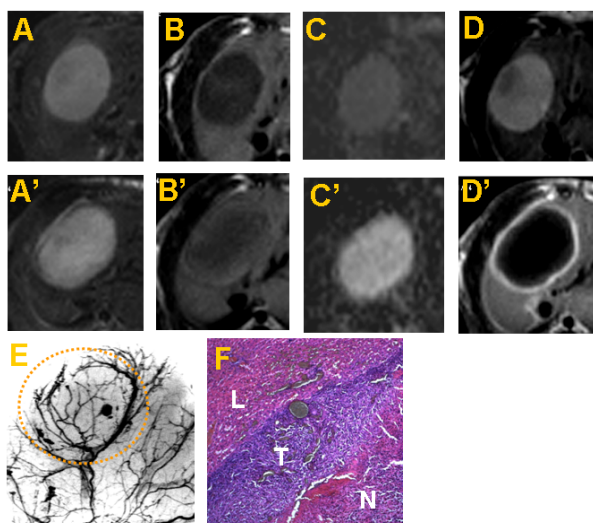


Fig. 1 In vivo and ex vivo findings with CA4P. At baseline, the tumor showed homogenous hyperintensity on T2WI (A) and ADC (C), hypointensity on T1WI (B), and homogeneous enhancement on CE-T1WI (D). At 120h after CA4P, there was no obvious change of signal intensity (SI) on T2WI (A') and T1WI (B'). However, SI in central part of tumor was higher due to extensive central necrosis, while lower SI of peripheral part indicated the recurrence of tumor on ADC (C'), which corresponded with the central un-enhanced area and thin ring enhancement on CE-T1WI, respectively (D'). Postmortem microangiography revealed that almost all of the vessels in the center disappeared with the plentiful neovascularization emerging in the periphery (E). Photomicrograph (F) confirmed the viable tumor (T), ZD6126-induced tumoral necrosis (N) and normal liver (L).

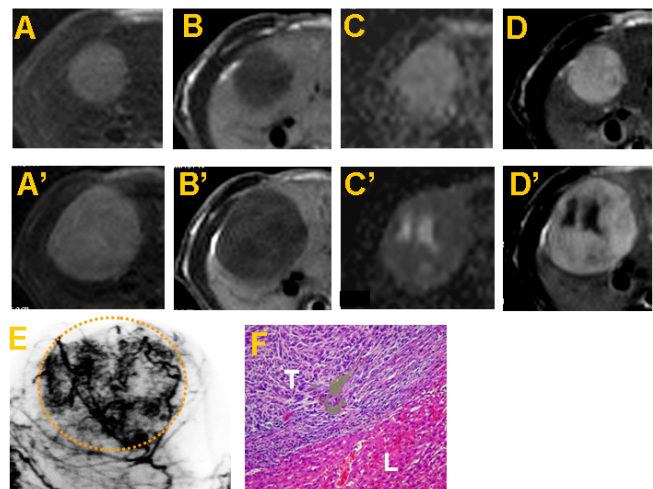


Fig. 2 In vivo and ex vivo findings with ZD6126. At baseline, the tumor showed homogenous hyperintensity on T2WI (A) and ADC (C), hypointensity on T1WI (B), and homogeneous enhancement on CE-T1WI (D). At 120h after ZD6126, there was no obvious change of SI on T2WI (A') and T1WI (B'), while the tumor size increased significantly fast compared to CA4P. Notice the small area of necrosis in the center with higher SI and peripheral recurrence with lower SI on ADC (C'), corresponding with the thick ring enhancement and small unenhanced central area on CE-T1WI, respectively (D'). Postmortem microangiography showed the abundant tumor staining of new vessels in the center, which accounted for the thick ring of recurrence on CE-T1WI (D'). Photomicrograph (F) confirmed the viable tumor (T) and normal liver (L).