

THE NEW VASCULAR DISRUPTING AGENT – OXI4503 – SIGNIFICANTLY ENHANCES THE ANTI-CANCER EFFECT OF RADIOTHERAPY COMBINED WITH MILD HYPERTHERMIA.

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Purpose of the study. Vascular Disrupting Agents (VDAs) are drugs that target dividing endothelial cells, facilitating a tumor specific activity. Numerous studies have demonstrated that VDAs can significantly enhance the effect of chemo-, radio- and/or thermotherapy. The leading VDA is the clinically relevant Combretastatin-A4-disodium-phosphate. A new and more potent analogue, Combretastatin-A1-disodium-phosphate (OXi4503), has recently been made available. The purpose of this study is to investigate the effect of OXi4503 on hyperthermia especially in combination with radiotherapy.

Materials and methods. All experiments were performed using our well established murine C3H-mammary carcinoma grown subcutaneously in the rear right foot of female CDF1 mice. Treatments were performed when tumors reached a size of 200 mm³. Hyperthermia was performed locally by submerging the tumor bearing foot into a thermostat controlled waterbath set 0.2 °C above the targeted temperature. OXi4503 (supplied by OxiGene Inc. Watertown, MA, USA), was administered intraperitoneally (i.p.) at a dose of 50 mg/kg (injected at a relative volume of 0.02ml/g). Radiation was administered as a single local dose using a conventional X-ray machine. Radiation treatment was assessed using a tumor control assay. The number of animals showing local control 90 days after treatment was recorded for each treatment group and the radiation dose required to control 50% of the tumors calculated (TCD₅₀). Hyperthermia and VDA-treatment was assessed using a Tumor Growth Time (TGT) assay. Tumor volume was registered 5 times weekly, and the time required to reach 5 times the treatment volume recorded (TGT₅).

Results. The linear relationship between heating time at a specific temperature and TGT₅ revealed slope values in the range of -0.003 days/min to 0.09 days/min at temperatures from 40.0 °C to 42.5 °C. When giving 50 mg/kg OXi4503 3 hours prior to heat treatment this was significantly enhanced to between 0.008 days/min and 0.03 days/min at temperatures from 39.5 °C to 41.0 °C. No increase was observed above these temperatures. The radiation dose required to control 50% of the tumors was 52 Gy. This was significantly lowered to 41 Gy when injecting 50 mg/kg OXi4503 1-hour after radiation treatment. An additional decrease to 37 Gy was observed when heat treatment (41.5 °C for 1 hour) was applied 3 hours after the OXi4503 injection.

Conclusions. The new VDA OXi4503 significantly enhances mild hyperthermia. A synergistic effect is only registered at temperatures that do not induce growth delays as a monotherapy. Furthermore, OXi4503 significantly enhanced the response to radiotherapy as well as radiotherapy combined with mild hyperthermia.

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