Changes in tumor oxygen state after sorafenib therapy evaluated by 18F-fluoromisonidazole hypoxia imaging of renal cell carcinoma

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Changes in tumor oxygen state after sorafenib therapy evaluated by $^{18}$F-fluoromisonidazole hypoxia imaging of renal cell carcinoma xenograft (腎細胞癌モデルにおける sorafenib 治療後の腫瘍内酸素状態の変化を $^{18}$F-fluoromisonidazole 低酸素イメージングにより評価)
**Introduction:** A mechanistic dissociation exists between tumor starvation and vascular normalization after antiangiogenic therapy. Thus, better understanding of tumor responses (tumor starvation or vascular normalization) is important for optimizing treatment strategies. $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO) is widely used for imaging tumor hypoxia. To clarify the tumor response to an antiangiogenic drug sorafenib, we evaluated the changes in the tumor oxygen state using $^{18}$F-FMISO in mice bearing a renal cell carcinoma xenograft (A498).

**Methods:** Mice bearing A498 xenograft were assigned to the control and three sorafenib-treated groups, and administered sorafenib (0, 10, 20, or 40 mg/kg/day, p.o.) once daily for 3 days. One day after the last administration, the mice were injected with $^{18}$F-FMISO and pimonidazole (a hypoxia marker). $^{18}$F-FMISO accumulation in the tumor was determined by autoradiography. Immunohistochemistry of pimonidazole and CD31 (a vascular marker) was also performed.

**Results:** $^{18}$F-FMISO accumulation levels in the tumor significantly increased by 4.3-, 8.4-, and 8.6-fold that of the control group following 10, 20, and 40 mg/kg sorafenib treatments, respectively (0.07 ± 0.04, 0.32 ± 0.11*, 0.62 ± 0.15*, and 0.63 ± 0.23* (%ID/m$^2$) × kg for control, and 10, 20, and 40 mg treatments, respectively; *$p < 0.0083$ vs control). The number of pimonidazole-positive cells also significantly increased by 6.8-, 12.3-, and 20.2-fold that of the control group following 10, 20, and 40 mg/kg sorafenib treatments, respectively (0.78 ± 0.79, 5.36 ± 2.29*, 9.66 ± 1.58*, and 15.85 ± 4.59* %pimonidazole-positive cells; *$p < 0.0083$ vs control). The number of microvessels in tumors markedly decreased to be 33.5, 17.6, and 14.0% of the control following 10, 20, and 40 mg/kg sorafenib treatments, respectively (17.1 ± 2.5, 5.7 ± 1.0*, 3.0 ± 1.0*, and 2.4 ± 0.3* vessels/mm$^2$; *$p < 0.0083$ vs control).

**Conclusion:** The $^{18}$F-FMISO accumulation level in the tumor increased sorafenib-dose-dependently, which is consistent with the increase in the number of pimonidazole-positive cells and decrease in the number of microvessels. These findings indicate that the present sorafenib treatment protocol induces “tumor hypoxia/starvation” in the renal cell carcinoma xenograft (A498) owing to its antiangiogenic property.