Treatment response assessment of a novel vascular-disrupting agent on rabbit tumor model using DCE-MRI

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Purpose

Dynamic contrast-enhanced MRI (DCE-MRI) can be useful for the early clinical development of antivascular agents, as it is able to assess the microvascular response of tumors to anti-angiogenic drugs or vascular disrupting agents. Vascular disrupting agents (VDA) are a new class of drugs targeting pre-existing tumor vasculature leading to tumor cell ischemia and cell death. A novel tubulin polymerization inhibitors, CKD-516, was recently developed and found to have a potent antivascular activities and cytotoxic activity in in-vitro and in-vivo animal experiment. We aimed to evaluate the effect of the new VDA on the blood perfusion in tumors using DCE-MRI.

Material and Methods

In 37 rabbits with 72 VX2 tumors, repeated DCE-MRI using a 3D-radial-gradient echo sequence with K space weighted radial view-sharing scheme(KWIC) was performed with a 3 Tesla clinical machine before and after treatment with CKD-516 and normal saline. Rabbis were randomely divided into six groups (Table 1). The changes in kinetic DCE-MRI parameters (transfer constant [K-trans] and initial area under the gadolinium concentration curves [iAUC]) after treatment with CKD-516 and were measured. The parametric map of DCE-MRI parameters were correlated with the histologic vascular parameters using anti-CD 31 immunohistochemistry stain.

Results

The Ktrans and iAUC of the tumors significantly decreased in CKD-516 treated groups, while those parameters increased in saline-treated groups (P = .019, one-way ANOVA for groups 1-3; P = .001, one-way ANOVA for groups 4-6) (Table 1). Post-hoc analysis showed no significant difference between low-dose CKD-516 treated group and high-dose CKD-516 treated group (P > .05). When each group were stratified into two subgroups by initial Ktrans values (low Ktrans subgroups and high Ktrans subgroups), tumors with initial high Ktrans values showed greater reduction in Ktrans and iAUC values (P < .05 in all subgroups, t-test). The histologic vascular parameters in CKD-516 treated groups were significantly lower than those in saline treated groups.

Conclusion

A single dose of CKD-516 significantly diminished tumor blood supply until 36 hours post-treatment. Tumors with initial high Ktrans values, indicative of well-developed pre-existing vasculature, showed greater vascular shutdown effect to CKD-516.

Table 1. Changes in DCE-MRI parameters

Group	4 hours post-treatment groups			36 hours post-treatment groups		
	Control group* (group 1, n=12)	Low-dose group† (group 2, n=16)	High-dose group‡ (group 3, n=14)	Control group* (group 4 n=6)	Low-dose group† (group 5, n=14)	High-dose group‡ (group 6, n=10)
Ktrans change	15.3%	-21.0%	-33.9%	5.5%	-42.6%	-27.0%
iAUC change	5.9%	-38.2%	-55.1%	3.2%	-40.5%	-30.6%

* saline-treated; † 0.35 mg/kg CKD-516 treated; ‡ 0.7 mg/kg CKD-516 treated

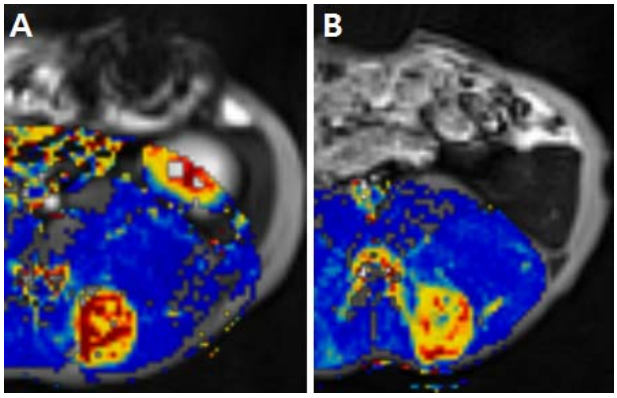

Figure 1. Change of tumor Ktrans value after CKD-516 treatment. (A, pre-treatment Ktrans map ; B, post-treatment Ktrans map)
The Ktrans value of the tumor decreases from 0.321 on initial DCE-MRI (A) to 0.191 on 4 hours post-treatment DCE-MRI (B) after low-dose CKD-516 administration.

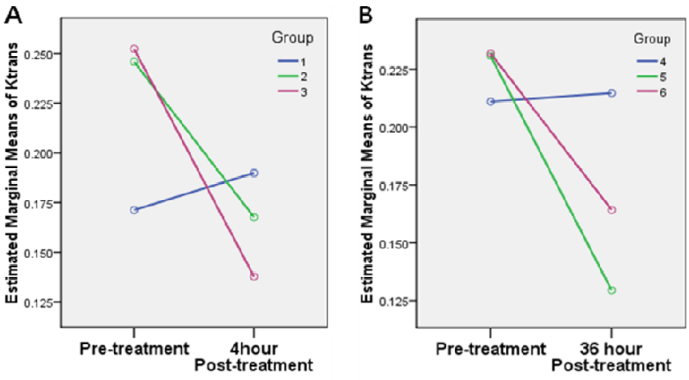

Figure 2. Change of mean Ktrans value of the tumors after CKD-516 treatment.
(A) 4 hour post-treatment change
(B) 36 hour post-treatment change