RRx-001 Oxidation of Redox Sensitive Protein Thiols in Tumors Measured by Gd-LC7-SH Enhanced MRI in Preclinical Tumor Models

Natarajan Raghunand, Jan Scicinski, Bryan Oronsky, Gerald P. Guntle, Elizabeth Bruckheimer, Ronald L. Korn

1The University of Arizona, Tucson, AZ; 2RadioRx, Inc, Mountain View, CA; 3Imaging Endpoints, Scottsdale, AZ

ABSTRACT

SCID mice were inoculated in the flank with either CHP-100 Ewing’s Sarcoma, HT-29 colorectal carcinoma, or Panc-1 pancreatic carcinoma cells. MRI was performed when tumors were 250-400 mm³ in volume. Mice were imaged before treatment and at 1h, 24 h, 72 h and 72 h post-treatment with 10 mg/Kg RRx-001. T1 maps were acquired pre-contrast and at various times post-contrast. Results are displayed in Table 1. T2* maps were acquired BOLD MRI on a separate cohort of mice as per an analogous schedule. The primary objective of this study was to investigate the mechanism of action and pharmacodynamics of RRx-001 using thiol-sensitive MRI. Enhanced by Gd-LC7-SH, longitudinal relaxation time (T1) maps were acquired before treatment and at 1h, 24 h and 72 h post-treatment with 10 mg/Kg RRx-001. Results are displayed in Table 1. T2* maps were acquired BOLD MRI on a separate cohort of mice as per an analogous schedule.

METHODS

SCID mice were inoculated in the flank with either CHP-100 Ewing’s Sarcoma, HT-29 colorectal carcinoma, or Panc-1 pancreatic carcinoma cells. MRI was performed when tumors were 250-400 mm³ in volume. Mice were imaged before treatment and at 1h, 24 h and 72 h post-treatment with 10 mg/Kg RRx-001. T1 maps were acquired pre-contrast and at various times post-contrast. Results are displayed in Table 1. T2* maps were acquired BOLD MRI on a separate cohort of mice as per an analogous schedule.

RESULTS (contd.)

CONCLUSIONS

BOLD MRI results suggest that RRx-001 action does not produce a change in oxidation state of the Fe in hemoglobin and/or result in significant iron deposition in the tumor tissue, either of which would have manifested as a perturbation of tumor T2*. Although redox-sensitive MRI supports alkylation of thiols by RRx-001 as a mechanism of action, the known redox activity of RRx-001 together with its very short half-life in vivo strongly suggest an indirect drug effect on albumin and exofacial thiols in the tumor that manifests as smaller ΔT1 values on Gd-LC7-SH MRI imaging. These effects could be attributed to the oxidation or nitrosylation of tumor exofacial thiols by ROS and RNS derived from RRx-001. The anti-proliferative activity of RRx-001 may not only be due to glutathione depletion and NO release under hypoxia, but also to an increase in intratumoral ROS burden leading to a direct redox modulation of exofacial thiols integral to tumor protein function.

REFERENCES