

## VASCULAR DISRUPTING AGENTS FOR IMPROVING THERMORADIOTHERAPY: DEPENDENCY ON DRUG TYPE AND HEATING TEMPERATURE

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**Purpose.** Vascular disrupting agents (VDAs) are drugs that specifically damage tumour vasculature and as a result of the subsequent decrease in tumour blood flow they can preferentially enhance tumour response to thermoradiotherapy. The aim of this study was to investigate the role of the drug type and heating temperature on this enhancement.

**Methods.** C3H mammary carcinomas grown in the right rear foot of female CDF1 mice were used when at 200 mm<sup>3</sup> in size. The VDAs were prepared fresh before each experiment and injected intraperitoneally at a standard volume of 0.02 ml/g body weight. They included combretastatin A-4 disodium phosphate (CA4DP; 25 mg/kg) and the A-1 derivative (OXi4503; 50 mg/kg), and the TNF producing drugs flavone acetic acid (FAA; 150 mg/kg) and its derivative 5,6-dimethylxanthenone-acetic acid (DMXAA; 20 mg/kg). Radiation (240 kV X-rays) and heat (temperatures of 39.5°C-42.5°C for 60 minutes) were given locally to the tumour following immersion of the tumour bearing foot in a water bath. Timing and scheduling were radiation – 1 hour – VDA – 3 hours – heat. Response was the percentage of mice showing local tumour control at 90 days after graded radiation doses, and following logit analysis of the radiation dose response curves the TCD50 value (radiation dose producing tumour control in 50% of mice) was calculated. Statistical analysis performed using a Chi-square test (p<0.05).

**Results.** The TCD50 results for the different treatments are summarized in table 1.

Table 1: Effect of combining radiation, VDAs and heat on local tumour control

VDA	Heating temperature (°C)				
	Controls*	39.5	40.5	41.5	42.5
Control	53 Gy (51-55)	---	55 Gy (51-59)	47 Gy (44-51) <sup>a</sup>	47 Gy (44-50) <sup>a</sup>
CA4DP	48 Gy (46-51) <sup>a</sup>	---	---	33 Gy (31-37) <sup>a,b</sup>	---
OXi4503	41 Gy (38-46) <sup>a</sup>	---	---	37 Gy (32-42) <sup>a,b</sup>	---
FAA	42 Gy (39-45) <sup>a</sup>	---	---	28 Gy (22-35) <sup>a,b</sup>	---
DMXAA	47 Gy (42-52) <sup>a</sup>	44 Gy (41-48) <sup>a</sup>	41 Gy (38-44) <sup>a</sup>	30 Gy (26-35) <sup>a,b</sup>	---

Results show TCD50 values (with 95% confidence intervals). Those significantly different from radiation alone<sup>a</sup> or radiation + VDA<sup>b</sup> are indicated. \*Heated at 25°C.

**Conclusions.** The heat enhancement of tumour radiation response was temperature dependent; it became larger at higher temperatures. All the VDAs tested enhanced the tumour response to radiation alone and the combination of radiation with heat. For this latter effect there was no significant drug type dependency, but did appear to be dependent on the heating temperature; the results with DMXAA showed that the higher the temperature the larger the effect.

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